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Editorial

LIMITATIONS OF CONDUCTING COMMUNITY SURVEYS TO ASSESS THE EPIDEMIOLOGICAL IMPACT OF TB CONTROL PROGRAMMES ON THE INCIDENCE OF TB

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Tuberculosis (TB) remains a major health problem in India, and accounts for nearly 20-30% of the global TB burden. A comprehensive review[1] in 1993 of the National TB Control Programme (NTP), present in our country for four decades, documented the failure of NTP due to various drawbacks. These included poor management of the TB control programme, over-reliance on X-rays, poor treatment adherence, under-utilization of laboratory services, poor supply of quality drugs, inadequate funding and lack of proper documentation and case reporting. The Revised National Tuberculosis Control Programme (RNTCP), an application of the globally accepted WHO recommended Directly Observed Treatment Short-course (DOTS) strategy, was implemented in 1993 on a pilot basis, rapidly expanded from 1997 and achieved nation-wide coverage in March 2006[2-3]. The DOTS strategy, based mainly on scientific evidence from India, was found to be more cost effective and RNTCP has almost achieved the global target of 85% treatment success and 70% case detection. It should be remembered that this strategy was developed utilizing results from the pioneering studies conducted by the Tuberculosis Chemotherapy Centre, now renamed as the Tuberculosis Research Centre (TRC), Chennai, three to five decades ago which demonstrated the effectiveness of ambulatory treatment of TB, the concept of direct observation of treatment and the efficacy of intermittent treatment regimens[4-6]. Even though the DOTS programme is decentralized in our country and that treatment facilities are free and provided as close as operationally possible to the door step of patients, a large proportion of patients still seek TB care from the private sector and other alternate sources. The private sector, in the initial stages of RNTCP implementation, was not brought into participating in the TB control activities of the country. Now, however, the programme places great emphasis on public-private mix partnership for the provision of TB services.

After the implementation of the DOTS-based RNTCP in Tiruvallur district of south India by the Tamil Nadu Government in 1999, TRC has monitored the programme in one sub-district tuberculosis unit (TU), and has undertaken a series of TB disease prevalence surveys in a representative random sample of population to measure the impact of the implementation of DOTS services under RNTCP on the disease frequency over a period of time. Tiruvallur is a semi-urban area, 40 kms inland from Chennai city, and the study TU had an estimated population of 5,80,000 in 1999. This is the area where the famous 'Chingelput BCG Trial' was conducted during 1968-1986 to study the protective efficacy of BCG. This area was under TB surveillance on two more occasions in 1991-1992 and 1994-1996. Hence epidemiological data on TB is available from this area for about three decades. In addition, a good rapport with the local community has been established over the years. The availability of this background information has been very useful for evaluating the impact of the implementation of the DOTS strategy for TB control.

The first disease survey was carried out during 1999 to 2001. All adults aged $\geq$ 15 years included in the survey were first screened for TB by the use of two screening methods, namely elicitation of chest symptoms and chest radiography using MMR (mass miniature radiography). Those who were either

symptomatic and/or had an abnormal chest X-ray suggestive of tuberculosis, underwent sputum examination by smear microscopy and culture. This survey meticulously documented the baseline information on the disease prevalence at the time of implementation of the DOTS strategy in this area[7]. The second survey was carried out in the same population using the same methodology during 2001-2003. This survey has provided the estimates of TB disease prevalence after 2.5 years of implementation of the DOTS strategy.

An analysis of the data for the period 1968 to 1986 showed that there was no decline in the prevalence of sputum smear-positive pulmonary TB (PTB) cases in this area i.e. prior to the use of rifampicin-containing Short-Course Chemotherapy (pre-SCC) regimens[8]. After the introduction of rifampicin-containing SCC regimens (SCC), there was a 4.3% annual decline in prevalence during the period 1987-99. After the implementation of DOTS in this area, the decrease accelerated to 9.0% per annum, with the prevalence of smear-positive PTB cases decreasing from 328 to 259 per 100,000 populations. When the culture-positive cases, irrespective of smear results, were looked at separately, the corresponding rates of decline were 1.4, 2.1 and 11.3% respectively for the three periods of time[9].

TRC has thus demonstrated a substantial annual decline in the prevalence of smear positive (9.0%) and culture positive (11.3%) PTB cases in a sub-district area of Tiruvallur after the introduction of DOTS strategy. If this level of decline can be achieved and sustained across the country, or even a lower annual decline rate of 5%, the RNTCP is likely to meet the United Nations TB-related Millennium Development Goal (MDG) of halving the prevalence of TB by 2015 compared to 1990 levels[10].These results suggest strongly that, in the absence of a large epidemic of Human Immunodeficiency Virus (HIV) infection (<1% of TB patients in the survey area were found to be co-infected with HIV - TRC, unpublished data), DOTS can result in a rapid reduction of TB prevalence. If the results from the third survey, conducted during the period 2004-2006, are considered, the average annual decline over a 5-year period in the smear-positive and culture positive PTB cases is estimated to be 12.5% and 12.6% (TRC, unpublished data). However, the contribution to the documented decline in prevalence from changes in the socio-economic status, status of the HIV epidemic in the community and the intervention due to the active case finding activities attributable to the survey itself, have not been estimated during the analyses. But a substantial annual decline of 6% in the prevalence of tuberculosis infection and in the computed Annual Risk of Tuberculosis Infection (ARTI) has also been demonstrated from three tuberculin surveys conducted in the same area during the period 1999-2005[11].

Alternative methods of reporting of all diagnosed new TB cases have to be developed to enable better measurement of the “true” incidence of PTB. The incidence of PTB was measured in India in earlier longitudinal surveys through repeat surveys at fixed intervals which varied from 1 to 5 years. However, at that time, the programme efficiency was poor and the duration of treatment was longer (12 to18 months). Because of these factors, the duration of illness was usually about 3 years and this allowed for the detection of new cases occurring between two surveys. With the introduction of SCC, the duration of treatment was reduced to 6 to 8 months. The implementation of DOTS strategy under RNTCP has further shortened the duration of the sputum positivity among the new cases to 2 to 3 months. In this scenario, the earlier method of detecting new cases by repeat surveys at 2.5 year intervals will result in under-reporting of incidence.

Incidence changes as a result of the changes in the transmission of the disease in the community. Estimating incident cases from two community based disease prevalence surveys using X-ray as a screening tool for detection of cases with a mechanism to identify the new cases in between the surveys is very expensive, time consuming and requires enormous technical inputs that would be difficult to contemplate outside the context of a special study. All cases identified in the first survey conducted during 1999-2001 were prevalent cases. The new cases identified in the second survey (2001-2003) were incident cases and

the total cases, irrespective of new or treated, identified in the second survey were prevalent cases. However, there was no follow-up of the survey population in the period between the two surveys. TRC has made an attempt to correctly estimate the incidence of new PTB smear-positive cases by tracing out the new cases that developed between the first two surveys. We used the TB register maintained in the TU of the area, in order to identify the new smear-positive cases that reported from the survey area in the period between the surveys to health facilities for chest symptoms and were diagnosed as PTB, to the total of new cases detected by the second disease survey. Addresses of patients were collected from the TB Register and they were visited by the field staff and their identity confirmed. Definition of cases included as incident cases remained to the same. The incidence in those aged 15 years and above from the first two disease surveys (including the new cases from the routine programme) was estimated to be 126 per 100000 populations[12]. However, this estimated incidence is likely to be an underestimate of the "true" incidence due to a proportion of incident cases being missed by the surveys if diagnosed and treated in between surveys and/or if treated in the private sector.

An easier method would be to measure incidence and impact of the implementation of DOTS through routine case notifications under the programme provided all new cases are notified. The number of new smear-positive PTB cases notified annually to the health facilities in the study TU from mid-May 1999 to 2003 were 188, 386, 443, 464 and 455 respectively, and the corresponding annual notification rates, measured as the number of cases per 100,000 adult populations, were 69.5, 95.1, 109.1, 114.3 and 112.1 respectively. There was thus an increase in the notification rates seen in the early years but this seemed to have plateaued in the later years. Importantly, therefore, the routine notification rates here are found to be even much below the incidence rate estimated from the disease survey results, which itself may be an underestimate of the "true" incidence rate in the study population.

The primary aim of any TB control programme is to prevent the transmission of TB infection by treating all active TB cases to a complete cure. For this, all new cases should be notified properly to the RNTCP to reflect the "true" incidence of TB disease in the community. In India, a substantial proportion of TB patients, however, seek care from private practitioners and these cases treated by the private sector are generally not notified to the RNTCP[13]. These practitioners must however have a significant amount of information about their patients, their diagnosis, treatment and outcome. The data at such sources needs to be made available to the RNTCP to enable better use of this data in order to improve the quality and completeness of the TB control programme's reporting. All TB cases will be notified in a situation where there is a good surveillance system like that of a universal birth and death registration system. Unfortunately India, with its weak surveillance systems, will take a long time to achieve this goal. Therefore, a good networking system for notifying TB cases by all practitioners needs to be developed and implemented. Mandatory notification to the system of all TB cases could be considered, if practical.

The following are pre-requisites for a good notification system:

1. All TB cases attending either a private or public sector health facility should have an unique identification (ID) number along with other details of the patient such as age, sex, residential address, mode of diagnosis, type of TB, regimen prescribed, etc.
2. All TB cases should be notified to a central place in the district from where a summary report should be sent to the State level and to the Central TB Division, Ministry of Health and Family Welfare, Government of India in Delhi after amalgamation of the data.
3. The system should have an inbuilt mechanism of removing any duplicate reporting that arises when a patient seeks TB care from more than one provider.
4. Private sector should also use the same standard method of diagnosis and tratment as practiced by the public sector.

Unless and until the notification system is strengthened, the notification data will not reflect the epidemiological situation of TB to any high degree of accuracy. An increase in the notification rate does not necessarily indicate a worsening of the TB situation. Rather, it may well simply indicate an improvement in diagnostic and reporting activities. However in the long run, trends in the notification rate should reflect the actual trends in incidence in the respective community.

Alternatively incidence of TB disease can be estimated using Styblo's equation[14] between incidence of new smear PTB cases and ARTI rates. However the incidence estimates derived using this equation are uncertain because of the imprecise nature of the ARTI rates computed from prevalence of TB infection derived from tuberculin surveys conducted using different methodologies. This imprecision is magnified when an effective TB control programme and/or an on-going HIV epidemic are in existence. As a consequence, the case detection rates, measuring the proportion of the estimated incident cases of new smear-positive disease detected by the programme, are not very reliable.

Hence, to conclude the most appropriate long term solution is to have in place a strong routine notification system which over time will reflect the trends in the incident cases in the community and will measure the progress towards the MDG of halting and reversing the incidence of TB disease by 2015.

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DRUG RESISTANT TB - RNTCP RESPONSE**

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I consider it a great privilege and honour for me to deliver the P K Sen Oration on a topic that requires immediate collective action from all health care providers in the country.

On behalf of the Revised National TB Control Programme, I would like to share the concern and response to the threat of drug resistant TB to tuberculosis control in India.

RNTCP achievements and challenges

RNTCP is an application in India of the WHO recommended Directly Observed Treatment Short Course (DOTS) strategy to control TB with the objective of curing at least 85% of new smear positive TB patients and detecting at-least 70% of such patients. Following a stringent preparatory appraisal mechanism, all districts started implementing RNTCP in phased manner and the total population of India was covered under RNTCP on World TB day, March 24th, 2006. Since inception, more than 7.9 million patients have been initiated on treatment and with the treatment success rate of more than 85% among new TB cases and 70% among re-treatment cases, the programme can be termed as highly successful in achieving its objectives. This programme has been internationally recognized as the fastest expansion in the history of DOTS implementation and adopting innovative methods of programme management, especially with respect to monitoring, supervision, evaluation, involvement of other sectors such as NGOs, PPs and medical colleges. As the programme strives to achieve the millennium development goals related to TB it is faced with the several challenges such as consolidating and sustaining the achievements, addressing regional, state and district variation in programme performance, expanding the services for TB-HIV collaborative activities as outlined in the Joint National Framework to the whole country, and last but not the least is the threat of drug resistance to the ultimate goal of TB control.

Global situation of multi-drug resistant TB

A global project on anti-TB drug resistance surveillance was conducted from 1990-2004 in 109 settings in over 90 countries. WHO estimates that tuberculosis caused by strains of MTB which are resistant in vitro to at-least INH and Rifampicin (MDR-TB) causes over 400,000 cases of multi-drug-resistant tuberculosis every year across the world with estimated deaths of over 100,000 every year. China, India and the Russian federation contribute towards a majority of this global MDR-TB burden with India itself contributing to about 80,000 cases every year. This is mainly due to under investment in basic TB control, poor management of anti-TB drugs and transmission of drug-resistant strains. MDR-TB is much more difficult and costly to treat than drug susceptible TB, but recent work has shown that it is feasible and cost-effective even in settings of limited resources but very resource intensive.

Multi-Drug Resistant TB in India

Drug resistant tuberculosis has frequently been encountered in India and its presence has been known virtually from the time anti-tuberculosis drugs were introduced for the treatment of TB. There have been a number of reports on drug resistance in India, but most studies used non-standardised methodologies and biased or small samples, usually from tertiary level care facilities. To obtain a more precise estimate of the MDR-TB burden in the country, RNTCP has a generic protocol for carrying out representative drug resistance surveillance (DRS) surveys at the state level in selected states. Following training of

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the State TB Training and Demonstration centre (STDC) staff in DRS techniques, and of field staff in patient intake and sample collection mechanisms, state representative DRS surveys have been undertaken in Gujarat and Maharashtra (2005-2006). The results of these surveys indicate prevalence of MDR-TB to be ~3% amongst new cases and 12-18% in re-treatment cases. However, translated into absolute numbers the problem is huge. DRS surveys are planned for Andhra Pradesh, Orissa and Western UP in the near future. Besides estimating the drug resistance levels the DRS surveys also assess the success of the TB control programme which is reflected by the fact that there has been no increase in the levels of drug resistance over the past years which is shown by studies from Tuberculosis Research Center, Chennai.

Although the prevalence of MDR-TB in the country in term of percentage is quite small these rates translate into large absolute numbers (as stated earlier ~80,000). Moreover, MDR-TB patients often live a number of years before succumbing to the disease thus maintaining the chain of transmission of the drug resistant strains. This threatens the success of TB control strategies which is aimed at breaking the chain of transmission. It is estimated that MDR-TB prevalence may be three times greater than its incidence.

Causes of drug resistant TB

Though *Mycobacterium Tuberculosis* can acquire drug resistance by spontaneous mutation, most of the drug resistance is 'man-made'. When I say 'man-made', I mean it is due to inadequate regimen prescribed by the health-care-provider, inadequate supply or poor quality of drugs and poor adherence of the patient to treatment due to multitude of reasons like lack of information, social stigma and adverse drug reactions. Most of these occur if TB Control is attempted outside a structured programme setting.

Contrary to the popular belief I would like to say that "many failures are due to failure to take treatment and not failure of treatment *per se*". The evidence to the statement is the fact that about 60% cases which have failed Cat I and are presumed to be suffering from MDR-TB are being successfully treated with Cat II under the programme.

Extensively Drug Resistant TB

In the year 2006, MMWR (Mortality and Morbidity Weekly Report), for the first time reported on the detection of extensively drug resistant tuberculosis popularly known as XDR TB wherein the resistance has amplified from Rifampicin and INH to second line drugs. As per the latest definition, XDR TB is a subset of MDR TB with resistance to Fluoroquinolones and one of the three injectables namely Kanamycin, Capreomycin and Amikacin. In 2005, the United States Centers for Disease Control and Prevention (CDC), WHO and 14 SRLs initiated a study to determine the extent to which resistance to second-line anti-TB drugs had emerged among MDR-TB isolates. The data were published by WHO and CDC in March 2006 in an article in which XDR-TB was first defined. The study, which analysed 17,690 isolates from 49 countries, showed that 20% of all isolates collected were MDR-TB and that 2% were XDR-TB.

Extensively drug-resistant TB (XDR-TB) has been reported in all regions of the world and classified rapidly by WHO as a serious emerging threat to public health, especially, but not only, in countries with a high prevalence of the human immunodeficiency virus (HIV).

The potential destruction which can be caused by this virtually untreatable form of TB has been demonstrated in the KwaZulu Natal province of South Africa. In 2006 a deadly outbreak of XDR–TB occurred in the small town of Tugela Ferry in KwaZulu-Natal. Of 536 TB patients at the Church of Scotland Hospital, which serves a rural area with high HIV rates, some 221 patients were found to have MDR-TB and of these, 53 were diagnosed with XDR–TB. Fifty-two of these patients died almost instantaneously.

XDR TB in India

In India too, XDR TB has been reported by isolated studies with non-representative and highly selected clinical samples. The magnitude of the

problem remains to be determined due to the absence of laboratories capable of conducting quality assured second line DST.

However, what is frightening is the potential threat of XDR-TB in India with unregulated availability and injudicious use of the second line drugs along with non-existence of systems to ensure standardized regimens and treatment adherence for MDR-TB outside RNTCP.

Consequences of XDR-TB

The emergence of XDR TB in India and across the world raises the possibility that the current TB epidemic of mostly drug susceptible TB will be replaced with a form of TB with severely restricted treatment options. If this happens it would jeopardize the progress made in recent years to control TB globally as well as in India and would also put at risk the plans to progress towards a world where TB ceases to be a public health problem. Patients with XDR-TB would have to be managed like TB patients before the antibiotic era. The economic, social and health security of countries and communities with a high prevalence of TB would be threatened by virtually untreatable TB among the bread-winners, parents and economically productive age groups.

RNTCP response plan to the threat of MDR and XDR TB

Realizing this threat posed by the emergence of the drug resistant TB to the goal of TB control, RNTCP has developed a multi-faceted strategy to address the issue. The problem of MDR was recognized and an action plan was built into RNTCP Phase 2 Project Implementation Plan (2006-2011) with a vision of developing a network of RNTCP accredited quality assured intermediate reference labs (IRL) for culture and DST and one IRL and DOTS plus site for each in large state capable of enrolling, and providing care and management of at-least 5,000 MDR-TB cases a year. In the year 2007, RNTCP has been advocating a response which was developed by involving all the stake-holders through a series of consultative meetings to counter effectively the threat of MDR and XDR TB. The following are the components of the response:

1. MDR-TB prevention through sustained high quality DOTS implementation by all providers in the public and private sector
2. Improve laboratory capacity for diagnosing MDR-TB
3. Prevention of XDR-TB by effective treatment of MDR-TB through DOTS-Plus
4. Evaluate extent of threat of SLD resistance and XDR-TB
5. Review the supply and availability of SLDs and address their irrational and indiscriminate use

As you all can see, foremost is the prevention of drug resistant TB through sustained high quality DOTS implementation by all health care providers. The programme has been achieving a treatment success rate of more than 85% among new cases and about 70% among re-treatment cases under programmatic conditions. However instead of basking in the glory of its laurels, RNTCP is consolidating its achievements and striving to deliver quality DOTS services to the community. The programme is also taking adequate steps to reduce the default rate and forging linkages with the private sector and promoting International Standards of TB Care (ISTC) to improve the reach of DOTS services.

The response plan also directs us to work for the establishment of laboratory facilities for diagnosing MDR-TB across the country. Non-viable cultures, culture contamination, and unreliable DST results have major consequences for both individual patients and the TB control programme as a whole. Therefore, the programme is establishing a nation wide network of quality assured accredited Intermediate Reference Laboratories (IRLs) capable of performing culture and DST for the first line drugs. Realising the need for supplementing the diagnostic services which the IRLs will provide, the programme is also facilitating accreditation of existing culture and DST labs in Medical colleges. The programme is also exploring the possibility of engaging with private laboratories in supplementing the diagnostic services.

The response also includes the treatment of MDR-TB patients which RNTCP views as a "standard of care" issue. Recognizing that the treatment of MDR-TB cases is very complex, treatment will follow the internationally recommended DOTS-Plus guidelines and will be done in designated RNTCP DOTS-Plus sites. These sites will be in a limited number of highly specialized centres, at least one in each state, which will have ready access to an RNTCP accredited culture and DST laboratory, with qualified staff available to manage patients, using standardized second-line drug regimens given under daily DOT and standardized follow-up protocols, have systems in place to deliver ambulatory DOT after an initial short period of in-patient care to stabilise the patient on the second-line drug regimen, and with a logistics system and standardized information system in place. The DOTS-Plus sites will be initiated in a phased manner similar to that for the establishment of the culture and DST laboratory network, and sites will be linked geographically to the establishment of the RNTCP accredited Intermediate Reference Laboratories (IRLs). The programme has initiated the DOTS Plus services in the states of Gujarat and Maharashtra in early 2007 with the first MDR patients registered in August we are working towards establishing DOTS-Plus sites in other sites as per the plan of at-least one DOTS-Plus site per large state by 2010 as mentioned earlier.

In the interim, while RNTCP DOTS-Plus services are being expanded across the country a consensus statement guiding all health care providers in the public and private sector managing MDR TB cases has been developed. The statement was the outcome of a meeting at TRC, Chennai of national TB experts on drug resistant TB. The guidance document has been endorsed by the national task force workshop of medical colleges held at AIIMS in November 2007. The document is available on the programme website and is being disseminated through the state governments, state task force and professional bodies.

The programme is also determining the magnitude of the prevalence of XDR-TB by conducting second line DST for all the confirmed MDR patients initiated on Cat IV treatment in the states of Gujarat and Maharashtra. This is being supplemented by surveillance for second line drug resistance on isolates collected as a part of the recently conducted Drug Resistance Surveys in Gujarat and Maharshtra. However the programme also needs to understand the causes leading to the development of XDR and develop appropriate interventions to address the same. Keeping this in view the programme is planning to conduct a case control study of XDR cases identified from the Gujarat DRS survey.

As per a recent study by ORG the market for second line drugs in the country has seen a quantum jump in the past years. $8.4m worth of these drugs, primarily fluoroquinolones, have been consumed for the treatment of tuberculosis primarily outside the programme in 2006. The programme is live to the issue of the wide availability and injudicious use of the second line drugs which will amplify the magnitude of XDR TB in the country. The programme is sensitizing the National and state officials on the emerging threat of XDR TB and its prevention at all potential forums. There is a proposal for introduction of a system of notification of MDR TB patients requiring treatment with second line drugs which is being discussed at the highest level. This would be supplemented with a regulation promoting rational use of second line drugs with the support of professional associations.

At this point in time, in the history of tuberculosis control in our country, we are at cross-roads. There is apparently only one path that appears to be the most appropriate. The path of preventing the emergence of drug resistance by according highest priority to the implementation of quality DOTS services. I request the esteemed audience present here to pledge for the prevention of emergence of drug resistant tuberculosis.

I would like to end the oration quoting this statement from the Stop TB Startegy 2006:

"**Ensuring adherence to a full course of treatment is the key to curing TB patients and preventing the emergence of drug resistance"**

Original Article

PERCEPTIONS OF GENDER AND TUBERCULOSIS IN A SOUTH INDIAN URBAN COMMUNITY

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Summary

Background: The Revised National Tuberculosis Control Programme (RNTCP) in India advocating Directly Observed Treatment-Short course (DOTS) detects nearly three times more male than female TB patients. The reasons for this difference are unclear. An understanding of the community's health beliefs, perceptions on the disease and behaviour towards TB patients may throw some light on this issue.

***Material and Methods*:** A qualitative study using focus group discussions was conducted among men and women of younger and older age groups from lower income neighbourhoods. The information obtained was grouped into themes which included, understanding of TB, vulnerability, access to health care and social responses. Gender differences in community perceptions on TB seem to be critical in issues related to marriage.

Results: The stigma of TB is more visible in women than men when it comes to marriage. Men and children were perceived to get preferential attention by their families during illness. While the younger age group, irrespective of gender, accessed care from private providers, the older group preferred a government facility. Awareness of TB was acceptable but it seemed more associated as a respiratory disease and the common symptom associated with TB was cough.

Conclusion: This study highlights the need for gender specific intervention strategies to enhance better access of TB services. **[*Indian J Tuberc 2008; 55:*9-14]**

***Key words*:** Gender, Community, Tuberculosis

INTRODUCTION

The social and economic impact of Tuberculosis (TB) which claims lives of more than 4, 00,000 people every year is devastating, especially as it affects the economically most productive age group[1]. Furthermore, in virtually all countries, fewer female than male tuberculosis cases are notified[2]. In India, it has been found that more men report with chest symptoms than women and the Revised National Tuberculosis Programme (RNTCP) advocating Directly Observed Treatment-Short course (DOTS) detects nearly three times more male than female TB patients[3]. Higher tuberculosis notification rates in men may partly reflect epidemiological differences, exposure to risk of infection and progression from infection to disease[4]. However, this may not be the only factor influencing this disparity. It has also been generally observed that women in developing countries confront more barriers than men in accessing health care services due to a variety of socio-cultural factors[5,6].

The Revised National TB Control Programme is based on passive case finding which aims to diagnose and treat persons with TB symptoms reporting at various health facilities. The perceptions of TB prevailing in the community would influence the health seeking behaviour of people in accessing health care facilities for their symptoms. While there is information on the care seeking behaviour of chest symptomatic there is dearth of information on community perceptions on TB[7,8]. This study was carried out as part of a WHO/TDR collaborative multi-country project titled "Gender Differentials in Tuberculosis

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Control". The objective of this qualitative community based study is to find out gender differences in understanding of TB with reference (1) to symptoms, causes, spread and cure (2) perceptions about vulnerability to TB (3) gender differentials in care seeking, type of providers consulted, reasons for choice and perceptions about TB services (4) implications of TB on marriage, pregnancy and lactation.

METHODOLOGY

This is a qualitative study using focus group discussions (FGDs) to obtain information on the community's perception on TB with special reference to gender. We used this method as it has been proved a useful tool to collate information on the community's beliefs, values and understanding of health problems[9, 10].

A topic guide developed at the project development workshop on gender differentials in TB control in December 2000 was used to guide the FGDs. The topic guide included questions about awareness of TB, vulnerability to TB, care seeking behaviour and implications of TB on marriage and breast feeding. The topic guide was pilot tested for men and women separately and found to be culture specific and adaptable among men and women.

Study participants

Participants in the study were members of the community from Chennai city, belonging to the lower socio-economic strata. They were grouped into four different groups based on age and gender and were categorized as "old male" and "old female" (>40years) "young male" and "young female" (<40years). The help of a community leader of the area was used to identify eligible participants. They were first assessed for their willingness to be a part of the study and spare the time required for a discussion. If willing, the details of the study were briefly explained and their written consent obtained. Ineligible participants were below 18 years and above 80 years, as well as those persons who were too ill and hard of hearing. Each FGD lasted for one hour to 90 minutes. The team, which conducted the discussion, comprised trained medical social workers. One was a moderator responsible for leading the discussion and her role was purely as a catalyst. The other was responsible for recording the information, making detailed notes in addition to tape recording, noting down expressions and seeing to it that everyone in the group had an opportunity to participate. The moderator closed the FGD session when the saturation point was reached and no new information was obtained. Each discussion had 8-10 participants and was conducted in Tamil.

Study sites

The FGDs were conducted in places that were familiar to participants and at a time convenient to them. Community halls, residences of grass root level workers of the Non-Governmental Organizations (NGOs) and school premises were some of the venues used for the FGDs. A total of sixteen FGDs were conducted.

Statistical Analysis

The information collected was transcribed the same day and data entry completed within a week. The qualitative analysis was done using the MAXQDA software. Data was analyzed according to the different themes based on which the data was collected.

RESULTS

Understanding of TB (pertaining to symptoms, cause and spread)

Tuberculosis disease was familiar to both men and women in all the groups and considered as a respiratory disease. The main symptom that was associated with TB by all the groups, both among the men and women was "cough". Some of the participants mentioned continuous, severe cough with a whooping sound and expectoration and a few expressed cough with a yellow coloured sticky sputum as a symptom

of TB. Some of the men mentioned blood in the sputum, fever, breathlessness and many women expressed weight loss and loss of appetite as other symptoms of TB.

An often repeated response regarding the cause of the disease was "stamping on sputum". To illustrate from an often repeated response

"Since many people walk without slippers, they may get infected if they stamp on the sputum".

More males and a few females attributed smoking as a cause for TB. Drinking as a cause for TB among men was expressed more by the women. The women felt that eating stale food and breathing polluted air could be reasons for getting TB. Some women were also of the view that women being primary care givers were more prone to being infected, especially if there was a TB patient in the family. Some of the other responses among women were that contact with other TB patients, sharing of utensils, clothes and food with TB patients lead to the spread of disease.

Vulnerability to TB

Most of the respondents in all the groups were of the opinion that men were vulnerable to TB as they smoked, consumed alcohol and frequented dirty and polluted surroundings. In some of the groups, both male and female, it was felt that men were more vulnerable to TB since they had extra marital relationships.

Responses from women

"Men are likely to get TB more as they smoke, consume illicit liquor and take ganja."

"Men have extra-marital contacts and chances of getting TB are more".

Another interesting response among some of the females was that women were vulnerable to get TB since they cook using firewood and therefore, were exposed to smoke. Among older male groups, some of them said that TB was associated with age and elderly people are likely to get the disease.

Care seeking and perceptions about TB services

In all the groups, the general opinion was that children and men get priority in receiving care and attention from the family during any illness. Many of the women were of the opinion that men received more care being breadwinners, had to get well soon and return to work. Some of the women said that due to domestic responsibilities, women did not express their health problems or seek care till they were unable to bear their symptoms and other home remedies failed. A few women expressed the view that men generally sought care from good private doctors and got costly medicines as compared to women.

Among both men and women, the initial providers they approached when they had any health problems, were private doctors. This was mentioned more than once in the male groups. However, for serious illnesses requiring hospitalization and prolonged treatment, governmental health facilities were preferred by both men and women. It was also found that among older men and women groups, preference for a government facility was expressed. The reason attributed was that they were financially dependant on their children and hence could not afford to spend for their treatment.

With regard to care giving, both men and women were of the view that women were more concerned and were better at taking care of their family members when anyone in the family was ill. This point was stressed repeatedly by the women. The women justified this saying that men were busy with work and had 'no time' to look after women when they fell sick. Most women accepted the fact that the men had no patience in looking after the sick people.

With regard to treatment, most of the men and women said that treatment is available for TB and it is curable. However, a few of the males, both in the young and older age groups, and few females in the older age group felt that TB was incurable.

A female from the older group said "*Some may die of TB. Only one out of 100 gets cured*".

Most of the participants said that they were aware that treatment for TB is available in public health facilities. However, many of the males said that TB treatment was available only in specialized government hospitals dealing with TB treatment and not at all public health facilities. The duration of treatment for TB perceived by the groups ranged between three to 36 months. Longer duration of treatment was mentioned by females and to quote a remark from a female "Treatment for TB has to be taken till death".

With regard to regularity for treatment, most of the females, both young and old, were of the view that women would be more regular in taking treatment as they had the responsibility of taking care of the family, especially children. Many of the women and some of the men were of the opinion that men would be irregular for treatment due to pressure of work and dependence on alcohol.

Social responses (Implications of TB on marriage, pregnancy and lactation)

Men were of the opinion that it will be easier for males who are infected with TB or treated for TB to get married than females. Some of the males said that it would be easy for males to hide the fact that they had TB and get married as compared to women who were not expected to hide their TB diagnosis. A few of the men also felt that it would be difficult for women to hide their history of TB as relatives and neighbours would gossip about it and chances of her marriage would get affected. Another opinion among the males was that women treated for TB will have to pay a higher dowry. A few of the women said that TB would result in death and so it was better to avoid marriage.

Men and women said that a person with TB could get married but only after completion of treatment. Some of the younger males were of the opinion that those who have been treated for TB could be married but should have regular medical check-ups after marriage, even if cured. Among women, there was a strong opinion that the history of TB should not be disclosed to the prospective grooms and in-laws.

A response from a female.

"For the men it is not a big thing to get married after the treatment, but for women it would be a problem. The neighbours and relatives of the infected women would talk ill of her"

Response from a male

"It will be a problem for women to get married since beauty is needed for a woman and not for a man. If a woman is infected by TB she will become like a skeleton and her beauty will be spoilt".

All the groups emphatically said that women infected with TB should not conceive. Many of the males were of the opinion that the child will also be infected. Most of the females said that the tablets taken for TB will affect the child and hence they should not get pregnant. A few of the women, however, felt that women can conceive after consulting their doctor. Most of men and women said that TB infected women should not breast feed as the illness will pass on to the children through lactation.

Responses from older females

"A woman's blood is converted into breast milk. So a woman with TB cannot breast feed".

"A woman infected with TB should not breast feed as she will be passing on the infection to the infant".

Few of the older females and older males felt that TB infected women could breast-feed after consulting their doctor.

DISCUSSION

Gender differences in community perceptions on TB seem to be critical in issues

related to marriage. The stigma of TB is more visible in women than in men when it comes to marriage. It was generally felt among both men and women that it was easier for men infected or treated with TB to get married as compared to women. These views are in line with a qualitative research report from Pakistan where most participants of FGDs expressed the view that TB can have an adverse effect on the chances to get married more often in females than in males[11]. Another study from Mumbai also brought out that married women were concerned and anxious about rejection by husbands, harassment by in-laws and unmarried women worried about chances of marriage[12]. There were also concerns expressed by men and women with regard to conception and breast-feeding by women with TB.

There seemed to be more awareness about TB as a respiratory disease in line with qualitative research reports from Kenya and Viet Nam which have reported TB as a disease affecting lungs, chest or air passage[13,14]. Moreover, TB is more associated with cough and other cardinal symptoms do not seem to be known, especially among women. The cause of TB was attributed more to smoking, alcohol, stamping of sputum and airborne transmission did not seem to be expressed.

Another interesting view expressed was that men were more vulnerable to get TB as compared to women. This vulnerability was because of their social contacts, exposure to dust, smoking and consumption of alcohol. This was similar to a study from Viet-nam which also brought out that men have wider social contacts as compared to women and was more likely to get TB than women[14].

Finally, it is important to note perceptions in the community with regard to accessing health care with men availing proper and prompt care both from providers and family. On the contrary, women do not heed to health care till their symptoms aggravate and bear it no longer. This is in keeping with qualitative data from the Foundation for Research in Community Health (FRCH), among women in Pune, India, which has shown that a very important reason, particularly among women, for seeking help was a worsening of their symptoms[15]. Quantitative data from the EMIC interviews, which was part of the same WHO/ TDR study from Chennai, has also shown that the delay from the onset of symptoms to seeking first help was more among women than men. (Not published)

The study emphasizes the need for gender specific advocacy and intervention on TB and health care in the community which is crucial to enhancing proper and prompt care seeking behaviour.

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The Editor-in-Chief and the members of the Editorial Board of *Indian Journal of Tuberculosis* wish you all a Very Happy and Prosperous New Year 2008.

Original Article

OUTCOME OF MULTI-DRUG RESISTANT TUBERCULOSIS CASES TREATED BY INDIVIDUALIZED REGIMENS AT A TERTIARY LEVEL CLINIC

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Summary

Aim: To determine the clinical, radiological and drug resistance profile as well as the factors associated with treatment outcome of Multi-Drug Resistant Tuberculosis (MDR-TB).

Material and Methods: All newly diagnosed patients with pulmonary MDR-TB from August 2002 to December 2004 enrolled at New Delhi Tuberculosis Centre, were included in the study. They were followed up clinically, radiologically and bacteriologically by sputum smear, culture and Drug Susceptibility Testing (DST) at regular intervals. According to their DST pattern and previous history of Anti-Tubercular Treatment (ATT), individualized treatment regimens were tailored for each patient.

Results: Out of total 27 bacteriologically proven cases of MDR-TB included in this study, 19 were males (mean age and weight 38.5 years and 52.6 kgs, respectively) and eight females (mean age and weight 34.3 years and 40.7 kgs, respectively). A majority (18) were residents of Delhi and the rest hailed from different parts of North India. All of them had a history of previous treatment ranging from six to 34 months. Cavity on chest X-rays was seen in 81%, while 44% showed extensive involvement. The patients received at least four "second line drugs" during their treatment with a mean of 6.2 anti-tubercular drugs during their intensive phase. Of the 27 patients, 13 were cured, 10 defaulted, one died, one is still on treatment and two were referred for surgery. Radiological improvement was observed in two third of cases and chest X-ray of two patients showed a complete resolution. Six predictors were identified for successful outcome of MDR-TB. They include weight gain at six months, culture conversion, radiological improvement during treatment, disease with *M. tuberculosis* strains exhibiting resistance to less than or up to three anti-tubercular drugs, use of less than or up to three second line drugs in treatment and no change of regimen during treatment.

Conclusion: Default from treatment was observed to be a major challenge in the treatment of MDR-TB due to long duration and expense of ATT. ***[Indian J Tuberc 2008; 55:15-21]***

Key words: MDR-TB, Treatment outcome.

INTRODUCTION

MDR-TB poses a significant challenge to the physician, both in terms of diagnosis and treatment. Diagnosis calls for quality assured mycobacterial culture and DST. Treatment of MDR-TB requires the use of expensive and toxic second-line anti-tubercular drugs given for a longer duration which often results in decreased compliance and success rates[1,2]. The treatment strategies can be individualized based on DST results, or based on standardized regimens depending on the drug resistance patterns in the given geographic area[3-9]. We report here treatment outcome by individualized treatment regimens.

MATERIAL AND METHODS

The study was conducted at New Delhi Tuberculosis (NDTB) Centre, a referral centre for tuberculosis. All patients with pulmonary MDR-TB attending the outpatient MDR-TB clinic from August 2002 – December 2004 were included. The entire expenses for the purchase of medicines during treatment were incurred by the patients.

These subjects were evaluated for clinical, radiological and bacteriological parameters; the

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outcome of treatment; adverse drug effects and the predictors of successful treatment.

Initially, all patients were subjected to sputum smear microscopy and culture on Lowenstein–Jensen medium, on two consecutive days. Drug susceptibility tests (using resistance ratio method) were done for 12 drugs. The drugs were used in the following concentrations: isoniazid (0.4µg/ml[x]), rifampicin (128µg/ml[x]), ethambutol (8µg/ml[x]), streptomycin (16µg/ml[x]), kanamycin (64µg/ml), ciprofloxacin (8µg/ml), ofloxacin (8µg/ml), ethionamide (320µg/ml), cycloserine (160µg/ml), para-aminosalicylic acid (4µg/ml) and thiacetazone (4µg/ml). *M. tuberculosis* $H37R_V$ was used as a standard control.

Chest radiographs were obtained for every patient and classified according to the National Tuberculosis Association of USA (1961): **Minimal** (I)- Non-cavitary lesions involving one or both lungs but the volume of involvement regardless of distribution less than or equal to one zone. **Moderately advanced** (II)- More advanced lesions than minimal but the total involvement not more than the volume of one lung. Cavities, if present, not to exceed a total diameter (of all cavities) of 4 cm. **Far advanced** (III)- Any lesion more advanced than moderate. Two chest specialists reviewed the radiographs independently; in cases of disagreement, a third chest specialist's opinion (umpire reading) was taken as final**.**

Individualized treatment regimens were used as per the needs of individual cases according to their previous history of ATT and their initial DST patterns. The Intensive Phase (IP) consisted of at least five main drugs: any Aminoglycoside, any Fluoroquinolone, any thioamide and any two/more of the following: Pyrazinamide and Ethambutol, PAS or Cycloserine. Any other first line ATT was included as per treatment history of individual patients. In addition, Isoniazid was prescribed in most cases. Continuation Phase (CP) consisted of at least three of the most active and best-tolerated drugs to which either the bacilli were sensitive (DST) or the patient was responding in the form of negative smears and/ or culture. These included any one of the Fluoroquinolones (Ciprofloxacin, Ofloxacin or levofloxacin), any one Thioamide and any one /two or more of the following: Pyrazinamide and Ethambutol, PAS or Cycloserine in this order of preference.

The intensive phase, with a duration of three to six months (extended to nine months if necessary) was given till at least three consecutive smears and last available culture reported negative. If the culture results were positive, intensive phase was extended till negative smears were obtained, up to a maximum of nine months. In rare cases, where the patient remained sputum positive by culture at nine months and when patient was tolerating injectable drugs, injectables were continued till sputum conversion. Some patients required regimen changes during their IP due to failure of response to the initial regimen. The drugs in continuation phase were given for at least 18 months after culture conversion. In case of intolerance to any drug during treatment, the offending drug was replaced by an appropriate substitute, thus meriting a deviation from the initially prescribed regimen (as per DST pattern).

Patients were called up for the first follow-up after two weeks of starting their MDR-TB treatment to assess the compliance, tablet count and to monitor tolerance to ATT (side effects). Progress was monitored by sputum smears and cultures after the intensive phase on a monthly basis until at least three consecutive cultures were negative and then every three months until treatment completed. DST was repeated at three months or six months if the culture remained positive. Chest radiology was done every three months till the end of treatment.

The patients were evaluated by a physician at each follow-up. Appropriate treatment for co-morbidities was instituted simultaneously.

Patients, who met the criteria recommended

[x]Equivalent to INH (0.2mg/l), Rifampicin (40mg/l), Streptomycin (4mg/l) and Ethambutol (2mg/l)

Reference: Canetti GS, Froman S, Grosset J, Houduroy P, Langerova M, Mahler HT, Meissner G, Mitchison DA, Sula L. Mycobacteria laboratory methods for testing drug sensitivity and resistance. *Bull WHO* 1963; **29**: 565-578.

by Iseman[10], i.e. specifically drug resistance with a high probability of failure, sufficiently localized disease and the availability of drugs with adequate efficacy to be used post-operatively, were referred for surgery, after receiving at least six to nine months of treatment.

During treatment, response was defined as bacteriological and/or radiological response[11]. Bacteriological response was in the form of sputum-smear conversion (conversion of an initial positive smear to negative) and sputum culture conversion (conversion from an initial positive sputum culture to negative). Radiological response was clearing of pulmonary lesion(s) or improvement of grading seen on chest X-ray during treatment. Outcomes were broadly classified as ***successful*** (negative smears and cultures throughout treatment for at least six months), ***unsuccessful*** (*default* was withdrawal from treatment due to any reason; *death* was because of any cause during treatment) and ***still on treatment*** (*probable failure*- persistence of positive smears or culture despite treatment for at least 18-24 months).

The data variables were entered into MS Excel worksheets. Mean was calculated to represent the nominal variables. The data of the defaulting patients was censored at the last follow-up visit. The relation between the outcome of treatment and variables that might influence the outcome was analyzed using the chi-square test. The p value of less than 0.05 was considered to indicate statistical significance. Pearson's correlation co-efficient was calculated for each parameter to test the relationship.

RESULTS

There were 19 male and eight female patients with a mean age of 38.5 (range 10-62) years and 34.3 (range 18-55) years respectively and a mean weight of 52.6 kilograms and 40.7 kilograms respectively. Sixty-six per cent patients were residents of Delhi and the rest from different parts of north India.

Out of twenty-seven patients, 24 had only pulmonary tuberculosis while three had extra-pulmonary involvement (pleural effusion) in addition. Ten patients suffered from co-morbidities, six had diabetes mellitus, two were infected with HIV, one had concurrent chronic obstructive airway disease and one coronary artery disease. All patients had received ATT before enrolling into the study. A past history of ATT with 4-14 drugs for a period of 6-34 months was elicited from the patients. Sixteen patients had taken more than 12 months of ATT and more than five drugs. At presentation, all had radiographic evidence of tuberculosis; 22 patients had cavities on chest X- rays while 12 showed extensive disease and 14 had moderate disease radiologically.

Thirty-seven per cent patients had *M. tuberculosis* strains resistant to more than three anti-tubercular drugs (Table 1); 15 patients were infected by strains resistant to streptomycin, while eight were resistant to ciprofloxacin; seven resistant to Ofloxacin and six to Ethambutol. The DST revealed least resistance with one strain each to Kanamycin, PAS, Cycloserine, Ethionamide and Clarithromycin.

Eighteen individualized treatment regimens

Table 1: Drug susceptibility pattern of MDR-TB patients

Resistance to	Male (n=19)	Female (n=8)	Total (n=27)
Two drugs (HR)	7	1	8
Three drugs			
HRS	4	3	7
HRE	1	0	1
HRT	1	0	1
Four drugs			
HRSE	1	1	2
HR Ciprofloxac in Ofloxacin	2	1	3
≥5 drugs	2	3	5

Table 2: Predictors of successful outcome of ATT in MDR-TB patients

Variable	Successful patients(n=13) Total patients =27	p value	Correlation
Sex			
Male	9		
Female	4	0.9	0.02
Residence			
Within Delhi	10		
Outside Delhi	3	0.5	0.14
Weight gain			
Present	11		
Absent	2	**0.0097**	**0.49**
Co-morbidity			
Present	2		
Absent	11	0.1	0.29
Past H/o ATT			
Number of drugs ≤5	3		
Number of drugs >5	10	0.96	0.01
Duration of past ATT			
≤12 months	6		
>12 months	7	0.8	0.04
DST pattern			
Resistance to ≤3drugs	11		
Resistance to >3drugs	2	**0.02**	**0.41**
SLD classes used			
≤3	12		
>3	1	**0.0007**	**0.65**
Side effects to ATT			
Present	6		
Absent	7	0.2	0.32
Sputum conversion (direct smear)			
Yes	12		
No*	1	0.08	0.34
Sputum conversion (culture)			
Yes	13		
No*	0	**0.0005**	**0.68**
Radiological extent of disease			
Far advanced (III)	9		
Minimal to moderate (I and II)	4	0.2	0.27
Radiological improvement			
Yes	13		
No*	0	**0.00004**	**0.82**
Regimen changes on treatment			
None	12		
Once or more	1	**0.0007**	**0.63**

* Two patients had initial direct smears negative

were used. The most common regimen, used in four patients, comprised kanamycin, ofloxacin, ethionamide, pyrazinamide, ioniazid and ethambutol. Aminoglycosides were used for a mean duration of 4.1 months (range 1-10.5). The patients received a mean of 6.2 anti-tubercular drugs in the IP and a mean of four SLD classes during their treatment. About nine patients required regimen changes during treatment due to lack of response to initially prescribed regimen.

One-third patients had side-effects to ATT which required withdrawal of the offending drug. The most commonly implicated drugs were aminoglycosides (seen in four patients), followed by ethionamide, fluoroquinolones and pyrazinamide (in two patients each) and isoniazid, thiacetazone and cycloserine in one patient each. Oto-vestibular symptoms noticed in four patients, were the most common side effects, followed by skin pigmentation in three patients and hepatotoxicity/gastrointestinal effects in two patients.

Out of the 27 patients, 13 were cured, 10 defaulted, one died, one is still on treatment with two referred for surgery. At outcome, 15% patients had a normal chest skiagram with radiological improvement noticed in 67% cases.

In the thirteen successful patients, the first response to treatment was in the form of smear conversion (at a mean of 2.3 months) followed by radiological response (at a mean of 2.8 months) and culture conversion (at a mean of 4.4 months). The successful patients received mean 23 months of treatment with mean 4.6 months of IP.

Predictors or variables which may affect the successful outcome of treatment in MDR-TB patients were studied for any correlation. Weight gain at the end of six months of treatment (p value = 0.0097, correlation = 0.49), conversion of culture from positive to negative (p value = 0.0005, correlation = 0.68) and radiological improvement during treatment (p value = 0.00004, correlation = 0.8) were found to be positive predictors of a successful treatment outcome in MDR TB. Also disease with *M.tuberculosis* strains exhibiting resistance to less than or upto three anti-tubercular drugs (p value = 0.02, correlation = 0.41), use of less than or upto three SLD classes in treatment (p value = 0.0007, correlation = 0.65), and continuation of same regimen during treatment (p value = 0.0007, correlation = 0.6) were other positive predictors for success. Some factors, which did not influence the outcome of treatment included sex, residence, extent of radiological disease, side-effects to ATT, duration of past ATT, number of drugs used in the past, any co-morbidity and sputum direct smear conversion (Table 2).

DISCUSSION

Treatment of MDR-TB often poses serious challenge to patients and majority of such patients are usually referred to tertiary care. These patients are already resistant to most of the first line drugs and require judicious and optimal combinations of second line drugs. In this study, over 70% patients were already resistant to three or more anti-tubercular drugs at presentation. These patients had been extensively pre-treated with anti-tubercular drugs resulting in acquired resistance. In our cohort, majority of the strains were resistant to a large number of drugs and this was reflected in the lower success rate (48%).

The demographic profile of MDR-TB patients in our study was similar to other series, with a majority of male patients in the economically productive age group (25-54 years) [3,5,12-15].

Weight gain at six months during treatment was associated with a successful outcome. Thus, recording the weight during therapy for calculating the weight gain should be an essential component of follow-up. Radiological response to treatment, seen in the form of improvement of radiological grading, was another good predictor of a successful outcome with a strong correlation. The successful patients achieved radiological improvement during the early months of treatment, usually within three months. The third positive predictor was found to be conversion of culture from positive to negative during treatment. By seven months, all the successful patients had achieved culture negativity. The

predictive value for success at three months was 100%; the predictive value for failure at three months was found to be 56%. If the culture remained positive by seven months of treatment, the predictive value for failure approached 100%. These results are similar to those reported earlier[5,15]. Therefore, sputum culture for AFB during MDR-TB treatment (as recommended by WHO) is an integral part of monitoring response to predict outcome of therapy.

Disease with *M.tuberculosis* strains exhibiting resistance to less than or up to three anti-tubercular drugs was a predictor for success of ATT since cure rates are inversely related to the number of drugs to which the isolates are resistant[3,12,13,16]. Another predictor for a successful outcome was continuation of the initially prescribed regimen throughout the treatment without any changes. Changes in the initially prescribed treatment regimen were usually required when there was lack of response to the regimen being used. Only 10% of the patients requiring a regimen change during treatment had a successful outcome. The number of SLD classes used during treatment was also a predictor for success. This variable was influenced by both the above mentioned predictors. Since the patients of MDR-TB with strains resistant to a lesser number of drugs and continuation of the initially prescribed regimen throughout the treatment without any changes, required minimal use of SLD classes in their regimens, utilization of less than or up to three SLD classes in treatment was directly associated with successful outcome.

Unlike some previous studies, patients of both sexes had an equal likelihood of success as observed earlier in certain populations[4,5,6,8,12,14,17]. Perhaps this reflects the differences in the cohorts. The past history of ATT intake, both in terms of number of drugs used and duration of ATT, did not have any association with outcome. A Turkish study also failed to find any association between duration of previous treatment and outcome[4]. As observed earlier[5,6], the radiological extent also did not affect the outcome, probably because majority of the patients had extensive disease radiologically at presentation. Sputum direct smear conversion was also unable to predict outcome similar to the Hong Kong study[5]. The other factors, which did not influence the outcome of treatment, were residence, side effects to ATT and any co-morbidity.

A successful outcome was seen in 48% patients in our study which is comparable to the results seen previously in some studies[7-9,14,17-20]. However, this figure is relatively lower in comparison to cure rates of about 60% observed in Denver, New York and Netherlands, to over 80% seen in South Korea, Turkey, Hong Kong and Peru[3-6,12,13,16]. As the number of patients involved in our study was small (although was comparable to New York study with 25 patients[13]), the efficacy of individualized regimens could not be analyzed. There are probably a number of factors which contributed in lowering the success rates. Certain characteristics of our cohort such as the extensive prior history of ATT in all the patients, resistance to a large number of drugs and considerable disease as seen radiologically in the majority of the patients, could have been contributory. Procurement of drugs was done by the patients in their individual capacities. Also all the treatment was unobserved on an out-patient basis. Both these issues were responsible for the high default rate and thus lowering the success rates.

The treatment of MDR-TB requires the judicious use of anti-tubercular drugs, regular clinical, radiological and bacteriological follow-up in specialized centres with access to standardized tuberculosis laboratory for accurate *in-vitro* drug susceptibility testing. Default from treatment, is a major challenge in the treatment of multi-drug resistant tuberculosis and strategies to reduce number of defaulters are crucial in the treatment of multi-drug resistant tuberculosis.

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Original Article

IMPACT OF IMPROVED TREATMENT SUCCESS ON THE PREVALENCE OF TB IN A RURAL COMMUNITY BASED ON ACTIVE SURVEILLANCE

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Summary

***Objective*:** To study the impact of improved treatment outcome of a cohort of patients treated under DOTS strategy on the prevalence of pulmonary tuberculosis (TB) in the community.

***Design*:** The data from TB register of one Tuberculosis Unit (TU) in Tiruvallur district of Tamilnadu, and two TB disease surveys conducted in the same area during 1999-2003 were analysed. The successful treatment outcome was compared to the prevalence of TB in the subsequent cohort.

***Results*:** The proportion of patients who completed treatment successfully was 75.3% in the first cohort period. This higher proportion of treatment success among patients treated under DOTS in the first cohort period (1999-2001) compared to the 51-55% reported during SCC, resulted in a lower prevalence of smear-positive cases, irrespective of culture results observed in the survey conducted during 2001-2003 compared to that in the survey conducted during 1999-2001 (252 vs. 323 per 100,000; annual decline of 9%). Similarly, a decline in culture-positive cases, irrespective of smear results, was also observed (443 vs. 605; annual decline 11%).

***Conclusion*:** The higher proportion of successful completion of treatment after DOTS implementation was associated with a substantial decline in the prevalence of TB. These findings showed that we are in the direction towards achieving the Millennium Development Goals (MDGs). **[*Indian J Tuberc 2008; 55:22-27*]**

Key words: TB, DOTS, Cohort, Treatment outcome, Prevalence

INTRODUCTION

Tuberculosis (TB) is highly prevalent in India in terms of morbidity and mortality[1]. It is estimated that India accounts for one-fifth of world's new TB cases. World Health Organization (WHO) declared tuberculosis a global public health emergency in 1993 because of the high mortality rate among adults, its association with HIV infection and emergence of Multi-Drug Resistance (MDR) TB. After the failure of the National Tuberculosis Programme (NTP) as reviewed in 1992, Government of India revised the tuberculosis control and launched the Directly Observed Treatment Short course (DOTS) under the Revised National Tuberculosis Control Programme (RNTCP) with the aim of achieving 85% cure among new patients diagnosed to have pulmonary tuberculosis and detect at least 70% of the cases in the community[2].

The key components of DOTS strategy are political commitment, sputum diagnosis by smear microscopy, short course chemotherapy under direct supervision, uninterrupted supply of drugs, monitoring, recording and evaluation of the programme. This is an effective and successive programme for the control of the disease. Tuberculosis Research Centre (TRC) in collaboration with Government of Tamil Nadu established a centre in one TU of Tiruvallur district, Tamil Nadu for DOTS implementation, tuberculosis control, training and research.

Government of Tamil Nadu implemented the DOTS strategy in the year 1999 in Tiruvallur district. There are 17 health facilities (HFs) in the study area. Under the DOTS programme, patients are detected by symptom screening at this HFs through the examinations of three sputum smears for acid-fast bacilli. All patients diagnosed based on three sputum

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examinations are put on anti-TB treatment. In this strategy, smear microscopy is the most efficient means of case detection among those persisting with symptoms suggestive of pulmonary tuberculosis (cough of three weeks or more with or without other clinical symptoms). All patients diagnosed with tuberculosis are given directly observed treatment in accordance with RNTCP policies[2]. All the smears are stained and examined by Ziehl – Neelson microscopy for detection of tuberculosis. If the patient is positive on smear microscopy on at least two specimens and not treated previously for TB for more than one month, he is termed as new sputum smear-positive case and put on Category I regimen $2(HRZE)_3$ /$4(HR)_3$ (H-isoniazid; R-rifampicin; Z=pyrazinamide; E=ethambutol; S-streptomycin). Numbers before the letters indicates the duration in months and that in subscript indicates the number of times the drug given in each week). If the patient is sputum smear-positive and treated for more than a month, he is treated under Category II regimen $2(HRZES)_3$ /$1(HRZE)_3$ / $5(HRE)_3$. Such patients will be either a relapse case after declaring cure when treated first or failure case or default case. Other sputum smear-negative cases not seriously ill, extra pulmonary cases are put on Category III regimen $2(HRZ)_3$ /$4(HRE)_3$. In case, the smear is positive only on one specimen out of three specimens examined, the patient is prescribed for one week antibiotic treatment and reviewed after a week with a chest X-ray. If the symptom is still persisting, the patient is put on Category III regimen. Intensive phase treatment of patients in categories I and II is extended for one month if the smear is positive at the end of the intensive phase. Every dose of treatment is to be directly observed in the initial intensive phase of treatment and at least the first of the three doses is to be directly observed during the continuation phase.

Before the implementation of DOTS, the Government of India introduced Short Chemotherapy (SCC) on a pilot basis in the District Tuberculosis Programme in 18 districts spread over India. A concurrent cohort analysis of the data collected from these districts during 1985-1991 showed that the overall treatment completion for SCC was 51-55% with a case finding of 41%[3]. Two community surveys were conducted in Tiruvallur district, Tamil Nadu during 1999-2001 and 2001-2003 to estimate the prevalence of pulmonary TB. Patients who were diagnosed based on smear and/or culture were referred and treated under DOTS as per RNTCP guidelines. From the first survey, the prevalence of pulmonary TB was estimated to be 323 per 100, 000 for smear-positive cases and 605 per 100, 000 for culture-positive cases[4]. These estimates served as the baseline information at the end of the SCC and start of the DOTS implementation.

This paper describes the treatment outcome of a cohort of patients registered under DOTS and compares with the prevalence of TB as estimated from the disease surveys conducted after the implementation of the DOTS strategy.

MATERIAL AND METHODS

The study area is a rural population of Tiruvallur district in Tamilnadu where TRC monitored the DOTS programme for a period of about six years since its implementation in 1999. Patients diagnosed at any one of the HFs were treated for TB as per the RNTCP guidelines[2]. TRC has undertaken a series of disease surveys at every two and-a-half years to measure the epidemiological impact of DOTS implemented from 1999 in Tiruvallur district. These disease surveys were undertaken in a random sample of 82,000 adults aged 15 years or more. The sample size estimated for community disease survey was based on an annual incidence of culture-positive TB of 260 per 100,000 population, a precision of 20% at 95% confidence level, with the coverage of examined population 9% and a design effect of two. The methodology of survey is explained elsewhere[4]. In each survey, all persons in the selected villages/units were registered by door-to-door census and all adults aged $\geq$15 years were questioned about chest symptoms and underwent chest radiograph (70 mm photo-fluorogram posteroanterior view) at a nearby centre. For those with an abnormal radiograph suggestive of TB and/or chest symptoms, attempts were made to collect two sputum specimens. Those who were absent for examinations were revisited

the same day or on subsequent days until at least 90% had the required investigations. The sputum specimens were examined by fluorescence microscopy and cultured on Lowenstein-Jensen medium. Those yielding growth were subjected to identification tests for *Mycobacterium tuberculosis* and drug susceptibility tests. A case of tuberculosis was defined as a person with a positive smear (>3 acid-fast bacilli) irrespective of culture results.

The details of all patients started on treatment in a TU are entered in a register called Tuberculosis Register (TB Register) and these patients are monitored in accordance with the RNTCP guidelines. This register is maintained by the Senior Treatment Supervisor (STS). The TB Register is the backbone of the DOTS strategy. Every patient put on treatment is registered under a specific TB number. A TB patient is known by this number and the year in which he/she was registered. The particulars like name, age, sex, category, type, smear result at admission, 2^{nd} /3^{rd} month, 4^{th} /5^{th} month and at the end of treatment are the details entered in the TB Register. The treatment outcome of the patient is an important parameter of the programme available in the TB Register. The international definitions were followed to classify TB patients according to outcome as follows[5]:

1. **Cured**: Initially smear-positive patient who has completed treatment and had negative sputum smears, on at least two occasions, one of which was at completion of treatment.
2. **Treatment Completed**: Sputum smear-positive case who has completed treatment, with negative smears at the end of the initial phase but none at the end of treatment (or) Sputum smear-negative TB patient who has received a full course of treatment and has not become smear-positive during or at the end of treatment (or) extra-pulmonary TB patient who has received a full course of treatment and has not become smear-positive during or at the end of treatment.
3. **Default**: A patient who, at any time after registration, has not taken anti-TB drugs for 2 months or more consecutively
4. **Expired/Died**: Patient who died during treatment, regardless of cause.
5. **Failure**: Smear-positive case who is smear-positive at five months or more after starting treatment. Also, a patient who was initially smear-negative but who became smear-positive during treatment.
6. **Transferred out**: A patient who has been transferred to another TU/District and his/her treatment results are not known.

All new TB patients identified in the two prevalence surveys and treated under DOTS along with other new smear-positive cases detected from other areas not included in the sample and registered in the TU from May 1999 to June 2001 formed the study population.. The data collected from the study was computerized, edited and corrected for any discrepancies. The proportion of patients who successfully completed the treatment was obtained. The potential risk factors for a higher likelihood of default from treatment were identified. The prevalence of the smear-positive and culture-positive cases was estimated from the second survey and compared to that in the first survey. Chi-square test of significance was used to test the difference in proportions. A p value of ≤ 0.05 was considered as statistically significant.

RESULTS

A total of 805 new smear- positive TB patients were registered during the above period; successful treatment completion rate was 75.3% and 15.9% had defaulted. The prevalence of TB (smear-positive cases irrespective of culture results and culture-positive cases irrespective of smear results) estimated from the first survey and second survey is in Table 1[4]. The prevalence of smear-positive cases, irrespective of culture results, was 252 in the second survey as compared to 323 per 100,000 in the first survey. The corresponding figures for culture-positive cases were 443 and 605 per 100,000 respectively. The annual decline in the prevalence of smear-positive cases from the first survey and second survey was estimated to be 9%. The corresponding figure for culture- positive cases

Table 1: Prevalence of pulmonary tuberculosis (per 100000) in two disease surveys conducted during 1999-2001 and 2001-2003 in a TU in Tiruvallur district, Tamil Nadu.

Survey (round)	Population	Smear positive*	Culture positive**
First survey (1999-2001)	83390	323	605
Second survey (2001-2003)	85472	252	443
Annual decline (%)	-	9	11

* Irrespective of culture ** irrespective of smear

$$\text{Annual decline (\%)} = \frac{(P_1 - P_2) \times 100}{P_1 \times N}$$

P_1 and P_2 are the prevalence at two time points at an interval of 'N' years.

Table 2: Risk factors for default of patients registered during 1999-2001under a DOTS programme in Tiruvallur district, Tamil Nadu

Factors		Number*	Default (%)	P value
Age	<45	358	44 (12.3)	P<0.001
	≥45	376	84 (22.3)	
Sex	Male	581	114 (19.6)	P<0.01
	Female	153	14 (9.2)	
Education	Illiterate	316	56 (17.7)	P=0.1
	Literate	348	47 (13.5)	
Occupation	Un-employed	173	32 (18.5)	P=0.2
	Employed	493	72 (14.6)	
Patient's Delay	≤ 4 weeks	508	78 (15.4)	P=0.7
	> 4 weeks	136	19 (14.0)	
DOTS convenient	No	97	19 (19.6)	P=0.4
	Yes	447	72 (16.1)	
Smoking	No	350	32 (9.1)	P<0.001
	Yes	314	71 (22.6)	
Alcoholism	No	438	40 (9.1)	P<0.001
	Yes	227	63 (27.8)	
DOTS provider	Private	272	44 (16.2)	P=0.5
	Government	394	57 (14.5)	
DOTS centre	Private	333	60 (18.0)	P<0.05
	Government	333	41 (12.3)	
Supervision-during IP	No	203	27 (13.3)	P=0.4
	Yes	461	74 (16.0)	

*Those successfully completed treatment including default

Note: For variables except for sex and age, the number of patients is less than 734 due to non-availability of all patients at the time of interview.

was 11%. After the implementation of DOTS during this cohort period, case detection was about 80% with a cure rate of 75%. This has resulted in a lower prevalence of smear-positive as well as culture-positive cases in the subsequent survey (323 to 252 and 605 to 443 per 100,000 respectively).

Risk factors for default: The distribution of patients according to those successfully completed the treatment and defaulted is given in the Table 2. A uni-variate analysis showed that a higher default was significantly associated with patient's sex (male), aged < 45 years, smoking, alcoholism and the DOTS centre (private) where patients took treatment. A multivariate analysis showed that age and alcoholism were the independent risk factors associated with a higher likelihood of default.

DISCUSSION

The Tiruvallur area provides a unique opportunity to evaluate the TB situation before and after implementation of DOTS. The epidemiological data generated during the 15 year follow-up of BCG vaccine Trial in this area showed that there was no decline in the prevalence of smear-positive cases over the period 1968-1986 (pre-SCC period) [6]. Using available information indicated in NTP, the efficiencies were about 30% for case finding, 35% for case holding, 80% for chemotherapy and 50% for relative efficiency (ie. the proportion of patients with successful outcome even without completing their prescribed course of treatment relative to the proportion with a favourable response at the end of the prescribed course). From these estimates, the success rate was estimated to be only 16%[7]. The three tuberculin surveys conducted among children aged 1- 9 years in 1969, 1979 and 1984 in this area showed that there was no change in the prevalence of infection namely, 9.0%, 10.2% and 9.1% and the computed ARTI of 1.7%, 1.9% and 1.7% respectively[8].

A repeat survey conducted during 2001-2003 after the baseline survey (1999-2001) in the same population showed that the annual decline was of 9% and 11% for smear-positive and culture-positive cases respectively. The ARTI estimates from the three tuberculin surveys conducted in the same area among children aged <10 years during 1999-2005 were 1.6%, 1.4% and 1.2% respectively[9]. There was a significant decline in the trend of TB infection (annual decline of 6%). An increase in the success rate due to the implementation of the effective DOTS strategy was in association with a substantial reduction in the prevalence of TB and infection as demonstrated from the disease and tuberculin surveys carried out in the area.

The successful treatment outcome obtained in our study was less than the national expected average of 85%. The cure rate was 91% among the category I patients treated under DOTS in one of the chest diseases clinics run by the Municipal Corporation of Delhi[10]. The study concluded that the cure rate could have been more if tracing of defaulter had been intensified. Our study had a higher default rate and we identified old age and alcoholism as the independent risk factors necessitating targeted health education programme through Information, Education and Communication (IEC) for this group of patients. An earlier report from the same area also recommended retrieval action of defaulters in order to increase the successful treatment outcome[11].

We have correlated the activities of the HFs in this area and the programme indicators like conversion and cure[12]. Both were found to be well correlated indicating that success of the DOTS depends on the health function. This emphasizes the need for periodic evaluation of the functioning of each HF for better management of treatment.

CONCLUSION

The study showed that an increase in the successful treatment outcome of the patients treated under DOTS was associated with substantial decline in the prevalence of TB in the community. This would be a milestone towards achieving the MDGs of reverting and reducing the prevalence of TB by 50% in 2015 related to 1990 levels.

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Original Article

MYCOBACTERIAL INFECTIONS IN HUMAN IMMUNO-DEFICIENCY VIRUS SEROPOSITIVE PATIENTS: ROLE OF NON-TUBERCULOUS MYCOBACTERIA

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Summary

***Background*:** There is high prevalence of tuberculosis in patients with HIV infection; hence the role of non-tuberculous mycobacteria (NTM) in HIV patients has always been undermined. NTM may be responsible for clinical disease in a substantial number of immuno-compromised HIV sero-positive individuals even in a country endemic for *Mycobacterium tuberculosis* (*M. tuberculosis*). The study was designed to look for the contribution of NTM to morbidity in HIV seropositive patients.

***Material and Methods*:** In a prospective study of ninety-four HIV seropositive individuals presenting with pulmonary or extra-pulmonary symptoms suggestive of mycobacterial infection, appropriate samples were collected and processed. Detailed clinical history was utilized to differentiate colonization or contamination by NTM from true lung disease.

***Results*:** Fourteen samples grew mycobacterial species, 8(57.2%) being NTM. The distribution of NTM was- 3 *M. avium* complex, 2 *M. fortuitum*, 2 *M. vaccae*, 1 *M. phlei*. 6 isolates were *M. tuberculosis*.

***Conclusion*:** NTM may be responsible for a significant proportion of mycobacterial infections in HIV seropositive individuals. Despite the high endemicity of tuberculosis in developing countries like India, the presence of NTM should be ruled out; especially in immuno-compromised HIV seropositive individuals before instituting anti-tubercular therapy empirically. In addition, non-response of NTM to ATT may be wrongly attributed to multi-drug resistant tuberculosis.

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***Key words*:** Non-tuberculous mycobacteria, Immuno-compromised, HIV sero-positive individuals

INTRODUCTION

The pandemic of HIV infection has brought considerable change in the epidemiology of mycobacterial infections the world over. While it has led to the resurgence of *M. tuberculosis* in USA and Europe, it has also been associated with an increase in infections due to non-tuberculous mycobacteria (NTM)[1].

The prolonged and profound immuno-suppression of cell mediated immunity that characterizes AIDS provides opportunity for relatively avirulent NTM to cause disease. *Mycobacterium avium* complex (MAC) is now the commonest cause of systemic bacterial infections in AIDS patients in the United States and other developed countries[1]. In developing countries, especially India, where tuberculosis is endemic, *M. tuberculosis* has been reported to be the main secondary mycobacterial infection in AIDS patients. Little information exists about NTM disease incidence, mainly because of the resource poor health care system and the absence of mycobacterial culture[2]. Studies to assess the clinical significance and disease spectrum of NTM in HIV seropositive individuals are far and few.

In this study, HIV seropositive patients were investigated for mycobacterial infections. All mycobacterial isolates were identified and their drug susceptibilities determined.

MATERIAL AND METHODS

The study was conducted over a period of 18 months. Ninety-four HIV seropositive patients (positive for HIV 1and / or 2 by 3 ELISA kits as per NACO guidelines), who presented with suggestive

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clinical and radiological evidence of possible pulmonary or extra-pulmonary mycobacterial infection were included in the study after taking their informed consent[1]. Appropriate clinical samples were collected depending upon signs and symptoms, hence the likely system involved. Early morning well coughed out sputum specimens, broncho alveolar lavage, bronchial wash and endotracheal aspirate specimens were received from patients with clinical and radiological findings suggestive of pulmonary tuberculosis. Entire early morning urine specimens were received from patients suspected of urinary tuberculosis. Sterile body fluids such as cerebrospinal fluid (CSF), blood, pleural fluid and others were collected from patients suspected of disseminated mycobacterial infections. Biopsy specimens were obtained from patients with lymphadenitis. One hundred and five specimens comprising 80 expectorated sputum specimens, seven BAL specimens, 11 cerebrospinal fluid (CSF) specimens , three blood specimens, two each of urine and pleural fluid, one pericardial fluid specimen and one gastric biopsy specimen were collected . All specimens were collected with aseptic precautions in sterile leak proof containers and transported to the laboratory.

The specimens from 'unsterile' sites, such as sputum, urine and gastric juice were decontaminated by the Petroff's method[3]. Sterile fluid samples such as CSF were concentrated by centrifugation. The blood samples were processed by lysis centrifugation method using 0.05% saponin solution[4].

About 250µl of sediment was inoculated onto a pair of Lowenstein Jensen slants (LJ) containing glycerol and pyruvate. The inoculated media were incubated at 37°C and observed periodically for growth. In addition, 500µl of the sediment was also inoculated into BACTEC 12 B medium (Becton- Dickinson diagnostic instrument systems, Maryland, U.S.A.).

All mycobacterial isolates were identified to species level according to growth rate , growth at temperatures of 20, 37 and 42 °C , colony morphology , pigmentation , photoreactivity and a battery of biochemical tests[3] (niacin production, nitrate reduction , semiquantitative catalase, Tween 80 hydrolysis, tellurite reduction , arylsulfatase and urease production, NaCl tolerance , growth on MacConkey agar). Drug susceptibility profiles of all mycobacterial isolates were determined. For the slow growers, susceptibility to isoniazid (INH), rifampicin, ethambutol and ciprofloxacin was determined by proportion method[3]. The standard reference $H_{37}RV$ strain was included in each batch. For rapid growers (*M. fortuitum, M. vaccae, and M. chelonae)*, MICs were determined by microbroth dilution method against amikacin, erythromycin, azithromycin, ciprofloxacin and doxycycline[5].

RESULTS

Maximum patients (82%) were in third and fourth decades of their life with male preponderance (91%). Heterosexual contact (74%) especially with commercial sex workers was the common source of infection followed by blood and its product

Table 1: Characteristics of 14 patients with *M.tuberculosis* and NTM isolates

Clinical or radiological features	*M. tb* (n=6)	NTM (n=8)
Prolonged fever(> 1 month duration)	6	8
Cough	5	8
Weight loss	6	8
Haemoptysis	None	None
Radiographic cavitating disease	None	None
Alveolar infiltrates	4	6
Adenopathy	1	None
Effusions	1	None
Normal chest radiology*	1	2
Microscopy positive for AFB	5	6
CD4 Counts (< 200/mm^3)	5**	7

* One patient with *M. tuberculosis* CD4 counts; 142/mm^3. One patient with MAC isolate in the NTM group CDS counts: 113/mm^3

**In one patient with *M. tuberculosis*, CD4 counts could not be done.

transfusion (16%) and intravenous drug usage (9%) for HIV seropositivity.

Prolonged fever (>1 month duration) and weight loss (≥ 10 kg body weight) were the most common presenting symptoms present in all patients with mycobacterial infections followed by cough with expectoration (Table I). None of the patients had haemoptysis.

25/94 (26.8%) of HIV seropositive patients were found to have mycobacterial infections. There were a total of 17 isolates, of which 14 were identified to species level (three isolates were lost due to media spoilage). Eight samples were smear positive but culture negative. Of these eight patients, four were on ATT and one on isoniazid prophylaxis. Six isolates (42.8%) were found to be *M. tuberculosis and* eight isolates (57.2%) were identified as NTM. The species distribution of NTM was: *M. avium* complex (MAC) (*n*= 3), *M. fortuitum (n*= ***2***), and *M. vaccae (n*= 2), *M. phlei* (n=1). Five of the 6 *M. tuberculosis* isolates were from sputum and one was isolated from pleural fluid while all NTM species were isolated from sputum. 6/8 NTM isolates (Table: 2) were detected on smear as well as isolated in culture.

On chest radiography, cavitating disease pattern was not seen in any group (*M. tuberculosis* and NTM), however, alveolar infiltrates were found in both groups (Table I).

Table 2: Clinico-Microbiological profile of eight patients with NTM isolates.

S No.	Age/ Sex	Isolate species	No. of sputum samples submitted	No. of occasions direct microscopy positive	No. of occasions culture positive	CD 4 counts/ µl	Radiological features	Other features
1.	30/M	MAC	3	2	2	113	NAD	OC +ve
2.	35/M	M. *phlei*	3	Nil	1	455	NAD	
3.	18/M	MAC	3	2	2	51	Bilateral perihilar parenchymal opacities	OC +ve, Generalized Lymphadenopathy, Hepatosplenomegaly
4.	23/F	MAC	2	1	2	147	Patchy parenchymal opacities	Suspected case of MDR TB
5.	40/M	M. *vaccae*	3	Nil	1	57	Bilateral lower zone interstitial infiltrates	
6.	37/M	M. *fortuitum*	2	2	2	151	Bilateral diffuse parenchymal opacities	Taken ATT twice in the past
7.	45/M	M. *vaccae*	2	2	2	81	Patchy parenchymal opacities	Suspected case of MDR TB
8.	28/M	M. *fortuitum*	3	2	2	110	Bilateral Lower and middle zone opacities	OC +ve, Generalized Lymphadenopathy

OC: Oral candidiasis, ATT: Antitubercular therapy

Three of five *M. tuberculosis* isolates were sensitive to all four drugs tested (INH, rifampicin, ethambutol and ciprofloxacin). Resistance was seen in two isolates. Of these two isolates, one was resistant to INH and rifampicin (Multidrug resistant) while the other was resistant to ethambutol and ciprofloxacin.

All the three MAC strains were resistant to INH. Two were also resistant to rifampicin and ethambutol as well. The third strain was resistant to ciprofloxacin.

All the five rapid growers were sensitive to amikacin only and variably resistant to other drugs such as doxycycline, erythromycin and azithromycin.

DISCUSSION

Worldwide, there is an increasing awareness of the role of NTM as pathogens causing pulmonary disease or disseminated disease. Among NTM, MAC has been reported most commonly, followed by rapid growers and *M. kansasii* [1].

The exact disease burden of NTM infections still remains unclear in India. These infections are under diagnosed in many laboratories due to lack of proper culture facilities. Previous studies from India have documented presence of NTM in different clinical specimens at a varying frequency. Chakrabarthi *et al* from Chandigarh isolated NTM in 7.4% of clinical specimens and *M. fortuitum* was the commonest isolate[6]. Paramasivam *et al* from Chennai, South India reported 8.6% of NTM from sputum specimens of patients in BCG trial area[7]. *M. avium / intracellulare* was the species most frequently isolated in their study. Das *et al* reported isolation of 8.3% NTM from various clinical specimens from Delhi and Kasauli[8]. In a recent study from Vellore, 3.9% of all mycobacterial isolates were identified to be NTM[9]. Pus, biopsy specimens and sputum specimens yielded most of the NTM, of which *M. chelonae* (46%) and *M. fortuitum* (41%) accounted for the majority. However, in most of these reports, clinical significance of these bacteria couldn't be determined as these bacteria were isolated from single specimens. Besides, the HIV seropositivity status of the patients with NTM isolates in these studies was not known. Recently, Narang et al utilized paraffin slide culture technique to isolate NTM from 80 stools and 42 sputum samples from HIV seropositive tuberculosis patients[10]. MAC was isolated from stool in four cases and from sputum in two cases while *M. fortuitum* was isolated from stool in two cases. In another study from the same institute, of 67 blood samples from HIV patients with suspected pulmonary or extra pulmonary tuberculosis, MAC and *M. simiae* were isolated in three patients each, while NTM were isolated from none of HIV seronegative patients[11].

In the present study, HIV seropositive individuals were investigated for mycobacterial infections. All mycobacterial isolates were speciated and their antibiotic susceptibilities determined. Unlike most previous studies, clinical significance of the NTM isolates was ascertained by repeated isolation of these bacteria from patients. Besides, detailed clinical and radiological characteristics of the patients as well as their immunological parameters (CD4 counts) were also taken into account along with the microbiological parameters. Our study shows that NTMs are also important pathogens in immuno-suppressed HIV sero-positive patients, despite high endemicity of tuberculosis in India.

The isolation of NTM from a pulmonary source presents a diagnostic challenge as these patients may be infected with NTM without evidence of pulmonary disease. Such an infection may be transient but it may also reflect disseminated NTM disease or subclinical NTM pulmonary disease. In addition, some NTM species that are generally considered non-pathogenic have been associated with pulmonary disease in the HIV infected host. The American Thoracic Society (ATS) has published diagnostic criteria recommending repeated culture of specimens from non-sterile sites such as sputum before committing a patient to long term therapy with antibiotics. These guidelines recommend: (i) three positive sputum cultures with negative AFB smear results, (ii) at least two positive sputum cultures and one positive AFB smear in the presence of compatible clinical and radiological features[12].

Following the above ATS guidelines, isolation of *M. vaccae* in case number five (direct microscopy negative for acid fast bacteria on all three occasions and culture positive only on one occasion) and *M. phlei*, case number two (direct microscopy negative for acid fast bacteria and culture positive only on one occasion with a normal X-ray and CD4 counts of 455/mm^3 are not suggestive of significant NTM pulmonary disease and suggest mere colonization rather than a pathogenic role .

Clinical and radiological parameters are not accurate in differentiating *M. tuberculosis* from NTM infection. Symptoms of NTM pulmonary infection are variable and non-specific such as chronic cough, sputum production and fatigue. Malaise, dyspnoea, fever, hemoptysis, and weight loss can also occur with advanced NTM disease[1]. These symptoms are not unlike those of tuberculosis. In this study , patients of both groups (NTM/ *M.tuberculosis*) couldn't be distinguished on the basis of clinical symptomatology (Table 1). Similarly, radiological parameters weren't useful either(Table 1). NTM usually tend to cause thin walled cavities with less surrounding parenchymal infiltrates. However, in compromised AIDS patients, radiographic findings vary and may include diffuse or focal infiltrates, cavitary lesions, nodular and hilar lymphadenopathy[1]. Commonly, chest X-ray may be normal despite the presence of disseminated disease[1,13] . One patient with MAC infection and CD4 count 115/mm^3 (case no. 1) had apparently a normal X-ray. Chest X-rays are known to show a nodular, diffuse or patchy infiltrate with or without hilar or mediastinal adenopathy or commonly, may be normal (despite the presence of disseminated disease)[1,13]. In advanced HIV infection, TB often also has an atypical presentation. Chest radiographs rather than having apical cavitary disease may reveal adenopathy, apical infiltrates and miliary disease and occasionally, sputum cultures are positive for *M. tuberculosis* despite the presence of a normal chest X-ray (This pattern was seen in one patient in this study, Table: I). Majority of patients with mycobacterial isolates (both *M. tuberculosis* and NTM) in this study had advanced HIV infection (CD4 counts < 200/mm^3) Tables: 1 and 2. In a recent study from Delhi, infiltrative lesions on Chest X- ray were seen in 61.9% of tuberculosis patients with HIV[14].

Microscopic examination of acid fast bacilli is not reliable in discriminating *M. tuberculosis* from NTM[12]. Hence presumptive diagnosis of tuberculosis based on above parameters (clinical, radiological, and microscopic) in the absence of culture and speciation can be misleading resulting in institution of unnecessary and inappropriate treatment with ATT. Pattern of resistance and outcome of treatment of NTM infection are significantly different from those of tuberculosis [2.] In this study, three patients (one MAC and one *M. fortuitum*) were actually being treated for resistant tuberculosis. In a study from eastern India, NTM could be isolated in 17.4% of cultures from consecutive samples of patients with presumed fibrocavitary pulmonary tuberculosis. In this study, 14/15 patients with NTM isolates were already being treated for tuberculosis[15]. It is well documented that patients with disseminated MAC and *M. genavense* , who are treated , survive longer than those who are not treated. So, early treatment of pulmonary NTM is important to prevent dissemination and also improve survival [16].

To summarize, the present study shows that even in developing countries, with endemic tuberculosis, non-tuberculous mycobacterial infection may not be as uncommon as earlier thought to be. A high index of suspicion of NTM pulmonary disease, particularly in immuno-compromised AIDS patients corroborated with clinical, radiological and laboratory guided mycobacterial identification from repeated sampling, will help in institution of appropriate treatment and management.

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INAUGURATION OF 58TH TB SEAL CAMPAIGN – ANDHRA PRADESH

Under the auspices of the Tuberculosis Association of Andhra Pradesh, the 58th TB Seal Campaign was inaugurated on 2nd October, 2007 by His Excellency, the Governor of Andhra Pradesh Shri N.D. Tiwari in Raj Bhavan, Hyderabad. Dr. Ramesh Chandra, Director of Health, presided. Dr. T.V. Venkateswarulu, Honorary General Secretary of the Association, presented a report on the activities of the State Association. The Governor distributed the Rolling Shields, Institutional Awards, Special Awards and Mementoes. About 200 persons, including Medical Officers, Para-medical personnel and invitees, attended the function.

Continuing Medical Education

SPECIAL CONSIDERATIONS IN THE DESIGN, CONDUCT AND ANALYSIS OF PROPHYLAXIS TRIALS*

S. Radhakrishna**

A stitch in time saves nine
An ounce of prevention is worth a pound of cure

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***Summary*:** Methodological considerations in clinical trials apply to prophylaxis studies also. In addition, there are certain aspects that need special attention. These are the identification of a valid group of controls, the choice of the unit of randomization and its impact on subsequent analyses, the specificity and the sensitivity of case diagnosis and their impact on estimated efficacy and its reliability. The ethical aspects of the trial also need special consideration, bearing in mind that the intervention is on healthy individuals, and not patients with disease. These are discussed in the context of community prophylaxis trials of tuberculosis and leprosy undertaken in south India. **[*Indian J Tuberc 2008; 55:34-41*]**

Key words: Prophylaxis Trials, Methodological aspects

INTRODUCTION

There are innumerable branches of preventive medicine, in which there is scope for studies of prophylaxis. Broadly speaking, such studies are of two types. Thus, one can have trials of vaccines against tuberculosis, leprosy, AIDS, diphtheria, tetanus, poliomyelitis, influenza or measles. Alternatively, in diseases like tuberculosis, leprosy and chronic bronchitis, chemoprophylaxis – that is, prophylaxis with drugs – can be investigated. In general, well-documented considerations that apply to clinical trials [1-3,] are relevant to prophylaxis studies also. However, there are certain aspects that attain special significance in the field of prophylaxis and these are discussed here.

Need for and Choice of Controls

The Achilles heel of many a prophylaxis study is the absence of or improper choice of controls. A common occurrence is for public health workers to reach faulty conclusions by comparing the disease incidence in those that received prophylaxis in the study population with (a) the incidence in the general population, or (b) the risk in a similar population drawn from preceding years, without considering whether or not the two populations are similar with respect to disease-causing factors. Equally unsatisfactory is the practice of comparing the frequency of disease in those that volunteered for prophylaxis (e.g. vaccination) with those that did not. The volunteers may be older (or younger), comprise more males than females (or *vice versa*) or belong to a higher (or lower) socio-economic class. If adequate records are available, one can check whether such differences existed between the prophylaxis group and the others. But more subtle and undetected differences could still have existed. Thus, the volunteers may be persons who are more intelligent, better aware of the presence of epidemic diseases in the community, and in general more conscious of good health practices. These factors would lead to lower incidence in volunteers. It is also possible that the act of volunteering constitutes a greater risk from self-selection; for example, those that are prone to frequent attacks of cold may have volunteered

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for the prophylaxis while those not usually affected may have kept away. This could lead to a higher incidence in volunteers. To avoid such problems due to possible confounders, the ideal control should be made a random subset of those that agree to participate in the trial. Records should, however, be kept of those who did not volunteer, and their characteristics (sex, age etc.) for making a realistic recommendation on the prophylaxis policy studied.

Unit for random allocation

Prophylaxis trials often involve very large numbers of subjects and many investigators in several places, and so the method adopted for random allocation needs to be simple. With this in view, and also for operational convenience, the unit for random allocation is some times made relatively large. Thus, it could be the household or the family, the ward in a hospital, a city block or a village or a town. Simplicity apart, there could be other considerations that lead to the choice of larger sampling units. For instance, in studies of chemoprophylaxis, it would be unwise to allocate drug or placebo to individuals within a family or a household, since there could be an accidental mix-up or casual exchange of the medicament supplies of different individuals. If the family/household is made the sampling unit and all members within it given the same medicament, such confusion can be avoided.

Conversely, a very large sampling unit – for instance, a whole town – is not without its pit falls, especially if the total number of sampling units is small. For instance, if the investigator was proposing to evaluate a prophylactic measure in 10 towns, random allocation may not necessarily ensure that the 5 test towns and the 5 'control' towns are similar in all respects. A precaution would be to match the towns in pairs on important prognostic factors or baseline prevalence, and allocate one member of each pair to the test group and the other to the control group. This would constitute a Randomized Block design.[4]

Diagnosis

Since, many physicians may be involved in diagnosing cases in a large prophylaxis trial,

Table 1: Impact of lowered sensitivity and specificity (3000 Controls and 3000 Vaccinated subjects)

Sensitivity	Specificity	Series	No. of cases	No. of noncases	Total	Chi-square	Vaccine efficacy
100%	100%	Control	30	2970	3000		
		Vaccinated	15	2985	3000	5.04	50%
80%	100%	Control	80% of 30 = 24	3000 - 24 = 2976	3000		
		Vaccinated	80% of 15 = 12	3000 - 12 = 2988	3000	4.02	50%
100%	99%	Control	100% of 30 = 30 1% of 2970 = 30 60	3000 - 60 = 2940	3000		
		Vaccinated	100% of 15 = 15 1% of 2985 = 30 45	3000 - 45 = 2955	3000	2.18	25

Table 2: Sample size ratio for various combinations of disease incidence, vaccine efficacy, sensitivity and specificity

Disease incidence* (per 1000)	Vaccine efficacy (%)	Sensitivity (%)	Specificity (%)		
			100	90	80
		100	1.0	127	284
	30	90	1.1	160	370
		80	1.3	209	504
		100	1.0	139	311
1	50	90	1.1	175	406
		80	1.3	229	552
		100	1.0	153	344
	70	90	1.1	194	449
		80	1.3	253	611
		100	1.0	26	58
	30	90	1.1	33	75
		80	1.3	43	102
		100	1.0	29	63
5	50	90	1.1	36	82
		80	1.3	47	112
		100	1.0	31	70
	70	90	1.1	40	91
		80	1.3	52	123
		100	1.0	14	29
	30	90	1.1	17	38
		80	1.3	22	52
		100	1.0	15	32
10	50	90	1.1	19	42
		80	1.3	24	57
		100	1.0	16	35
	70	90	1.1	20	46
		80	1.3	27	62

* in unvaccinated subjects

uniformity of diagnosis is important. Standardization of diagnosis is essential and clear-cut definitions must be evolved as a certain amount of subjectivity may be involved in defining a case of, say, tuberculosis, leprosy or influenza. Finally, where some subjectivity is involved in diagnosing a case, an independent assessor, otherwise unconnected with the study and unaware of the 'group' the subject belongs to, should be asked to assess the findings and identify the cases.

An ideal diagnostic test, i.e. one with sensitivity of 100% and specificity of 100%, is rarely available under field conditions, and consequently one has to make-do with less efficient tests. While the crucial importance of correct diagnosis in an individual is fully recognized by both the doctor and the *individual* subject, it is some times thought that errors of diagnosis are not so critical in field trials, as they might be expected to occur to the same extent in both the test and control groups, especially if the study is made double-blind. This view is very mistaken. Situation A in which there are 30 true cases in 3000 controls over a 5-year period of follow-up (i.e. an annual incidence of 2 per thousand) and 15 true cases in 3000 vaccinated subjects (Table 1). Chi-square = 5.04 (P = 0.02), and vaccine efficacy estimate = 50%, with a confidence interval of 7% - 73%. Now, consider a practical situation where the sensitivity of the diagnostic test diminishes to 80%, but the specificity remains at 100%. The number of cases will be 24 and 12, respectively. Chi-square decreases to 4.02 (P = 0.045). The estimated vaccine efficacy is unaffected and is still 50%, but the 95% confidence interval is enlarged to 0% – 75%, and now includes 0%. If the decrease in Chi-square is to be compensated, the original trial size must be multiplied by (5.04/4.02), namely, 1.25, i.e. it needs to be increased by 25%. This increase will also restore the confidence interval to 7% - 73%. Situation B where sensitivity remains at 100% but specificity diminishes slightly to 99%. The number of subjects labelled as cases will increase to 60 and 45, respectively; Chi-square reduces to 2.18 (P = 0.14), and a substantial increase of 130% in trial size will be needed to compensate for this. It may also be noted that the estimated vaccine efficacy is

only 25% (cf original 50%), with a much larger confidence interval of minus 10% to 49%.

As demonstrated above, lowered sensitivity and lowered specificity lead to smaller Chi-square values and larger confidence intervals (indicating lowered reliability), which can be compensated for by increasing the trial size. This increase, as measured by the sample size ratio, is set out in Table 2 for various combinations of disease incidence (1, 5 and 10 per thousand), vaccine efficacy (30, 50 and 70%), sensitivity (80, 90 and 100%) and specificity (80, 90 and 100%). The following observations can be made:

(1) if specificity is 100%, change in disease incidence, vaccine efficacy or sensitivity has little impact on the ratio, which increases to at most 1.3;

(2) if specificity is less than 100%, the ratio is, in general, substantially large when the incidence is small (e.g. 1 per thousand), but decreases appreciably as the incidence increases; however, it tends to increase as vaccine efficacy increases;

(3) in contrast to (1) above, even if sensitivity is 100%, decrease in specificity substantially increases the ratio, although the magnitude of the increase is smaller with higher incidence;

(4) the ratio is consistently larger for, say, a 10% change in specificity level (sensitivity being fixed) than for the same change (10%) in sensitivity level (specificity being fixed); for instance, for disease incidence of 5 per thousand and vaccine efficacy of 50%, the ratio is 36 for 90% sensitivity and 90% specificity, and increases to 82 for a 10% decrease in specificity as compared to only 47 for a 10% decrease in sensitivity.

In summary, the implication of a decrease in the level of specificity is appreciably more marked than that of a similar decrease in the level of sensitivity.

Impaired sensitivity of the diagnostic test has very little impact on the estimate of vaccine efficacy (Table 3). However, lowered specificity has substantial effect. For instance, a vaccine with a protective efficacy of 90% would be estimated as having an efficacy of only 3-4% if the disease incidence is 1 per thousand and specificity is 98% (Table 3). With increasing incidence, the efficacy

Table 3: Estimated efficacy from field trial when true efficacy is 90%

Disease incidence (per 1000)	Sensitivity	Estimated efficacy (%) from trial for a 90% effective vaccine if diagnostic test has the following specificity			
		100%	98%	94%	90%
1	100%	90	4	1	< 1
	90%	90	4	1	< 1
	80%	90	3	1	< 1
5	100%	90	18	7	4
	90%	90	16	6	3
	80%	90	15	5	3
10	100%	90	30	12	7
	90%	90	28	11	7
	80%	90	25	10	6

Table 4: Number of sampling units required

Size of sampling unit	k = 0.25		k = 0.5	
	Number of towns	Population	Number of towns	Population
1	x	102,400	x	102,400
40,000	5	200,000	13	520,000
30,000	5	150,000	13	390,000
20,000	6	120,000	14	280,000
10,000	9	90,000	17	170,000

estimate also increases, but is still no more than 30% (cf true value of 90%) with a disease incidence of 10 per thousand. Increasing the trial size cannot correct for this bias; however, the true efficacy T can be estimated by multiplying the Observed efficacy in the trial by [I / (I + Specificity – 1)], where I is the Observed Incidence in unvaccinated subjects in the field trial.[5]

Since the adverse effects of lowered specificity (and lowered sensitivity) are greatest when the disease incidence is low (< 1 per thousand), a precaution that could be taken in vaccine trials is to choose a sub sample of the population having a relatively high risk of developing disease as the trial population, as for example, family contacts or persons of low socio-economic status. Other methods for minimizing the dangers from lowered specificity are:

(1) to repeat the diagnostic test on all persons with a positive finding and consider as cases only those who have both results positive;

(2) to undertake another diagnostic test also, and classify as cases only those persons who are positive on both diagnostic tests;

(3) combinations of (1) and (2) above.

Any prophylaxis trial would require eligible persons in the community to be identified by some measure — for instance, those with no tuberculous infection are identified for a BCG trial by undertaking a tuberculin test. Such tests also need to be highly sensitive and specific. If not, fewer of the true 'uninfected' will be detected (due to lowered sensitivity) and included in the trial, and some 'infected' subjects, wrongly labelled as uninfected (due to impaired specificity), will also be included. As before, this would lead to smaller values of Chi-Square and an underestimated efficacy. To overcome this, a repeat test and/or an additional test for diagnosing infection may be undertaken on all members in the community. Finally, ethical issues might arise if there is a failure to correctly identify high-risk subjects for a universal management policy of prophylaxis, or with the wrongful and needless inclusion of non high-risk subjects to the rigours of a randomized prophylaxis trial.

Table 5: Ethical issues considered in Tamil Nadu leprosy vaccine trial

Was the study protocol submitted for independent ethical review?
Was the Phase III trial of efficacy preceded by a Phase II trial for safety?
Does the study protocol respect the principles of autonomy, beneficence and justice?
Is the study randomized and double-blinded so that it is both more scientifically acceptable and ethical?
If a placebo is proposed, is it appropriate?
Was informed consent taken from participants?
Is compensation offered for any possible injury? Will such compensation serve as an inducement to participate?
Does the trial include pregnant or nursing women?
Is the ethical committee accountable?

Trial size

Sampling unit is an individual

If individual subjects are randomized to prophylaxis or control, the required sample size in each group (N) is given by the standard formula [4] (Poisson method)

$$N = \{(Z_1 + Z_2)^2 (P_1 + P_2) / (P_1 - P_2)^2\}$$

where Z_1 and Z_2 are the Normal deviates corresponding to Type I error and Power, P_1 and P_2 are the incidences in control and test groups

If the annual disease incidence in unvaccinated 1 per thousand (P_1) and vaccine efficacy of public health interest is 50%, designated Type I error (1-tail) is 0.05 and desired Power is 90%, the required trial size is 102,400 (Table 4, first row). The likelihood of dropouts is greater in

prophylaxis studies than chemotherapy studies. Allowing for a dropout of 10% over 5 years, the modified trial size would be 102,400/0.9 = 113,70

Sampling unit is a community

If the sampling unit for randomization is large (say, a town comprising n = 40,000 persons), P_1 is the incidence in the control group and P_2 the incidence in the test group (and P is the average of the two), to detect an efficacy of 50% with Type I error of 0.05 (1-tail) and Power of 90%, the number of towns (N) to be studied in each group is given by:

$$N = 1 + \{(Z_1 + Z_2)^2 [2 P (1-P) /n + k^2 (P_1^2 + P_2^2)] / (P_1 - P_2)^2\},$$

where Z_1 and Z_2 are the Normal deviates corresponding to Type I error and Power, n is the number of person-years of observation, and k is the coefficient of variation of the true proportion among the towns in each group.[6] An estimate of k will sometimes be available from previous data in similar towns or from a pilot study. If not, one will have to make a plausible assumption, and this could be k = 0.25, which implies that the true proportions in each group lie roughly between $P_1 + 2kP_1$ and $P_2 + 2kP_2$. In the above example, $P_1 = 0.001$, $P_2 = 0.0005$, P = 0.00075, $Z_1 = 1.64$, $Z_2 = 1.28$, and N = 5 (Table 4), yielding a result of total of 10 towns and a trial size of 400,000. If the towns are smaller in population size, say 30,000, 20,000, and 10,000, the required number of towns in each group is 5, 6 and 9, respectively (Table 4). The total trial population for two groups studied would be 300,000, 240,000, and 180,000 (Table 4) as compared with 102,400 if the random sampling unit were the individual. Thus, the larger the unit for randomization the larger would be the total trial size required.

If the co-efficient of variation of the true proportion among the towns in each group is substantial, e.g. k = 0.5 (instead of 0.25), the number of towns required would be larger, namely, 13, 13, 14 and 17 for town sizes of 40,000, 30,000, 20,000 and 10,000, respectively (Table 4, right half).

Design of the trial

The most commonly employed design is the Completely Randomized design, followed by the Randomized block design,[4] but there is scope for more complex designs. Thus, a BCG trial against tuberculosis was undertaken in South India,[7] using a factorial design,[4] with BCG at two strengths (0.1 and 0.01 mg/ml) and the BCG strain itself from 2 sources (Danish, French). All these are fixed size trials. A trial where sample size depends upon running outcomes, and is not fixed in advance, is called a sequential trial. Such a trial (randomized double-blind, placebo controlled trial) was undertaken in Brazil,[8] and showed that prophylaxis with promethazine did not prevent early anaphylactic reactions to antivenom in 109 subjects bitten by bothrops snakes. A novel design, the Stepped-wedge design,[9] was utilized in Gambia to evaluate the protective efficacy of hepatitis B Vaccination (HBV) on liver cancer rates — the vaccine was introduced in to the routine child vaccination programme (EPI) over a period of 4 years, employing 17 vaccination teams. The order in which the different vaccination teams began to use the vaccine (EPI, HBV) was random. At the end of 4 years, there was a cohort of children who had received the vaccine and a cohort who had not, and these were compared for the incidence of liver cancer. The 'Power' of this approach, compared to a simple allocation of groups to one or other arms, is of the order of 75 – 80%, depending on the number of groups.

Ethical considerations

An obvious difference between chemotherapy trials and prophylaxis studies is that chemotherapy trials are undertaken in patients with overt manifestation of disease while prophylaxis studies are on apparently healthy subjects who are at risk of developing disease. It follows that there is a much greater ethical need in prophylaxis studies to consider the possibility of risks – that is, frequency, nature and severity of side effects from the preventive measure - and balance this against the expected benefits. This is particularly true of universal prophylaxis for a general population for diseases such as tuberculosis, where it might be

necessary to give drugs to a very large number of individuals in order to prevent disease in a few. Ethical committees can be particularly strict and the investigator asked searching questions. One such instance comes to mind when a lawyer on the ethical committee took exception to a third of the at-risk subjects (selected at random) being given a placebo while the rest received BCG, his question being "Is it not unethical to deny BCG (that may be beneficial) to at-risk subjects?" The answer that eventually satisfied him was that it was not the national policy in those days to give every body BCG, and therefore subjects that received a placebo were on par with the run-of-the-mill Indian and, further, that giving BCG may not only have been non-beneficial but could have led to adverse side effects. Besides the use of a placebo, there could be several other issues to be sorted out to with the Ethical committee. Detailed guidelines for this purpose have been laid down by national and international bodies. A good illustration is an ICMR leprosy vaccine trial in Tamil Nadu.[10] Several issues were considered in depth,[11] and some of these are highlighted in Table 5.

In situations where previous studies, perhaps using short-term end points, indicate that an intervention is likely to be beneficial, withholding it in some for the duration of the trial could pose ethical problems. An approach that could be adopted in this case is the phased introduction of the intervention on a group-by-group basis until the entire target population is covered (a prolonged period is invariably a practical necessity) - this is the Stepped-wedge design described above.[9]

Statistical techniques

If randomization is done at the level of the individual subject, conventional statistical tools are employed, namely, tests for equality of proportions and means, log rank test and survival analysis methods.[4] In studies where communities are randomized, the same procedures are sometimes mechanically employed which is incorrect. The statistical test of significance should be based on summary measures for the community (such as the mean). If the number of randomized communities is large, confounding variables are likely to balance out between the groups. But if these are few in number (even though the community within may be large), confounding may become a potentially serious problem; this would need some adjustment in the analysis – e.g. standardization by 'direct' or 'indirect' method.[1] If the summary values are relatively few, a non-parametric test may be undertaken. If the communities were matched initially in pairs, and one member of each pair was allocated at random to the 'test' group (the other going to the 'control' group), a paired non-parametric test could be undertaken.[4]

It is possible that compliance rates may not be high, especially if chemoprophylaxis is to be self-administered over a prolonged period. Therefore, an intent-to treat analysis [12] that is effectively based on all subjects admitted to study should also be undertaken for obtaining a more realistic and pragmatic assessment of the benefit from the intervention.

CONCLUSION

When designing prophylaxis studies, the choice of appropriate controls, the size of the sampling unit for random allocation and its impact on trial size and on subsequent analyses, correct identification of subjects as 'at high risk' or not and accuracy of disease diagnosis and the effect of these on estimated efficacy and its reliability, and the ethical aspects of the community trial must be kept in mind. For subsequent analyses, there is a need for deriving a satisfactory estimate of the true incidence in the community, using the sensitivity and specificity levels of various definitions of a 'case'.

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PLANNING A CLINICAL TRIAL! PLEASE REGISTER BEFORE ENROLLING

Lalit Kant*

Go ahead and click-on www.ctri.in – the website of the Clinical Trial Registry of India. The registration is easy, free, on-line and voluntary.

Why should you register?

By registering your trial, you are contributing to generation of evidences for decision-making. If all of us register, then these open access clinical trial registries are likely to have information to address ethical and scientific problems which arise when trial results are either delayed or not completely revealed to public or researchers; when volunteers consent to a trial with the understanding that the study will inform medical knowledge and then the results are not made public; future volunteers are at risk for being misled and harmed when their consent and trial design are not fully informed by prior research; ethical committee members are unable to weigh the risks and benefits when some unknown proportion of relevant data is unavailable for review[1].

Clinical trials Registers

On 20th July 2007, India joined a select group of countries like Australia, United Kingdom and United States of America that have made provisions for registering clinical trials.

For various well known reasons, India is emerging as one of the most preferred sites for conducting clinical trials. Globally, pharmaceutical companies are under immense competitive pressure to develop interventions and market them quickly. In this haste scientific, ethical and regulatory principles, at times, have and are being compromised especially by the 'fly by night' investigators. Communities in developing countries fall easy prey to them. Some of these trials have caught national and international attention and have succeeded in whipping up considerable public debate. One of the recommended options to curb the menace of such incidents is to encourage registration of all interventional trials.

There are several hundred registers of clinical trials around the world, but each has been started with different objectives and philosophy. They collect varied information to meet their objectives.

International Committee of Medical Journal Editors

The crusade of increased transparency and accountability in conduct of clinical trials received a shot in the arm when the International Committee of Medical Journal Editors (ICMJE) proposed a comprehensive trials registration as a solution to problem of selective awareness and announced that all eleven ICMJE member journals will adopt a trials registration policy to promote this goal[2].

This Policy applies to any clinical trial starting enrolment after July 1, 2005. The ICMJE did not advocate any particular registry but did lay down the minimum parameters which it must meet. Though ICMJE established policy for its member journals, many other journals have adopted the trial registration recommendation.

Two years after the ICMJE laid down its guiding principles it re-evaluated its policy in mid-2007. It concludes that the research community has embraced trial registration. This is evident from the sharp increase in the numbers of clinical trials which have been registered in five major registries that met the ICMJE's criteria[3].

International Clinical Trial Registry Platform

Around the same time as the ICMJE's policy statement the WHO's initiative of International Clinical Trial Registry Platform had been launched,

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aimed at standardizing the way information on medical studies is made available to the public through a process of registration. Within two years' time this too has developed. It has recommended 20 key details to be disclosed at the time studies begin. The WHO's effort aims to bring uniformity in the data being recorded in each registry by providing a set of standards for all registers. In addition, it is developing into a network of primary and partner registers that meet the WHO-specified criteria[4].

Primary registers are the WHO-selected registers managed by not-for-profit entities that will accept registration for any international trials, delete duplicate entries from their own register and provide data directly to the WHO. The ICMJE will accept registration of clinical trials in any of these primary registers. Partner registers, on the other hand, are registers that submit data to primary registers but limit their own register to trials in a restricted area (such as a specific disease, company, academic institutions or geographic region). Registration in a partner register is insufficient[3].

Clinical Trials Registry – India

The Clinical Trials Registry – India (CTRI) meets the requirements of WHO of a Primary Register (along with Australian, New Zealand Clinical Trials Registry, Chinese Clinical Trial Register, and ISRCTN.org; although not a primary register, data from United States National Library of Medicine sponsored ClinicalTrials.gov is also included in the WHO Search Portal)[5].

Hosted by the National Institute of Medical Statistics – one of the 26 permanent institutes of the Indian Council of Medical Research (ICMR), the CTRI requires declaration of few additional items (than the WHO mandated 20 issues) before enrollment of the first patient. Thus to register a study, trailists will need to submit information as per the requirements of Registrational Data set. Some fields are mandatory for registration. If all the necessary fields are filled with valid and informative entries, the trial will be officially registered and allocated a unique registration number.

Incomplete entries receive a provisional registration number. The provisional registration number does not suffice for purposes of publication in journals that endorse the ICMJE recommendations for trial registration. The CTRI is scalable to cover other countries in the region.

The setting up of this Registry is an eloquent example of inter-agency collaboration and is jointly funded by the Department of Science & Technology, Ministry of Science and Technology; the World Health Organization and the Indian Council of Medical Research.

All interventional clinical trials conducted in India and involving Indian participants should be registered. The Clinical Trial Registry - India would go along with the ICMJE's decision to implement the WHO definition of clinical trials that begin enrolment on or after July 1, 2008, This definition states that "an interventional clinical trial is any research study that prospectively assigns people to one or more wealth health related interventions to evaluate their effects on health related outcomes"[3]. Examples include, but are not limited to preventable care, drugs (including herbal), surgical procedures, behaviour treatments, medical devices, etc). All phases of trials, trials of marketed or non-marketed products, randomized or non-randomized trials – all should be registered. If in doubt, register.

Putting in place a clinical trial registry is unlikely to solve all problems. A number of trials may never get registered (as registration is voluntary). The issue of incomplete disclosure of results would persist. Unanticipated adverse events may not be recognized due to relatively small sample sizes and incomplete publications of results from pre-approval studies. Important lessons are being learnt from the registries which have been in operation for a long time[1,3].

Universalization of clinical trials needs actions at various levels. Some 'push' and 'pull' mechanisms like legislative steps and incentives may be helpful. Ethical committees can encourage investigators to register and so can the funding and regulatory agencies. The editors of biomedical

journals can adopt the ICMJE policy and insist on a registration number. Each one of us can and should do our bit and contribute towards bringing in greater transparency and public trust in conduct of clinical trials.

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TUBERCULOSIS HEALTH VISITORS' COURSE

The 2008-2009 Tuberculosis Health Visitors' Course of nine months' duration will be conducted at the New Delhi Tuberculosis Centre. The minimum qualification for admission to this course is 10 + 2 with science and/or hygiene. Science education up to class 10 is essential. Application forms for admission to the course can be obtained from the Secretary General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-110 001. The last date for receipt of applications is 30th April, 2008.

Indian J Tuberc 2008; 55:

STATUS REPORT ON RNTCP*

Revised National Tuberculosis Control Programme has continued almost to touch its twin objectives in this quarter too! At the national level, the Annualized New Sputum Positive (NSP) case detection rate for the third quarter 2007 stood at 53 per lakh population (70%) and cure rate at 84 % for the third quarter 2006 patient cohort. Through this, we are moving in the right direction of consolidating and sustaining our achievements with the ultimate goal of achieving TB control.

RNTCP performance in third quarter 2007

During this quarter, over 1.6 million pulmonary TB suspects were examined and 222,108 sputum positive TB cases were diagnosed. A total of 374,254 TB cases were registered for treatment, of which NSP cases were 149,242, new smear negative (NSN) pulmonary TB 100,429, new extra-pulmonary TB (EP-TB) 52,315 and the rest 72,268 were re-treatment cases. The annualized total case detection rate is 132 per lakh population. The treatment success rate amongst the NSP cases registered in the 3rd quarter 2006 is 86%, for NSN cases 87%, new EP-TB cases 90% and for smear positive re-treatment cases it is 69%.

The default rate of 6.4% among NSP cases, 8.3% among NSN cases 5.4% among new EP-TB cases and especially 16.4% amongst the smear positive re-treatment cases, is an area of concern which the programme managers at all levels must focus on. The programme is focusing on patients who miss doses and their retrieval back onto treatment, and the same has been conveyed to states

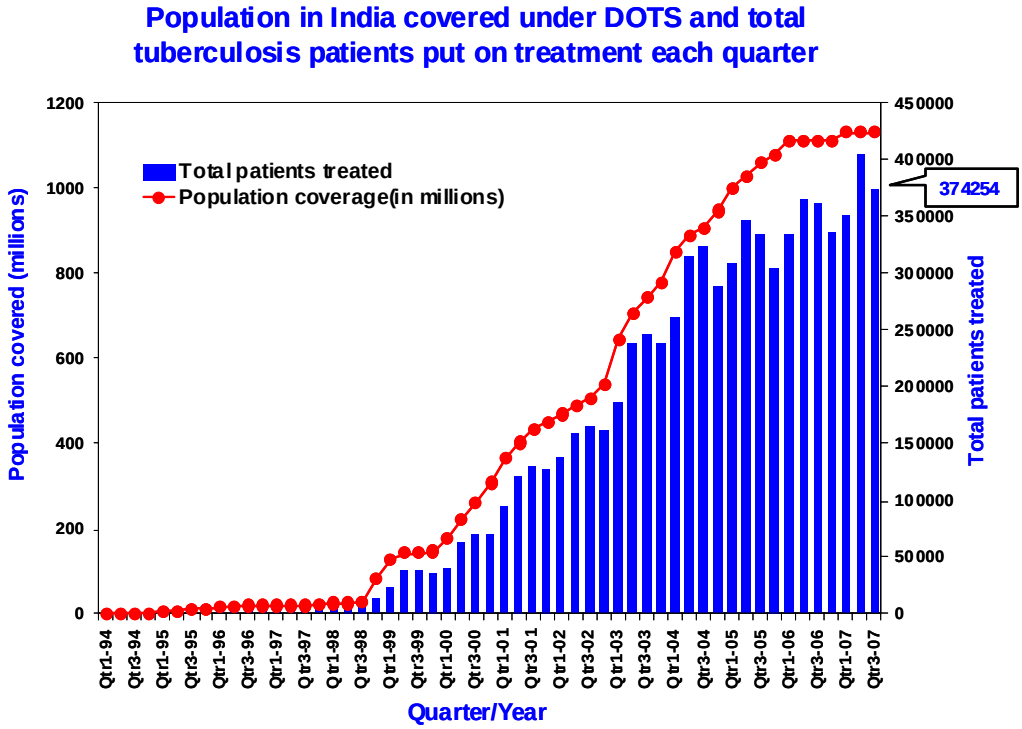

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Table: Performance of RNTCP Case Detection (2007 Third quarter), Smear Conversion (2007, Second quarter), and Treatment Outcome (2006, Third quarter)

State	Population (in lakh) covered by RNTCP[1]	Suspects examined per lakh population	No of Smear positive patients diagnosed[2]	Total patients registered for treatment[3]	Annualized total case detection rate	New smear positive patients registered for treatment	Annualized new smear positive case detection rate (%)		No of new smear negative cases registered for treatment	No of new EP cases registered for treament	No of smear positive re-treatment cases registered for treatment	3 month conversion rate of new smear positive patients	Cure rate of new smear positive patients	Success rate of new smear positive patients
Andaman & Nicobar	4	202	91	191	190	70	70	93%	49	48	20	92%	88%	88%
Andhra Pradesh	813	148	18448	27557	136	12279	60	81%	7740	2829	3786	91%	84%	87%
Arunachal Pradesh	12	239	311	654	221	217	73	98%	171	104	85	91%	88%	89%
Assam	295	116	5472	9506	129	4205	57	76%	2717	973	934	89%	85%	86%
Bihar	923	78	10525	20591	89	7833	34	45%	7294	1415	2084	84%	74%	83%
Chandigarh	10	356	447	668	258	205	79	83%	129	206	84	94%	85%	85%
Chhatisgarh	233	115	3035	6740	116	2502	43	54%	2733	757	440	89%	85%	88%
D & N Haveli	3	164	60	86	135	35	55	69%	13	12	12	95%	85%	85%
Daman & Diu	2	391	64	94	205	30	66	82%	20	10	17	85%	85%	88%
Delhi	166	239	6123	12363	299	3469	84	88%	2379	3650	1723	88%	85%	85%
Goa	16	190	294	503	127	167	42	53%	119	112	62	91%	74%	75%
Gujarat	556	161	14577	20073	144	8702	63	78%	2904	2442	4378	91%	87%	87%
Haryana	234	173	5992	9342	160	3387	58	61%	1993	1440	1967	89%	85%	85%
Himachal Pradesh	65	251	2046	3472	214	1264	78	82%	665	731	676	93%	88%	90%
Jammu & Kashmir	120	155	1825	3247	108	1339	45	47%	592	764	426	89%	86%	88%
Jharkhand	296	110	5134	9385	127	4029	54	73%	3209	696	752	89%	86%	89%
Karnataka	568	173	10854	16711	118	6564	46	62%	3677	3078	2497	83%	75%	78%
Kerala	339	161	3380	5473	65	2500	29	39%	1043	1229	541	84%	81%	83%
Lakshadweep	1	103	1	7	41	1	6	8%	2	2	2	100%	50%	50%
Madhya Pradesh	680	116	12223	21075	124	7750	46	57%	6580	2303	3259	88%	82%	85%
Maharashtra	1055	149	19494	35064	133	13646	52	65%	9000	5712	4125	90%	85%	86%
Manipur	26	160	396	1309	202	310	48	64%	492	252	82	86%	84%	85%
Meghalaya	25	165	529	1260	201	356	57	76%	301	311	137	86%	85%	86%
Mizoram	10	207	254	563	233	187	77	103%	129	178	43	96%	93%	93%
Nagaland	22	140	334	753	139	285	53	70%	183	136	91	94%	89%	89%
Orissa	395	123	6759	12047	122	5216	53	62%	3137	2014	1018	89%	82%	87%
Puducherry	11	339	312	352	133	160	60	81%	53	58	73	89%	84%	84%
Punjab	263	152	5598	9435	144	3700	56	59%	1972	1817	1505	87%	82%	85%
Rajasthan	635	146	19061	29689	187	11093	70	87%	8460	3389	5739	91%	88%	89%
Sikkim	6	368	181	400	273	118	80	107%	69	128	60	88%	90%	90%
Tamil Nadu	658	211	11603	21096	128	8201	50	66%	5758	4249	2364	89%	82%	83%
Tripura	35	124	470	669	77	395	46	61%	108	96	63	93%	87%	89%
Uttar Pradesh	1874	132	38051	63881	136	25334	54	57%	20428	6494	9530	89%	83%	87%
Uttarakhand	94	184	2365	3374	144	1328	57	60%	815	503	586	92%	89%	90%
West Bengal	868	148	15799	26624	123	12415	57	76%	5495	4177	2939	89%	87%	87%
Grand Total	**11310**	**144**	**222108**	**374254**	**132**	**149292**	**53**	**70%**	**100429**	**52315**	**52100**	**89%**	**84%**	**86%**

1 Projected population based on census population of 2001 is used for calculation of case-detection rate. 1 lakh = 100,000 population

2 Smear positive patients diagnosed include new smear positive cases and smear positive retreatment cases

3 Total patients registered for treatment includes new sputum smear positive cases, new smear negative cases, new extra-pulmonary cases, smear positive retreatment cases and 'Others'

to ensure measures to prevent patients from defaulting.

In the quarter, the programme has initiated the first patients on Category IV MDR-TB treatment in Gujarat and Maharashtra in August and September 2007 respectively. With this first step, the programme has started on the provision of services for MDR-TB cases which the programme considers as a 'Standard of TB care issue'. From the Q1 2008 report onwards, data on the provision of Category IV services will routinely be included in this quarterly performance report. The management of MDR TB is a huge task and a lot of challenges will emerge over time. The programme, however, is fully committed to the cause and will undertake all measures that are required to address the challenges that emerge. At this juncture, before we get lost in trying to visualize all the challenges in the management of MDR-TB, we would like to strongly reiterate that our greatest responsibility is to prevent emergence of MDR-TB by continuing to implement quality DOTS services.

Other Initiatives

1. Central level internal evaluations were undertaken in the states of Goa, Karnataka, Punjab and Uttarakhand. The respective state and district health authorities actively participated in these evaluations and committed to undertake actions on the recommendations to further enhance the quality of programme implementation at all levels.

2. The zonal task force (ZTF) workshops for 2007 were held in all five zones during the third quarter of the year. 246 medical colleges now have DMCs and DOT centres. Approximately 8-10% of the sputum positive patients are being diagnosed at the medical college DMCs. There was renewed commitment to advocating for and practising the rational use of second line anti-TB drugs in the management of MDR TB by faculty staff.

3. The 12th meeting of the RNTCP Lab Committee was held at NTI, Bangalore on 28th and 29th September 2007. The meeting focused on the status of IRL strengthening in the various states; review of DRS and DOTS-Plus activities and to discuss the progress of second line drug susceptibility testing at the NRLs. The committee also discussed the JMM recommendations related to EQA and gave suggestions for improving the quality assurance mechanism which are being looked into. There is an urgent need to adhere to the timelines for the IRL strengthening and initiation of DOTS -Plus services as outlined in the minutes of the meeting by the concerned states in order that MDR-TB treatment services may be expanded rapidly.

4. The annual training of the state IEC officers was held during August 2007. The "Base-line IEC document" has been completed and is available at the RNTCP website (www.tbcindia.org). A media agency has been hired at the national level for undertaking media activities.

5. The operationalisation of Co-trimoxazole Prophylaxis Therapy (CPT) for TB patients who are HIV-infected, which has been pilot tested in three districts of Andhra Pradesh, was evaluated by a joint team from CTD, NACO and WHO-India in September 2007. The evaluation concluded that decentralized delivery of CPT by RNTCP is operationally feasible and that it should be extended to the other high HIV prevalent districts in the country.

6. Two trainings on 'Procurement and Drug Logistic Management' for STOs, State Pharmacists and State Drug Store In-charges have been organized in this quarter to train them as trainers and also to built their capacity to manage drug inventory at state level.

Case Report

PRIMARY TUBERCULOSIS OF TONSIL AND POSTERIOR OROPHARYNGEAL WALL

A. Chakravarti[1], Swatilika Pal[2] and J.K. Sahni[3]

(Original article received on 4.6.2007. Revised version on 21.8.2007. Accepted on 11.10.2007)

Summary: Pharyngeal tuberculosis is rare and usually occurs in association with primary pulmonary disease. Primary tuberculosis involving the palatine tonsils and the posterior oropharyngeal wall is still a rare clinical entity. We report one such case of primary tuberculosis involving both the palatine tonsils and the posterior oropharyngeal wall in a 22 year-old male. The patient responded to anti-tubercular treatment with complete disappearance of lesion and no sign of recurrence on one year follow-up. The final diagnosis was based upon histopathological report. ***[Indian J Tuberc 2008; 55:48-50]***

Key Words: Tuberculosis, Oropharynx

INTRODUCTION

Tuberculosis of oral cavity is uncommon and pharyngeal lesions are extremely rare. Pharyngeal tuberculosis is usually secondary to pulmonary disease[1]. This report presents an unusual case of primary oropharyngeal tuberculosis. The purpose of this report was to point out that a high index of suspicion should be kept in mind to reach the diagnosis in patients presenting with sore throat, fever and malaise.

CASE REPORT

A 22 year-old male presented with history of sore throat, odynophagia, occasional fever, malaise for one year duration. He had been taking treatment in form of various courses of antibiotics, analgesics, antihistaminics since then without any relief. He had no previous history of any serious illness, chronic cough, other chest symptoms or Human Immunodeficiency Virus (HIV) exposure.

While the general physical examination revealed normal findings, oral examination showed enlarged tonsils and multiple ulcerated areas over the surface. The posterior pharyngeal wall showed granular hypertrophic areas (Fig. 1). There was no cervical lymphadenopathy. Routine hematological evaluation revealed a raised Erythrocyte Sedimentation Rate (ESR) of 50mm in first hour. Mantoux test was positive. Chest radiography was normal. Throat swab and sputum for acid fast bacilli were negative. With a high index of clinical suspicion of tuberculosis, biopsy was taken from ulcerated

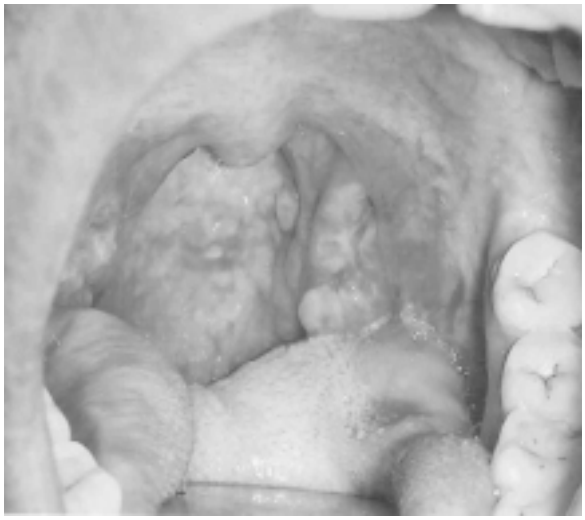

Fig.1: Tonsilar enlargement with multiple ulceration and granular hypertrophic areas on posterior pharyngeal wall

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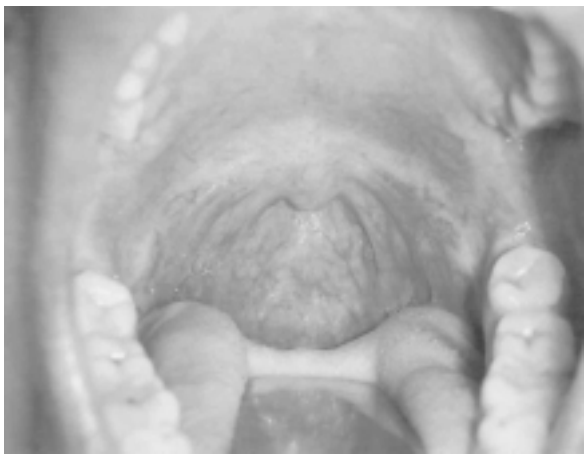

Fig. 2: Recovery after 6 months of anti-tubercular treatment

area of both tonsils and granular area of the posterior pharyngeal wall and sent for histopathological examination. Histology revealed granulomatous dense sub-mucosal lymphoid infiltrate with multiple epithelioid histiocyte granulomas, including multimucleate giant cells and caseous necrosis consistent with the diagnosis of tuberculosis (Fig. 3). Serological tests for Acquired Immunodeficiency Syndrome (AIDS) and syphilis were negative. Patient was managed with anti-tubercular treatment in standard doses for six months. The patient had a good symptomatic response within the first month of treatment with total disappearance of ulcers and granular areas after completion of treatment (Fig. 2). On one year follow-up, there had been no evidence of recurrence.

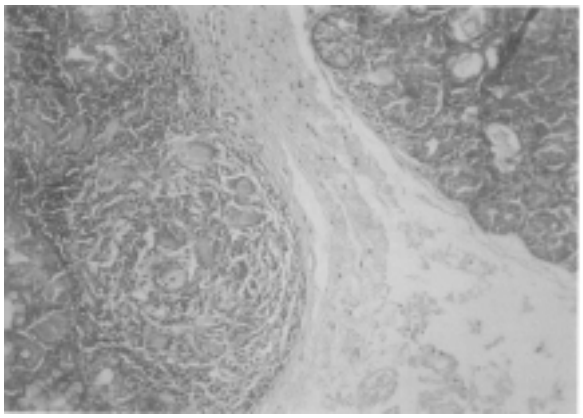

Fig. 3: Granulomatous dense submucosal lymphoid infiltrate with multiple epithelioid histiocytes, multinucleate giant cells and caseous necrosis. (H & E stain; 10X)

DISCUSSION

Tuberculosis of upper respiratory tract is rare and is usually secondary to pulmonary disease[1]. Primary tuberculosis affecting palatine tonsils and posterior oropharyngeal wall is still extremely rare[2]. Present case is unique in its presentation as lesions were present both in the palatine tonsils and posterior oropharyngeal wall concomitantly. Available literature does not reveal simultaneous involvement of both sites in the same patient.

The upper respiratory tract is generally resistant to tuberculosis. Saliva by virtue of its cleansing action is thought to have an inhibitory effect on tubercle bacilli[3]. It is also postulated that presence of saprophytes, the antagonism of striated musculature to bacterial invasion and thicknesss of the protective epithelial covering of the oropharyngeal mucosa have an inhibitory effect on tubercle bacilli[4].

Isolated pharyngeal lesions affecting the nasopharynx, palatine tonsil or posterior oropharyngeal wall are acquired by inhalation with harbouring of disease in waldeyer's ring[5]. Extra-pulmonary localizations of tuberculosis are rare, commonly encountered in patients with poor host reaction due to chronic alcoholism, HIV infection, etc.[6] Our patient neither had any chronic illness nor was immuno-compromised.

Pre-disposing factors for primary oral tuberculosis include poor oro-dental hygiene, dental extractions, periodontitis and leucoplakia[1,3]. The present case did not have any such predisposing factors.

Differential diagnosis of oral and pharyngeal tuberculosis includes traumatic ulcer, aphthous ulcer, Plaut-Vincent's tonsillitis, haematological disorders, actinomycosis, syphilis, midline granulomas, Wegener's disease, carcinoma and lymphoma[6,7]. Diagnosis, however, is based on high index of clinical

suspicion, histopathological findings and the identification of tubercle bacilli.

A case with a history of long standing sore throat with clinical evidence of ulceration over tonsils and granular appearance of posterior oropharyngeal wall, should alert the clinician to the possibility of tuberculosis as a causative factor, especially in developing countries and in regions where the incidence of tuberculosis is high.

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FIRST INTERNATIONAL CONFERENCE OF SOUTH EAST ASIA REGION (IUATLD) JOINTLY ORGANISED WITH 63rd NATIONAL CONFERENCE ON TUBERCULOSIS AND CHEST DISEASES

First International Conference of South East Asia Region jointly organized with 63rd National Conference on TB and Chest Diseases will be held fro m 8th to 10th September, 2008, at the Stein Auditorium, Habitat World, India Habitat Centre, Lodhi Road, New Delhi-110 003. We request you to kindly block these dates for attending the above Conference. We also request you to kindly bring this to the notice of all the TB and chest diseases workers and others, who are interested to attend the above Conference and request them to present their papers on TB and Lung Diseases. For further information, please contact the Secretary General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-110 001.

Case Report

TUBERCULOSIS OF ORAL CAVITY

Ramakant Dixit, Sidharth Sharma and Paras Nuwal*

(Original article received on 31.7.2007. Revised on 2.11.2007. Accepted on 7.11.2007)

***Summary*:** Tuberculous involvement of oral cavity is very rare. A 34-year-old male presented with non-healing ulcer at upper lip mucosa. Biopsy from ulcer revealed tuberculous lesion. He also had asymptomatic pulmonary tuberculosis diagnosed during work up for primary site of the disease. **[*Indian J Tuberc 2008; 55:51-53*]**

***Key words*:** Tuberculosis, Oral Cavity

INTRODUCTION

Tuberculous oral lesions are a relatively rare occurrence.[1] Studies vary, but the incidence has usually been reported as less than one per cent of the tuberculosis population.[2-4]

Oral tuberculous lesions may be either primary or secondary in occurrence. Primary lesions are uncommon, seen in younger patients and present as single painless ulcer with regional lymph node enlargement. The secondary lesions are common, often associated with pulmonary disease, usually present as single, indurated, irregular, painful ulcer covered by inflammatory exudates in patients of any age group but relatively more common in middle aged and elderly patients.[1]

The present communication describes a case of tuberculous ulcer at upper lip mucosa that had asymptomatic pulmonary tuberculosis also.

CASE REPORT

A 34-year-old male farmer presented with painful ulcer of upper lip mucosa for last one year. He had no other symptoms. He took several courses of multi-vitamins, anti-inflammatory agents (oral dexamethasone), antibiotics and local preparations such as boroglcerine, xylocaine with tannic acid, etc., but without any response. To begin with, ulcer was small and painless but gradually progressed in size and became painful. Patient was non-smoker non-alcoholic but tobacco chewer for last 10 years.

Physical examination revealed an ulcer at upper lip mucosa extending to the cheek on left side. The margins of ulcer were bluish and undermined with indurated pinkish white base (Fig. 1). There was slight serosangunious discharge. The general physical examination and other systemic examination were absolutely normal.

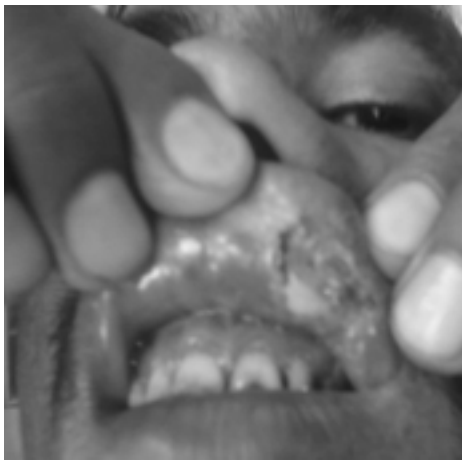

Figure 1: Photograph of patient showing typical tubercular ulcer over upper lip mucosa extending towards cheek.

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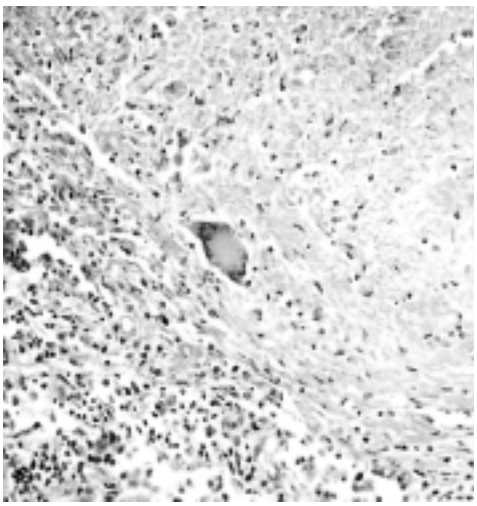

Figure 2: Photomicrograph of ulcer biopsy showing typical tubercular granulation tissue (H&E x 100).

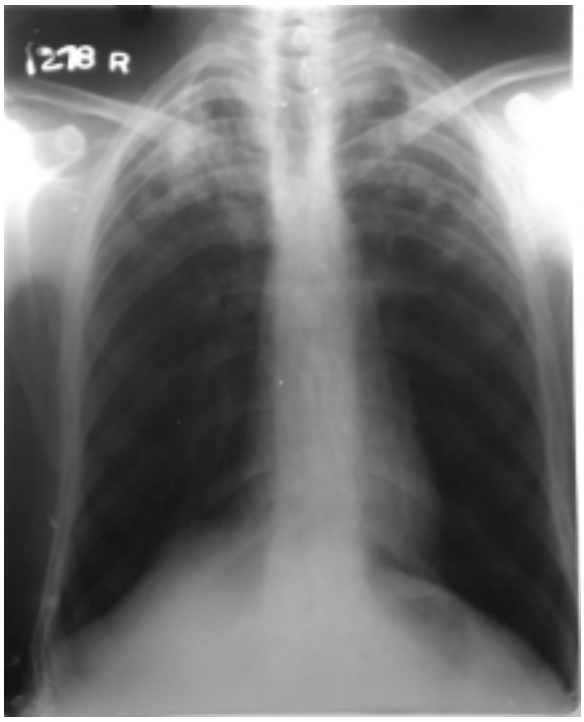

Figure 3: X-ray chest of patient showing bilateral inhomogenous infiltrates at upper and mid zones.

His investigations revealed hemoglobin 11.6 gm%, total leukocyte count 9800/ mm^3 (polymorphs 73%, lymphocytes 25%, eosinophils 1% and monocytes 1%), erythrocyte sedimentation rate 42 mm in first hour by Wintrobe's method and normal urine analysis. His blood biochemistry was normal and serological tests for VDRL and HIV were non-reactive. Oral saliva cytology was negative for any specific pathology and micro-organisms. Multiple biopsies from the ulcer revealed chronic granulomatous inflammation consisting of epitheloid cells, Langhan's giant cells, lymphocytes, plasma cells, macrophages with areas of caseation necrosis on histopathological examination (Fig. 2). With this unusual tissue diagnosis of the oral lesion, patient was subjected to rule out pulmonary tuberculosis. His chest X-ray showed bilateral inhomogeneous infiltrates in upper and mid zones (Fig. 3). Induced sputum was negative for acid-fast bacilli in three samples but Mantoux test revealed an induration of 30 mm with blister formation. Patient was started on Category I treatment under Revised National TB Control Programme as directly observed therapy. He has completed intensive phase therapy and both oral as well as pulmonary lesions are showing signs of improvement.

DISCUSSION

Tuberculous involvement of oral cavity is an extremely rare development, even in populations with high incidence of the pulmonary disease. Saliva is believed to have a protective effect, which may explain the paucity of tuberculous oral lesions, despite the large numbers of bacilli contacting the oral cavity mucosa in a typical case of pulmonary tuberculosis.[1,5,6] Other factors that attribute to relative resistance of oral cavity for tuberculosis are presence of saprophytes, resistance of striated muscles to bacterial invasion and thickness of protective epithelial covering.[7] It is believed that the organisms enter the mucosa through a small break in the surface. Local factor that may facilitate the invasion of oral mucosa includes poor oral hygiene, leukoplakia, local trauma and irritation by clove chewing, etc.[8] Self-inoculation by the patient usually results from infected sputum or by hematogenous or lymphatic dissemination.[9,10] In the present case,

patient had long history of tobacco chewing that might have caused minor breach in the oral cavity mucosa, and favoured the deposition of mycobacteria through infected sputum.

Oral tuberculosis may occur at any location on the oral mucous membrane, but the tongue is most commonly affected. Other sites include the palate, lips, buccal mucosa, gingiva, palatine tonsil and floor of the mouth. The oral lesions may present in a variety of forms, such as ulcers, nodules, tuberculomas and peri-apical granulomas.[9-11] The typical presentation is that of a single indurated painful ulcer with irregular borders covered by inflammatory exudates, but atypical cases with multiple lesions or asymptomatic ulcers have also been described.[9] Dimitrakopoulos et al reported two cases of primary oral tuberculosis that presented with painless ulceration of long duration and enlargement of the regional lymph nodes.[12] In the present case, patient presented with painful ulcer having bluish undermined edges and indurated pinkish white base at the upper lip mucosa that was extending towards cheek.

Oral cavity tuberculosis is difficult to differentiate from other conditions on the basis of clinical signs and symptoms alone. While evaluating a chronic, indurated ulcer, clinicians should consider both infectious process such as primary syphilis and deep fungal diseases and non-infectious processes such as chronic traumatic ulcer and squamous cell carcinoma. If there is no systemic involvement, one should go for excisional biopsy for tissue diagnosis and bacteriologic examination with culture for a definitive diagnosis.[11, 13]

The identification of a tuberculous lesion in any location in the mouth is an unusual finding and its discovery is usually indicative of underlying pulmonary disease. Therefore, in all cases of oral cavity tuberculosis, search for primary site of the disease should always be considered even in the absence of any signs and symptoms. This was true in our case also where pulmonary tuberculosis was asymptomatic. This helps not only in complete diagnosis but also in better patient management. All such cases should promptly receive anti- tuberculosis therapy because oral lesions pose a potential infectious hazard to dental personnel. Medical personnel are also at risk, as illustrated by the case of a physician who developed naso-labial infection after mouth-to-mouth resuscitation on a tuberculosis patient.[14] Practising infection control techniques can limit the threat posed to medical personel.[13]

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Indian J Tuberc 2008;55:54-55

SIXTY-SECOND NATIONAL CONFERENCE ON TUBERCULOSIS AND CHEST DISEASES: A BRIEF REVIEW

M.M. Singh[1], V.K. Dhingra[2] and K.K. Chopra[3]

The 62nd National Conference on Tuberculosis and Chest Diseases (NATCON 2007) was organized by the New Delhi Tuberculosis Centre under the auspices of the Tuberculosis Association of India (TAI) from 14th to 16th December, 2007. The venue of the Conference was auditorium of the Maulana Azad Medical College, New Delhi. Dr.V.K. Dhingra and his team worked hard to make the conference a grand success. The team worked under the advice and guidance of Dr. V.K. Arora, Chairman, New Delhi Tuberculosis Centre and Dr. M.M. Singh, Chairman, South East Asia Region (SEAR) of IUATLD.

Around 350 delegates attended the Conference. Due to financial constraints and paucity of time, the conference was organized at a short notice of three months.

The conference was inaugurated by the Hon'ble Union Health Minister Shri Anbumani Ramadoss. In the inaugural function, Dr.M.M.Singh, Vice-Chairman (OR), welcomed the Union Health Minister and the guests. After lighting the lamp, the key-note address was given by Dr. R.K. Srivastsava, Chairman, TAI and DGHS followed by address of Dr. S.P. Agarwal, President, TAI. Delivering his address, Dr. S.K. Katiyar, President of the Conference, highlighted the enormous global burden of tuberculosis with estimated 1.6 million deaths i.e. around 4400/day. He also stated that in India alone, around 0.37 million died of tuberculosis and the disease imposed a huge financial burden on the government. He also referred to social stigma due to the disease, problem of TB/HIV co-infection and drug resistant tuberculosis and impending threat of XDR-TB. He discussed about the other problems in the field of tuberculosis like need for newer diagnostics, methods like DNA finger printing, vaccine development, gene replacement therapy, immunomodulators, drug delivery system and threat of misuse of MDR strains as a weapon for bioterrorism and the important issue of development of new drugs for tuberculosis. He also stressed about improving teaching and training at undergraduate medical curricula. He also expressed his views about other respiratory diseases like COPD, Asthma and tobacco, smoking and also air pollution in the context of tuberculosis.

Dr. Anbumani Ramadoss then addressed the gathering. He exhorted that India accounts for 1/5th of the world TB cases and is a high burdened country. India has achieved 100% coverage under the DOTS/RNTCP Programme and appreciated the efforts of Central TB Division. He added that RNTCP is one of the successful programmes of his Ministry, however, he sounded that intensity of problem increases every year. He also desired that since BCG does not give 100% protective effect, a newer vaccine should be developed by our country. He also appreciated the working of the NGOs like TAI and other national institutes like NTI, Bangalore, TRC, Chennai, LRS Institute and New Delhi TB Centre. He desired that a strategy has to be planned, so that we achieve our goal in a foreseeable future, if not by 2015. He also released a book on tuberculosis written by Dr. V.K. Dhingra and a souvenir brought out on the occasion of the Conference. While releasing the Fact Sheets on Epidemiology of TB, ACSM, Smoking and XDR-TB, he commended the work of TAI.

Dr. V.K. Arora, Vice-Chairman, TAI read out the citations for various awards of TAI which were presented to the recipients by the Union Health Minister. The inaugural function ended with a vote of thanks by Dr. V.K. Dhingra, Organising Secretary of the Conference.

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1. Vice-Chairman (OR), TAI & Chairman, SEAR 2. Director, New Delhi Tuberculosis Centre & Organising Secretary, NATCON 2007 3. Deputy Director, New Delhi Tuberculosis Centre

The Scientific Programme Committee of the Conference had chalked out a very useful programme. Besides three prestious orations, five guest lectures and four panel discussions, there were 27 free papers presented and 35 poster presentations. Dr. P.K. Sen TAI Gold Medal Oration was delivered by Dr. L.S. Chauhan, DDG(TB), on the subject of "Drug Resistant Tuberculosis – RNTCP Response". Dr. Robert Koch-Ranbaxy Oration was delivered by Dr. S. Rajasekaran on the subject of "Challenges in Management of TB & HIV – Tambaram's experience". Lupin-TAI Oration was delivered by Dr. Prahlad Kumar on the subject of "Present status and Role of Medical Colleges for TB Control". A special appreciation award was given to the Secretary General, TAI, Shri S.C. Goyal. Meetings of the Standing Technical Committee and Secretaries of State TB Associations were held on 15th December, 2007. It was decided that President of the 63rd National Conference on Tuberculosis and Chest Diseases, which will be held jointly with SEAR-IUATLD Conference from 8th to 10th September, 2008, will be Dr. R.K. Srivastava, DGHS and Chairman, TAI.

NATCON 2007 held in New Delhi was an excellent package of academic, social and cultural feast. The hospitality offered by the Organising Committee was superb and the delicious food picked from the old Delhi were the highlights of the various lunches wherein different menu was served on different days.

In the Business and Concluding Session, the President of the Conference, Dr.S.K. Katiyar gave a brief resume of the Conference activities from the start till the conclusion of the Conference wherein it was highlighted that all the sessions were well attended and the younger workers were participating in large numbers. He also said that larger number of delegates should be enrolled for 2008 Conference. The delegates were informed that the First International Conference of South East Asia Region (IUATLD) and the 63rd National Conference on Tuberculosis and Chest Diseases will be held in New Delhi from 8th to 10th September, 2008. For further enquiries, delegates may contact TAI, Chairman, SEAR (IUATLD) Dr. M.M. Singh, Chairman, Organising Committee Dr. V.K. Arora and Organizing Secretary Dr. V.K. Dhingra. It was also decided that the Secretaries of State TB Associations will help in raising funds and making the Conference a grand success.

Under Rule 3 (xiii) of the Rules and Regulations of TAI, Drs. V.K. Dhingra, K.B. Gupta, S. Rajasekaran, Jai Kishan and K.K. Chopra were elected as representatives of the National Conference to serve on the Central Committee who will hold office till the next National Conference.

Dr. Prahlad Kumar proposed a vote of thanks on behalf of the delegates and Dr. V.K. Dhingra on behalf of the Organising Committee.

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Indian J Tuberc 2008; 55:56-60

ABSTRACTS

Reducing the number of sputum samples examined and thresholds for positivity

M. Bonnet, A. Ramsay, L. Gagnidze, *N.* Githui, P.J. Guerin and F. Caraine. *Int J Tuberc Lung Dis* 2007; **11(9):** 953-958.

The objective was to evaluate the impact on tuberculosis case detection and laboratory workload of reducing the number of sputum smears examined and threasholds for diagnosing positive cases. In this prospective study, three Ziehl-Neelsen stained sputum smears from consecutive pulmonary TB suspects were examined blind. The standard approach (A), ≥2 positive smears out of 3, using a cut-off of 10 acid-fast bacilli (AFB)/100 high-power fields (HPF), was compared with approaches B, ≥2 positive smears (≥4 AFB/100 HPF) out of three, one of which is ≥10 AFB/100 HPF; C, ≥2 positive smears (≥4 AFB/100 HPF) out of 3; D, ≥1 positive smear (≥10 AFB/100 HPF) out of 2; and E, ≥1 positive smear (≥4 AFB/100 HPF) out of two. The microscopy gold standard was detection of at least one positive smear (≥4 AFB/100 HPF) out of three. Among 644 TB suspects, the alternative approaches detected from 114 (17.7%) (approach B) to 123 cases (19.1%) (approach E) compared to 105 cases (16.3%) for approach A ($P < 0.005$). Sensitivity ranged between 82.0% (105/128) for A and 96.1 % (123/128) for E. The single positive smear approaches reduced the number of smears by 36% compared to approach A. Reducing the number of specimens and the positivity threshold to define a positive case increased the sensitivity of microscopy and reduced laboratory workload.

Ethambutol in paediatric tuberculosis: aspects of ethambutol serum concentration, efficacy and toxicity in children

S. Thee, A. Detjen, D. Quarcoo, U. Wahn and K. Magdorf. *Int J Tuberc Lung Dis* 2007; **11(9):** 965-971.

Ethambutol (EMB) is used as a fourth drug in paediatric anti-tuberculosis treatment. In current recommendations the dosage of EMB is calculated per kg body weight. The objective was to present two studies investigating an appropriate 3MB dosage in children, and observational data on its toxicity and efficacy. EMB serum levels in children of different age groups were determined after single oral administration of EMB alone as well as after EMB combined with rifampicin, and optimal dosages were established. The efficacy and toxicity of these EMB dosages were examined retrospectively. EMB serum levels were lower than those expected in adults receiving a similar oral dose, due to different pharmacokinetics and pharmacodynamics in childhood. Thereafter, children were treated with EMB doses calculated by body surface ($867/m^2$). Ocular toxicity occurred in 0.7% of cases and relapse in 0.8%. Current recommended EMB dosages in childhood tuberculosis lead to subtherapeutic serum levels. It appears to be more valid to calculate the EMB dosage on the basis of body surface rather than body weight, leading to higher dosages especially in younger children. With these dosages, therapeutic serum levels are reached in all age groups, leading to a high efficacy of anti-tuberculosis treatment without increased ocular toxicity.

Micro-nutrient supplements and mortality of HIV-infected adults with pulmonary TB: a controlled clinical trial

R.D. Semba, J. Kumwenda, E. Zijlstra, M.O. Ricks, M. van Lettow, C. Whalen, T.D. Clark, L. Jorgensen, J. Kohler, N. Kumwenda, T.E. Taha and A.D. Harries. *Int J Tuberc Lung Dis 2007; 11(8): 854-859.*

The aim of the trial was to determine whether daily micro-nutrient supplementation reduces the mortality of human immuno-deficiency virus (HIV) infected adults with pulmonary tuberculosis (TB). It was a randomized, controlled clinical trial of micronutrient supplementation for HIV-positive and HIV-negative adults with pulmonary TB. Participants were enrolled at the commencement of chemotherapy for sputum smear-positive pulmonary TB and followed up for 24 months. A

total of 829 HIV-positive and 573 HIV-negative adults were enrolled. During follow-up, 328 HIV-positive and 17 HIV-negative participants died. The proportion of HIV-positive participants, who died in the micronutrient and placebo groups was 38.7% and 40.4%, respectively (P = 0.49). Micronutrient supplementation did not reduce mortality (hazard ratio [HR] 0.93, 95%CI 0.75-1.15) among HIV-positive adults. Micro-nutrient supplementation at the doses used in this study does not reduce mortality in HIV-positive adults with pulmonary TB.

Evaluation of post-treatment health-related quality of life (HRQoL) among tuberculosis patients

M. Muniyandi, R. Rajeswari, R. Balasubramanian, C. Nirupa, P.G. Gopi, K. Jaggarajamma, F. Sheela and P.R. Narayanan. *Int J Tuberc Lung Dis* 2007; **11(8)**: 887-892.

Health-related quality of life (HRQoL) measures the impact of a disease by assessing the health status of patients. The objective was to assess the HRQoL of tuberculosis (TB) patients one year after treatment completion. Patients registered under the TB control programme from July 2002 to June 2003 in a TB Unit in South India were interviewed one year after successful completion of treatment. Data on HRQoL were collected using the SF-36 questionnaire, which covers physical, mental and social well-being components. Data on economic well-being were also collected. Scores were given for all domains. Of 436 TB patients interviewed, the mean scores for social, physical, mental and economic well-being were respectively 84, 74, 68 and 62 on a scale of 100. The well-being scores were significantly related to age, sex, education, employment and persistent symptoms. There was a significant association between economic and social well-being. This study suggests that the HRQoL of TB patients one year after successful completion of treatment under the TB control programme was normal for most of the domains studied and was associated with age, literacy and employment, income, smoking, alcoholism and persistence of symptoms.

Is it valuable to examine more than one sputum smear per patient for the diagnosis of pulmonary tuberculosis?

Aydan Oszkutuk, Gulfem Terek, Huseyin Coban and Nuran Esen. *Jpn J Infect Dis* 2007; **60:** 73-75.

The simplest, cheapest, and fastest diagnostic method for tuberculosis is the detection of acid-fast bacilli by microscopy. The algorithm advised for the diagnosis of TB recommends examination of three consecutive sputum specimens from TB suspects for the presence of AFB. In the present study, we evaluated the contribution of each specimen to the final detection of TB suspect patients with culture-proven disease. The collection and analysis of retrospective data on patients with culture-proven pulmonary TB, from June 2002 to August 2006, at Dokuz Eylul University Hospital, Turkey, have enabled us to assess the value of examining two sputum specimens in diagnosing this disease. AFB were detected from one or more sputum specimens with direct microscopy in 42% of the cases. An analysis of results of smear examination showed that 97% of AFB were detected from the first specimen and only 3 % were obtained from the second smear. The third specimen did not have any additional diagnostic value for the detection of AFB by microscopy. As a conclusion the present study shows that examining two sputum smears is sufficient for the early detection of AFB in our laboratory.

Comparison of the tuberculin skin test and the quantiferon test for latent *mycobacterium tuberculosis* infections in health care workers.

D. Ozdemir, A.N. Annakkaya, G. Tarhen, I. Sencan, S. Cesur, O. Balbay and E. Guclu. *Jpn J InfectDis* 2007; **60**: 102-105.

Aim of this study was to compare the efficacy of the tuberculin skin test (TST) and the quantiferon test (QFT) for detecting latent tuberculosis infection (LTBI) in health care workers (HCWs). Seventy-six participants who were working in Duzce University Hospital, where tuberculosis patients were being treated, were included in the study. TST was performed according to the Mantoux technique. QFT was performed in accordance with the manufacturer's instructions. A

positive TST result was defined as an induration diameter of ≥ 15 mm. TSTs were positive in 41 of 76 participants (53.9%) and QFT was positive in 65 of 76 participants (85.5%). There was a significant difference between the numbers of QFT- positive and TST-positive cases *(P* = 0.02). When the induration diameter of TST was ≥20 mm, QFT positivity was 100%. Multivariate analysis revealed that there was a significant correlation between the percentage of patients with QFT positivity and the induration diameter of TST *(P* = 0.009). QFT thus seems to be more effective for LTBI diagnosis than TST. However, large-scale trials including quantitative measurement of QFT in subgroups taking into account the division where HCWs are employed and the different results of TST might clarify the usefulness of QFT in LTBI diagnosis

Correlation of sputum culture with serology against *Mycoplasma pneumoniac* in patients with bronchial asthma

Rameshchandra Sahoo, K. Vishak Acharya, M. Shalini Shenoy, R. Anand and Rama Keshava Reddy. *Indian J of Chest Dis & Allied Sci* 2007; **49(4):**209-212.

Mycoplasma pneumoniae is implicated in acute exacerbations of bronchial asthma and is also a factor in chronicity of asthma. We attempted to isolate *M. pneumoniae* in sputum specimen samples by culture technique and also by serological estimation of immunoglobulin (lgM, IgG) antibodies against *M. pneumoniae* by enzyme linked immunosorbent assay (ELISA) in 100 patients with bronchial asthma and 50 subjects without asthma who served as controls. *Mycoplasma pneumoniae* was isolated by sputum culture in 17% of patients with asthma and in none of the control subjects. Immunogloublin (lgG / IgM) antibodies against *M. pneumoniae* were found in 37% of patients with asthma and 6% of control subjects. On correlating culture with serology, it was found that 15% patients were both culture and seropositive, 2% patients were culture positive but seronegative, 22% patients were culture negative but seropositive while 61 % patients were both culture and seronegatives. The sensitivity and specificity of culture were 73.5% and 88.2%, respectively. For the serological method, sensitivity and specificity were 88.2% and 73.5%, respectively. Use of a combination of sputum culture and serological methods are reliable investigational tools for the diagnosis of *M.* pneumoniae infection. The significant association observed between *M. pneumoniae* and bronchial asthma justifies the inclusion of antibiotics, such as the macrolides, in treating these patients.

Interleukin-12B and interleukin-l0 gene Polymorphisms in pulmonary tuberculosis

S. Prabhu Anand, P. Selvaraj, M.S. Jawahar, A.R.Adhilakshmi and P.R. Narayanan. *Indian J MedRes* 2007; **126**: 135-138.

Cytokines play an important role in anti-tuberculosis immune response. Skewing of immunity from protective to pathogenic may involve a shift in Th1- Th2 paradigm. Cytokine gene polymorphism is known to be associated with functional differences in cytokine regulation and altered clinical performance in a variety of diseases. The aim of this study was to know whether Interleukin-12B 3' UTR (Taql) (A/C) and Interleukin-10 (-1082 G/A) gene polymorphisms were associated with susceptibility to pulmonary tuberculosis. IL -10 (-1,082 G/A) and IL-12B gene polymorphisms were studied in 132 pulmonary TB (PTB) patients and 143 normal healthy subjects (NRS), using DNA based polymerase chain reaction (PCR) with sequence specific primers and restriction digestion. The allelic as well as genotypic frequencies of Interleukin -10 (-1082) and Interleukin -12B (3'UTR Taq 1) did not differ significantly between the patients and controls. Our findings suggested that IL -10 (-1082 G/A) and IL -12B 3'UTR (Taq I) (A/C) gene polymorphisms were not associated either with susceptibility or resistance to pulmonary tuberculosis in the south Indian population.

Association of mycobacteria wih Eales' disease

K.L. Therese, P. Deepa, J. Therese, R. Bagyalakshmi, J. Biswas and R.N. Madhavan. *Indian J Med Res* 2007; **126**: 56-62.

Eales' disease is an idiopathic disease resulting in retinal neovascularization, recurrent haemorrhages, with or without retinal detachment predominantly affecting healthy young males (97.6%) in the Indian subcontinent. In spite of several studies, the aetiology of Eales' disease is not clear. The isolation

of *Mycobacterium fortuitum* from the aqueous humour of a patient with classical Eales' disease, led us to hypothesize that rapid growing non-tuberculous mycobacteria (RGNTM), particularly *M. fortuitum* and *M. chelonae* could be associated with Eales' disease. We, therefore, undertook this study to detect DNA of these RGNTM and also of *M. tuberculosis* in vitreous fluids (VFs) from patients with Eales' disease and non-Eales' disease. We developed and optimized seminested polymerase chain reactions (SnPCRs) to detect DNAs of *M. fortuitum* and *M. chelonae* on archival ERMs (33) and VFs (19) of Eales' and control patients along with conventional mycobacteriological investigations. In this retrospective study, 70 per cent ERM samples were positive for one or more *Mycobacterium spp.* tested by snPCR. *M. fortuitum* and *M. chelonae* were isolated from two VFs, which were also positive by sn PCR in the prospective study. Statistical evaluation of the results of both retrospective and prospective investigations showed a statistically significant association of *Mycobacterium spp.* with Eales' disease. The results of the present study suggested the involvement of *mycobacterium spp*. in the aetiopathogenesis of Eales' disease. Further studies on a larger sample will be required to confirm these findings.

Molecular typing of *Mycobacterium tuberculosis* isolates from different parts of India based on 1S6110 element polymorphism using RFLP analysis

D.S. Chauhan, V.D. Shanna, Deepti Parashar, Aradhana Chauhan, D. Singh, H.B. Singh, R. Das, B.M. Aggarwal, B. Malhotra, Amita Jain, Meera Shanna, V.K. Kataria, J.K. Aggarwal, Mohamad Ifanif, Aruna Shahani and V.M. Katoch. *Indian J Med Res* 2007; **125**: 577-581.

IS 6110 based typing remains the internationally accepted standard and continues to provide new insights into the epidemiology of *Mycobacterium tuberculosis.* The aim of the study was to characterize *M tuberculosis* isolates obtained from different parts of India based on IS 6110 element polymorphism using restriction fragment length polymorphism (RFLP) analysis. RFLP was analyzed among 308 isolates of *M. tuberculosis* deposited in the Mycobacterial Repository Centre, Agra, from different parts of India. DNAs isolated from these strains were restricted with Pvu II, transferred on to nylon membrane and hybridized with a PCR amplified DIG-labelled 245 bp IS6110 probe. Based on the copy number, *M. tuberculosis* isolates were classified into four groups, *(i)* lacking IS6110 element (*ii)* low copy number (1-2); *(iii)* intermediate copy number (3-5); and *(iv)* high copy number (6-19). Copy number higher than 19, however, was not observed in any of the isolates studied. At the national level, 56 per cent of the isolates showed high copy number of IS6110, 13 per cent showed intermediate copy number, 20 per cent showed low copy number, whereas 11 per cent isolates lacked IS 6110 element. At the regional level, there was not much difference in the RFLP profiles of isolates (IS 6110 copy numbers/patterns) from different parts of the country. IS 6110 DNA based finger printing could be a potentially useful tool for investigating the epidemiology of tuberculosis in India.

Urine levels of rifampicin and isoniazid in asymptomatic HIY-positive individuals.

Geetha Ramachandran, A.K. Hemanth Kumar, K. Sarala, C. Padmapriyadarsini, S. Anitha, C.B. Tharani, V Kumaraswami and Soumya Swaminathan. *Indian J Med Res* 2007; **125**: 577-581.

AIDS and its associated gastro-intestinal complications may impair the absorption of anti-tuberculosis (TB) drugs. Impaired absorption of anti-TB drugs could lead to low drug exposure, which might contribute to acquired drug resistance and reduced effectiveness of anti- TB treatment. The aim of this study was to obtain information on the status of absorption of rifampicin (RMP) and isoniazid (INH) in asymptomatic HIV-positive individuals, who are less immuno-compromised. The D-xylose absorption test was also carried out to assess the absorptive capacity of intestive. The absorption of RMP, INH and D-xylose was studied in 15 asymptomatic HIV-positive individuals with CD4 cell counts >350 cells/mm^3 and 16 healthy volunteers, after oral administration of single doses of RMP (450 mg), INH (300 mg) and D-xylose (5 g). Urine was collected up to 8 h after drug administration. Percentage dose of the drugs and their metabolites and D-xylose excreted in urine were calculated. A

significant reduction in the urinary excretion of INH and D-xylose in HIV-positive persons compared to healthy volunteers was observed. The per cent dose of RMP and its metabolite, desacetyl RMP was also lower in HIV-positive persons compared to healthy volunteers, but this difference was not statistically significant. Decreased urinary excretion of D-xylose and INH are suggestive of intestinal malabsorption in HIV-positive individuals. HIV infection could cause malabsorption of anti- TB drugs even at an early stage of the disease. The clinical implications of these findings need to be confirmed in larger studies.

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