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Editorial

TB AND DIABETES – THE DUAL EPIDEMIC: IS IT A MATTER OF CONCERN?

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Non-communicable diseases (NCDs) such as diabetes mellitus, cardiovascular diseases including stroke, cancer and chronic obstructive lung disease have emerged as the leading cause of death and disability worldwide and these diseases have gradually emerged as the global epidemic of the twenty-first century. These are predicted to be the cause of death in over three-fourth of global deaths by 2030[1]. WHO estimated that 285 million people were living with diabetes mellitus (DM) in the year 2010, of whom seven million people developed the disease during that year and 3.9 million died of that disease[2,3]. This number increased alarmingly from 153 million in 1980 to 347 million in 2008, according to a global analysis involving 199 countries and 2.7 million persons[4]. It is predicted that the prevalence of diabetes will be between 439 million and 472 million by 2030 and 80% of these cases will be prevalent in developing countries[5-7]. The world prevalence of diabetes among adults between ages 20-79 years was 6.4% and that will increase to 7.7% by the year 2030. Between 2010 and 2030, there will be a 69% increase in number of adults with DM in developing countries and a 20% increase in developed countries[2]. Although diabetes is a global epidemic, Asia is the epicentre of this increase in number[4,8]. India and China are, and will be, the two countries with the highest number of diabetes mellitus patients with 40% of the total burden (138 million in 2008). India is considered as the "diabetes capital' of the world. An earlier national survey in India reported age standardized prevalence of DM and impaired glucose tolerance to be 12.1% and 14% respectively, with no gender difference[9]. This showed increasing trend with age. A subsequent national non-communicable disease risk factor surveillance conducted in different geographical locations in India between 2003-2005 with a total of 44,523 individuals (15-64 years) revealed that self-reported DM in rural areas was 3.1%, followed by peri-urban/slum (3.2%) and the same was 7.3% for urban areas[10]. It is estimated that in 2010, the prevalence of diabetes was 7.1% in 2010 that will be 8.6% in 2030 adjusted to national population. The number of adults with DM in 2010 was 50.768 million that will increase to 87.036 million in 2030[2]. However, a recent estimate in 2011 multi centric study reported that of the 16,607 individuals selected for the study, 14,277 (86%) participated, of whom 13,055 gave blood samples. The weighted prevalence of diabetes (both known and newly diagnosed) was 10.4% in Tamilnadu, 8.4% in Maharashtra, 5.3% in Jharkhand, and 13.6% in Chandigarh. The prevalences of prediabetes (impaired fasting glucose and/or impaired glucose tolerance) were 8.3%, 12.8%, 8.1% and 14.6% respectively[11]. Multiple logistic regression analysis showed that age, male sex, family history of diabetes, urban residence, abdominal obesity, generalised obesity, hypertension and income status were significantly associated with diabetes. Significant risk factors for prediabetes were age, family history of diabetes, abdominal obesity, hypertension and income status. Maharashtra will have six million individuals with diabetes and 9.2 million with pre-diabetes, Tamilnadu will have 4.8 million with diabetes and 3.9 million with pre-diabetes, Jharkhand will have 0.96 million with diabetes and 1.5 million with pre-diabetes, and Chandigarh will have 0.12 million with diabetes and 0.13 million with pre-diabetes. Projections for the whole of India would be 62.4 million people with diabetes and 77.2 million people with pre-diabetes.

Population growth, ageing, global shift towards a western lifestyle of unhealthy eating and physical inactivity are attributable to this increase in the number of diabetes cases in the world as a whole.

There were an estimated 8.8 million incident cases of TB (range, 8.5 million–9.2 million) globally in 2010, and 1.1 million deaths (range, 0.9 million–1.2 million) among HIV-negative cases of TB and an additional 0.35 million deaths (range, 0.32 million–0.39 million) among people who were HIV-positive. Although globally, the absolute number of incident TB cases per year has been falling since 2006 and the incidence rate (per 100 000 population) has been falling by 1.3% per year since 2002[12], this is rather slow. In India, the prevalence is about 3.1 (2.0–4. 6) million with a rate of 256 (161–373) per 100,000 population and the incidence is 2. 3 (2.0 –2. 5) with a rate of 185 (167–205) per 100,000 population (*these* ranges represent uncertainty intervals*).

Thus, the global burden (also India) of both DM and tuberculosis is huge. While about 95% of the tuberculosis patients live in the developing world (21% in India), 70% of the DM patients also live in developing countries, mainly in the South-East Asian and Western Pacific countries. There is growing evidence that these two diseases are connected and therefore, is it a matter of concern?

Of many risk factors for tuberculosis including HIV/AIDS, malnutrition, silicosis, smoking, immune-suppression, alcohol, crowded living conditions, and indoor air pollution, diabetes is considered as one of the important ones. The association of the two diseases has been shown since Roman times and more recent unequivocal evidence has shown a strong association between the two[13]. A systemic review, using Pub Med and EMBASE databases from 13 studies reported that DM is associated with an increased risk of tuberculosis[14]. In the three cohort studies analyzed, while the relative risk of tuberculosis in patients with diabetes was found to be 3.1 (95% CI 2.27-4.26), the case-control studies found the odds ratios ranged from 1.16 to 7.83. The risks were higher in younger people and in countries with a high background incidence of tuberculosis. Another Medline search involving studies published after 1995, found an increase in risks or odds for tuberculosis in patients with DM ranging from 1.5 to 7.8[14]. Prospective studies have also supported this hypothesis[15]. As per report from India, in 2000, DM accounted for nearly 15% of pulmonary TB cases and 20% of smear-positive cases[16]. However, it is not clear whether DM has any effect on tuberculosis case notifications or estimated case numbers at country level. TB infection may progress at a faster rate in people with diabetes than in those without diabetes[13-16]. The clinical presentation of TB in people with diabetes may be altered and change the sensitivity and specificity of conventional diagnostic algorithms. A large proportion of patients of DM will have lower lung involvement, in contrast to patients without diabetes, who will have upper lobe disease. However, many unanswered questions still remain, including the influence of poor glycemic control on death and recurrence of tuberculosis, the timing and etiology of death in diabetes patients, the reasons for recurrent disease, and interventions that may reduce the frequency of these adverse events. These questions can be answered with certainty through prospective rather than retrospective studies. The association of diabetes and tuberculosis is supported by the fact that DM patients have impaired cell-mediated immunity, renal failure, micronutrient deficiency and pulmonary microangiopathy, all of which can predispose to the development of tuberculosis. DM affects innate and adaptive immune responses, and poor diabetes control affects *in vitro* innate and cell mediated immune cytokine response[17]. Among those with active TB, diabetes may adversely affect TB treatment outcomes by delaying the time to microbiological response, reducing the likelihood of a favourable outcome, and increasing the risk of relapse or death[18]. Patients with diabetes have a risk ratio for the combined outcome of failure and death of 1.69 – 4.95. Diabetes is also associated with an increased risk of relapse (RR 3.89). Diabetes may also accelerate the emergence of drug-resistant TB, especially multidrug-resistant TB among those receiving TB treatment, although the evidence is limited[18]. Studies assessing sputum culture conversion after two to three months of anti-tubercular therapy are heterogeneous with relative risks varying between 0.79 and 3.25. DM thus, appears to increase the risk of tuberculosis.

Conversely, tuberculosis may trigger the onset of diabetes, and worsen glycemic control in existing diabetes like any other chronic infection. Data presented in the recently held National Stakeholders Seminar

on tuberculosis-diabetes mellitus, at New Delhi from 11th-12th October, 2011, showed that in Kerala the prevalence of Diabetes in patients with tuberculosis was as high as 45%, although there were methodological issues. Finally, TB medications may interfere with the treatment of diabetes through drug interactions, and diabetes may interfere with the activity of certain anti-TB medicines. Rifampicin may have hyperglycemic effect as a result of direct and indirect interactions with oral hypoglycemic drugs[19]. Uncontrolled diabetes can eventually lead to renal impairment and an increased risk of drug toxicities. Hepatotoxicity of anti-tubercular drugs is increased in diabetes patients, eventually increasing the risk of adverse treatment outcomes[20].

Over the past two decades, national TB control programmes worldwide have implemented TB control through DOTS and the Stop TB Strategy with evident success, including substantial increase in rates of case detection and improved treatment outcomes[12]. However, improvements are still needed to tackle some of the important issues. Countries must ensure complete and early case detection of all types of TB. During 2005-2009, the global TB case detection rate stagnated at around 60%[21], although recent WHO reports showed reduction in the incidence, prevalence and mortality[12]. In many countries, these rates are even lower, and long delays for diagnosis and treatment still occur in most countries further aggravating transmission. Case detection of smear-negative TB and of multidrug resistant-TB also must be substantially improved. While the rate of treatment success globally has surpassed the target of 85%, treatment outcomes are suboptimal in many settings and for some subpopulations. Where adverse treatment outcomes are frequent, reasons may include poor adherence to treatment, high prevalence of drug-resistance and/or vulnerability related to co-morbidities such as HIV, under-nutrition, substance dependency, tobacco smoking-related conditions, and if diabetes is associated with tuberculosis, the outcome will be still worse and the management becomes difficult. As mentioned, even if the rates of incidence, prevalence and death from TB are decreasing globally, the rate of decline is much slower than forecast. Given this slow rate of decline, the Millennium Development Goal target of halving TB prevalence and TB death rates by 2015, compared with their levels in 1990, may not be met in all WHO regions. Furthermore, the world as a whole, as well as in most regions, are far from the trend required to reach the long-term rates of eliminating TB (defined as less than one incident case of TB per one million population by (2050). Additional interventions are therefore required to meet the goals for TB control and elimination. Most urgently, this should involve further efforts to improve TB case detection and treatment outcomes, with the ultimate aim to get as close as possible to 100% case detection rate and treatment success rate. India as country has set a goal to detect 90% of all cases of tuberculosis and to achieve a treatment success rate of 90% during the coming 12th five year plan. With such a huge burden of diabetes and tuberculosis (syndemic of TB and DM), this becomes more challenging. Moreover, new tools for TB diagnosis, prevention and treatment are needed. Additional efforts should also include prevention by intervening on known social determinants and risk factors of TB that include diabetes mellitus.

Thus there is an urgent need for synergies of collaborative activities between the two problems. The link between diabetes and TB has potential additional implications for all the above-mentioned challenges to TB control. First, given that people with diabetes are at higher risk of TB, screening for TB in people with diabetes may be warranted in populations with high TB prevalence to help improve early case detection. Second, because diabetes may increase the risk of adverse treatment outcomes in TB patients, special attention may be needed to ensure high-quality TB treatment in people with diabetes. This requires screening for diabetes among people with TB in settings where under-diagnosis of diabetes is common. Third, broad primary and secondary prevention of diabetes will help prevent TB at the population level. Finally, TB preventive therapy could be potentially indicated in people with diabetes who have had recent exposure to TB.

Improved collaborative activities would also potentially improve care and prevention of diabetes. Under-diagnosis of the disease is common in low-income and middle income countries, and could be improved by screening people with TB for diabetes. Management of diabetes must be optimized in general and in particular

during TB disease, as during all types of infections. Improved management of diabetes could build on the successes of the DOTS strategy, emphasizing support to patients and supervision of their treatment; standardized protocols, a reliable supply of quality-assured medicines, regular monitoring and evaluation, and management and administrative procedures; as well as political commitment.

An important step to handle and fight against tuberculosis and diabetes has been the development of a WHO-Union (International Union against Tuberculosis and Lung Diseases) Framework for Collaborative activities to guide policy makers and implementers in reducing the dual burden of DM and TB[22]. The WHO gave clearance to develop a framework rather than Guidelines due to lack of strong evidence to support some of the suggested interventions. The Framework essentially consists of three components: (A) To establish the mechanisms of collaboration through setting up means of co-ordinating DM and TB activities, to conduct surveillance of TB disease prevalence in patients with DM in medium and high burden settings, to conduct surveillance of DM prevalence in TB patients in all countries, and to conduct monitoring and evaluation of DM and TB activities; (B) To detect and manage TB in DM patients through intensive detection of TB disease among DM patients, to ensure TB infection control in health care settings where DM is managed and to ensure high quality TB treatment and management in people with DM; (C) To detect and manage DM in patients with TB by screening TB patients for DM, to ensure high quality DM management among TB patients[23-26]. The management of chronic non-communicable diseases like DM is poor in most resource-limited settings, and the 'directly observed therapy, short course' (DOTS) frame work for tuberculosis control has been proposed as a feasible way to improve this situation. This DOTS model is already being tried in Malawai and seems to be working[27].

While there may be a sound argument for combating both the diseases to have better control of both in a co-ordinated and collaborative fashion, certain amount of caution will be required. It must be realized that while tuberculosis is a curable disease and the treatment is over within few months, diabetes is non-curable and requires life-long treatment, and the management is rather complex with possibility of many system involvement requiring specialized care. Then comes the question of smooth handing over of the patient of DM to the physician/endocrinologist after tuberculosis is treated and the patient is assured of treatment of diabetes with insulin or other oral hypoglycemic agents. Of course, with introduction of the Non-Communicable Diseases Control programmme in the country, this will be easier. We need to have prospective studies to generate data in the country about TB in DM and DM in TB. Action is already being started in Kerala State, the Revised National Tuberculosis Control Programme has already initiated screening of TB patients for DM and is assessing its effect on TB treatment outcomes under routine programme conditions as mentioned earlier. Some data is also available from Tamilnadu. This can be taken up as an important operational research topic with common protocol representing the whole country. While there is a case for such a collaboration and one can work out the modalities, the focus/attention should not be diluted or diverted from our basic DOTS or DOTS-Plus strategy.

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TUBERCULOSIS – CHALLENGES AND OPPORTUNITIES*

R. C. Jain**

Tuberculosis (TB) is a disease that physicians have recognized and grappled with for thousands of years. The disease in the beginning was considered incurable. Our ancient scripture – Atharveda (400 BC) counsels "The physician, who values his reputation, should not undertake to take care of a patient, who has three great symptoms – fever, cough and bloody sputum".

Tuberculosis has been a disease of challenges since long. Initial challenges were what is the cause of disease, how to prevent the disease and what is the effective treatment. Mankind has always liked challenges. Physicians, microbiologists, scientists and philanthropists in every country joined hands to meet the challenges thrown by the disease.

Beginning of the success story

Success story started with discovery of tubercle bacillus in 1892 by Robert Koch, followed by development of BCG vaccine for prevention in 1922. After 60 years of discovery of tubercle bacillus, Schatz, Bugie and Waksman published their papers on streptomycin, heralding a reliable cure for TB. Discovery of streptomycin in 1944 and other anti-tuberculosis drugs for effective cure followed next to get over the disease. In one decade, from 1944-1954, the prognosis for an individual with TB changed from dismal to expectation of cure. Implementation of National Tuberculosis Control Programme in 1962 with the development of strategy of prevention, treatment and health education heralded the beginning of an effective control measure in India.

In pre-chemotherapeutic era, everybody thought that effective drugs were the answer to all the problems of TB. After the discovery of drugs, TB workers and public took it as granted that TB is cured and controlled and it would not be a problem at all. But drugs had also opened a Pandora's box of problems like patients stopping the drugs prematurely, non-availability of drugs, drug resistance, lack of knowledge, etc.

GOVERNMENT INITIATIVES

Government took the problem of tuberculosis seriously and opened sanatoria, hospitals, clinics, Non Governmental Organizations, accepted BCG vaccination as national policy, conducted National Sample Survey, opened research institutions and started the National TB Programme, etc.

National Tuberculosis Control Programme

Government took a strong initiative for control of tuberculosis and launched National Tuberculosis Programme (NTP) in 1962. Our programme was quite effective. Various countries followed our programme and succeeded initially and then failed. We also succeeded but later on our programme also failed. Why we failed? The main cause of NTP failing was complacency and lack of resources, especially financial. We knew the problems, drawbacks and shortcomings of our programme but adequate funds were not available to sort them out on a national level. India was the first country to advocate supervised chemotherapy but could not implement it because of financial crunch. There was a boon in disguise in the form of resurgence of TB in the US in eighties. A strong feeling developed amongst the rich countries and international agencies like IMH, WHO and other international agencies to start DOTS strategy. Accordingly, our programme was also renamed as RNTCP (Revised National Tuberculosis Control Programme).

Revised National Tuberculosis Control Programme

Revised National Tuberculosis Control Programme was introduced in 1993 after a review of

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our national programme in 1992 by national, WHO and SIDA experts. I have an honour to be Head of Review Committee that visited South India and was closely associated with DOTS strategy and RNTCP. Implementation of DOTS was the best strategy which could have happened to our TB programme. RNTCP, by and large, is a success story as a public health strategy and has been able to achieve 70% case detection rate with over 85% cure rate at national level and is sustaining it.

Challenges

Our own experience and the success of RNTCP have thrown a large number of challenges.

International Agencies funded programme

DOTS strategy is a foreign-funded and expensive programme. Foreign funds may not be available forever. A strong political will needs to be developed so that adequate funds are provided to RNTCP in such an eventuality, otherwise the programme will collapse. Researchers and scientists should develop some alternative strategies and ways which are less expensive with same success. I am sure we have the capabilities to do it as we have given the world the concepts of 'Domiciliary treatment' and 'Supervised therapy'. It is hoped that our national and state research institutions and all other TB workers will accept this challenge.

Rapid programme expansion

It is good that programme could be expanded rapidly by March 2006 to cover the entire country. Rapid expansion has outpaced the capacity of national and state health authorities to supervise the programme and to maintain high quality. It has led to decline in case detection and cure rate in some areas. So efforts are needed to reverse decline in case detection and cure rates in those areas.

Achievements and success

The programme has been able to achieve 70% case detection rate and 95% cure rate. It is a noteworthy achievement and needs to be applauded. But these achievements and success need to be sustained and maintained. To have an impact an epidemiology of TB, programme needs to maintain and sustain high case detection and success rate for decades. Complacency has no place in TB programme. The example is before us, we have recently seen resurgence of TB and drug resistant TB in US because of complacency. Remember, our NTP also did well for 15-20 years but then complacency set in and the programme started failing. So we must learn from our mistakes. Therefore the challenge is to continue and sustain full commitment and enthusiasm in TB workers. It is easily said, but difficult to fulfill. It would be a real challenge for administrators and managers of the programme to sustain the success.

Defaulters

Defaulters are a serious problem in TB control and are persisting in RNTCP also. Default rate in new sputum positive (NSP) patients is of an order of 7% and amongst the retreatment cases, it is 16%. It is not acceptable because the retreatment cases have amongst them MDR and XDR cases – a serious threat to control of TB. So default rate of 16% is quite high and not acceptable. The challenge is to reverse the default rate for which strengthening of default retrieval system is a must. There has been some improvement in default retrieval recently, as default rate in 2007 in retreatment and NSP cases is 14.9% and 6% respectively but is still high.

Relapse

No figures are given of relapse rates under RNTCP, an important parameter of success. It is hoped that necessary infrastructure changes may be made to have this important information.

CHALLENGES OF DRUG RESISTANT TUBERCULOSIS

MDR and XDR-TB are serious forms of TB. Management of MDR-TB is difficult, much expensive, challenging and quite often leads to failures. Not only that MDR is a potential threat to control of TB, it is full of challenges starting from diagnosis to treatment, drug delivery, etc.

Early and reliable diagnosis of resistant tuberculosis

Patients of MDR and XDR-TB are diagnosed very late, due to which resistance to a large number of drugs develops, making treatment difficult. Main reason for late diagnosis is lack of mycobacteriology laboratories in the neighbourhood which can perform culture and susceptibility testing with reliability. The challenge is establishing quality assured laboratories for diagnosis and monitoring of MDR-TB. We must have a wide network of such laboratories all over the country. It also requires trained manpower and specialized equipment which are also not available presently at many laboratories.

Treatment of MDR and XDR TB

Second line drugs are less potent, more toxic and very costly. These are required to be given for about two years. Providing daily DOTS of drugs which can have severe adverse reactions, for a period of two years is a real challenge for DOT provider. Not only that, DOT provider should possess social skills to maintain patients on such a prolonged treatment with repeat motivation. Defaulter retrieval mechanism needs to be strengthened.

Challenges in rural area

In rural areas, problems are quite different. In rural area, the DOT provider should be able to give intramuscular injection nearer to the patient's residence. DOTS centre should not be established far away from the residence of the patient. DOT provider should be able to manage adverse reactions and should have skills to motivate patients to complete treatment. It may not be easy to find such a DOT provider in rural areas.

Drug Delivery

Availability of uninterrupted supply of quality assured drugs would be a challenge in resistant TB as shelf life of some drugs is less than the treatment duration. Patient-wise boxes are not possible because of long duration of treatment and the number of drugs. So packing of drugs, transporting to the field, handing it over to the DOT provider and ultimately to the patients require constant supervision and monitoring at every step. It is not easy, but a real challenge.

TB and HIV Co-infection

TB is the single largest killer of AIDS patients in India. Worrying points are HIV continues to spread AIDS and TB epidemic in new wave countries like India, South Africa, etc. MDR and XDR TB strains if mixed with HIV- the combination is lethal. Challenge is that RNTCP should be able to reverse the increases to TB burden due to HIV spread.

Information, Education and Communication (IEC)

Still there is an appalling ignorance and superstition about the disease, its spread and causation etc. even in those areas where DOTS is being provided. So it may become difficult to sustain cure rate of over 85% and case detection at 70% of estimated cases. Default rate may also increase due to ignorance about the disease among patients. There is a dire need for creating awareness so as to remove myths about TB. Not enough is being done in this respect under RNTCP. This is only possible with enhanced IEC activities by providing pamphlets, booklets in simple language with photographs to each and every general patient and public who are attending DOTS Centres. There should be a small photo session of IEC at DOTS Centres and also use of other means like TV, Radio, etc. for IEC.

Diagnosis of TB

It is important to diagnose TB as early as possible. In most of the countries, the approach to diagnosis has not changed much in a qualitative sense in the past 100 years. Clinical suspicion, chest radiographs, staining for acid fast organisms and culture for mycobacteria from sputum specimens together form the diagnostic armamentarium available.

Current approaches to diagnosis have significant cases undetected. Sputum smear examination can detect only 50% of cases. This means under diagnosis. For individuals with smear negative disease, reliance on smear examination means that they

will go undiagnosed for longer periods which may lead to more morbidity if not more mortality from tuberculosis. Molecular epidemiology techniques have shown that even smear negative cases contribute significantly to transmission of disease. TB in children and extra pulmonary TB are also difficult to diagnose. We have ignored culture which as a matter of fact should be done from day one and susceptibility studies on initial isolates for R & H or at least R in order to detect serious forms of primary resistance which is of the order of 3%-4%. Culture will also improve the diagnostic yield.

The challenge is to develop an ideal diagnostic test for active TB that should have the following characteristics : Rapid (result available within a day), high sensitivity and specificity, inexpensive, robust (i.e. able to provide reproducible results in a variety of settings), highly automated (or not requiring a great deal of sample preparations or highly technically trained personnel), able to provide drug susceptibility data, and a test should be able to differentiate latent infection from active disease – a more elusive goal.

At present, no technology currently in use, achieves these goals. For paediatric and extra pulmonary TB, immune diagnostic tests might be of help.

Non-availability of accredited laboratories

There is an acute shortage of accredited laboratories in our country as the culture should be used from day one. Rapid culture methods have come to stay, are easier to perform and reliable. Secondly, this problem of non-availability of reliable laboratories, we have been complaining for the last 50 years and no efforts have been made to develop proper laboratories. If efforts had been made, then India would have had reliable laboratories all over the country. Though it is very late, let us make genuine efforts from now on.

New Drugs

New drugs are required for shortening total duration of therapy, providing more widely spaced intermittent treatment, to be effective against susceptible and resistant strains, compatible with antiretroviral therapy for TB-HIV co-infected patients, less toxic, of low cost and provide more effective treatment of latent TB infection in programmes that are able to use them like USA and Western European countries.

No new anti-TB drug has come in the market in the last 40 years or so. If any new drug is being used for TB, like fluroquinolones, it is just by coincidence that the drug has been found to be effective against *Mycobacterium tuberculosis*. This is a big challenge as no new effective drug is expected in near future also.

Challenges of developing new anti-TB drugs

Problems of developing a new anti-TB drug are: huge investment but insufficient profit as cost of developing a drug varies from 115 to 240 million dollars, difficult to identify new compounds which are bactericidal and effective on persisters (dormant) organisms, evaluation of new compounds requires animal studies and no ideal animal model has been found, and for clinical testing gold standard is relapse rate which takes a long time to assess.

Time required for developing a new drug is not less than 10 years. A drug has to pass through many phases – drug discovery, pre-clinical development and clinical development Phases I, II and III. Table below shows the time required for new drug development:

Drug Discovery	Preclinical Development	Clinical Development
2-6 years	For safety and efficacy of drug 1-2 years	Phase I, II and III For safety, efficacy in human/TB patients 4-8 years.

Problems faced include inadequate infrastructure in countries with high TB burden, very long approval time for drug trials, limited knowledge about Good Clinical Practice (GCP) guidelines and lack of good laboratories.

So what is the scenario regarding new drugs? Scenario is that several candidate anti-TB drugs are undergoing clinical trials like Fluroquinolones (Gatifloxacin, Moxifloxacin), Diarylquinolone (LTMC 207), Ethyleanadimine (SQ-109), Nitroimadazoles (PA-824 & opc-67693), Pyrrole (LE-3858) and Myxopyronin (it is believed that bacteria will not become resistant to this drug and it may be able to reduce treatment time). A new compound - R 207910- has also been found. In mice, it was found to be at least as active as the triple combination of rifampicin, isoniazid and pyrazinamide. Three drug combinations containing pyrazinamide and R-207910 have the potential to significantly shorten the duration of TB treatment in patients. R-207910 is claimed to be more effective in killing dormant or physiologically 'turned off' bacteria as compared to replicating one.

Indian response to discovery of new anti TB drug

CSIR has launched an Open Source Drug Delivery (OSDD) aimed for discovery of drugs without patent as acquiring patent makes the drug costly. A fund of Rs. 150 crores has been allocated to OSDD. To begin with, OSDD has taken up research on discovering new drugs for treatment of TB. CSIR initiative has encouraged development of a new drug for TB by LUPINS and it has completed Phase I studies for its lead molecule LL-3858. At the global front, it is now hoped that at least one new drug would be ready for registration by 2010-2011.

Drug quality control

Good quality drugs with proper bioavailability are important. Recent reports suggest that fixed dose combinations (FDCs) of anti tuberculosis drugs (RHZE) are associated with quality problems such as loss of bioavailability of Rifampicin and instability of the drugs in the combination. Bioavailability problems were observed in seven out of 10 formulations tested. These problems were attributed to low content of rifampicin. Chemical instability of FDCs is found to occur due to two reasons: direct interaction of rifampicin (R) with isoniazid (H) and acceleration of the reaction between rifampicin and isoniazid by pyrazinamide and ethambutol (the two co-drugs presently usually in FDCs). This problem does not exist in two drug combinations.

Solution for this lies in preventing the two drugs R & H from coming into contact with each other in stomach. Sites of absorption of all four drugs have been determined. Results showed that R, Z, E could be released in stomach and H in intestine. Based on this concept – a modified tablet – in tablet formulation has been developed in which H will be released in intestine.

Problems with ethambutol quality

Ethambutol is known to exist in three forms: R, R form – (inactive and toxic form), S, S form – (therapeutically active form) and R, S form – (16 times less active form).

Various molecules at different stages of drug development

Phase I :	SQ -109 (Sequella) LL-3858 (Lupins)
Phase II :	TMC-207 (Tibotec) OPC -676783 (Otsika) PA824 (TB Alliance)
Phase III:	Moxifloxacin (TBA/Bayer) Gatifloxacin (Oflotub)
Preclinical :	TBK – 613 PNK-100480

Presence of therapeutically inactive form (R, R) of ethambutol hydrochloride in the range of 30%-100% is found in approximately 30% of the available products. It means low quality TB drugs and may be contributing to the developing resistance. Samples were collected from bulk drugs, commercial products available with local chemicals and DOTS centre. DOTS centre supply was also found to contain 97% of the less active form (R, S form). The problem was primarily restricted to IP labelled products, however the BP and USP labelled products for export were not found to be contaminated.

Challenge is to assure good quality drugs with proper bioavailability, open more drug testing laboratories of international standard and pharmaceutical industry to be advised to follow good quality drug practices. It is a very unfortunate policy of some of our pharmaceutical firms to have two standards, one for the Indian market and other for export.

Vaccine

Prevention of TB is most important for control and eradication of TB. Vaccine is the best tool to do this. However, no effective vaccine is expected in near future. This is a big challenge for all of us to develop a vaccine as early as possible. When the first vaccine - BCG was developed in 1922, we all had great hopes from BCG. It was given to more than 2.5 billion children all over the world. It provides some protection against severe forms of pediatric TB but has been shown to be unprotective against adult TB which accounts for most of the disease burden worldwide. There is an urgent need for newer, more effective vaccine that would prevent all forms of TB including drug resistant strains, in all age groups and among people with HIV. More than 250 TB vaccine candidates have been screened for their ability to protect against *M. tuberculosis* infection in mice and guinea pigs. A few of the successful candidates identified in the experimental models are now ready for clinical testing.

MVA 85A is a very promising vaccine currently in phase II trials. Another one, BCG 30, entered clinical trials in 2004. Some of these vaccines can be administered without needles, making them safe for use in HIV patients also.

Any vaccine to be used in TB control programme should have at least 80% efficacy. Various studies on BCG efficacy in India have shown efficacy to vary from 0 to 80% in preventing TB, but the incidence of serious forms of TB (meningitis, miliary and disseminated) has shown significant decline. So we should continue to use BCG till we get a better alternative.

Teaching and training

TB control is a long battle to fight. We need trained manpower. Training has to be a continuous process. There is a shortage of doctors trained in TB, both physicians and surgeons. DTCD programmes should continue. Doctors with Diploma in Tuberculosis are the backbone of TB control programme.

There is shortage of thoracic surgeons to operate patients of tuberculosis – MDR/XDR-TB, haemoptysis, empyema, bronchopulmonary fistula, etc. RNTCP should address these shortcomings and if required a new course of M.Ch. Thoracic Surgery should be started in various universities. The present M.Ch is in Cardiothoracic Surgery and these surgeons engage themselves in cardiac work and have no interest in thoracic work. They also lack thoracic training.

MCI may be persuaded to start M.Ch Thoracic Surgery Course

So the challenge is to have long term plan of quality training programmes with suitable changes as required from time to time and as per need of the area. Doctors teaching programmes should also be modified according to the requirement and if necessary MCI to be persuaded to open new course like M. Ch Thoracic Surgery.

Opportunities

There are a lot of opportunities which are expected in near future. New drugs are coming up and would undergo clinical trials. Vaccines are also ready for clinical trials. Cost of clinical trials in India is

much less that in western countries. This is a big opportunity for TB workers and the country, but we lack proper infrastructure.

To avail this opportunity, we should develop and identify: Clinical trial centres, appropriate clinical laboratories and regulatory expertise, develop skills in monitoring, training and protocol development, have good management practices and laboratory support to measure the end points and have training in GCP and GLP.

All these facilities have to be of international standard. Without active support of the government, it is not possible to create world class facilities. So government has to come forward and take the initiative and avail these opportunities.

I would like to conclude my Oration with following note:

To defeat TB, we require both rigour and persistent efforts. We should develop a strong political will for TB control. Researches have to be done to find out an ideal diagnostic test, develop new drugs and vaccine, and an alternate and less expensive strategy than DOTS with same or better effectiveness. Programme achievements and successes have to be sustained and maintained for decades to have an effect on epidemiology of TB. Complacency has no role in TB Control.

Review Article

BRONCHIAL THERMOPLASTY

Prince James* and Richa Gupta*

(Received on 4.5.2010; Accepted after revision on 5.9.2011)

***Summary*:** Even with the use of maximum pharmacological treatment, asthma still remains uncontrolled in some cases. For such cases of uncontrolled asthma, a novel therapy – Bronchial Thermoplasty (BT) - has shown some promising results over the past few years. BT is application of controlled radiofrequency heat *via* catheter inserted through a flexible bronchoscope, to the bronchial walls. It reduces the smooth muscle mass in bronchial wall and thus results in decreased contractility. Three major trials of BT show that it does not cause any improvement in FEV1. However, BT causes improvement the quality of life and decreases the future exacerbations and emergency hospital visits due to asthma. But the benefit observed was too small to be clinically significant. Follow up (two to five years) results of these BT trials did not show any significant long term adverse event related to BT. However, further independent large randomized controlled trials and results of application of BT in real hospital settings are needed to define its role in asthma management. **[*Indian J Tuberc 2011; 58:* 155-159]**

(Abbreviations: AIR: Asthma Intervention research, ACQ: Asthma control questionnaire, AQLQ: Asthma quality of life questionnaire, BT: Bronchial thermoplasty, RISA: Research in severe asthma).

***Key words*:** Bronchial asthma, Bronchial thermoplasty

INTRODUCTION

Asthma is one of the most common chronic diseases in the world. Globally, about 300 million people are suffering from asthma[1,2]. About 15 million Disability Adjusted Life Years (DALYs) are lost worldwide annually due to asthma. Mortality wise, asthma accounts for one in every 250 deaths worldwide.[1,2]. With the timely and correct use of inhaled corticosteroids, beta 2 agonists, Leukotriene antagonist, theophyllines and allergen control measures, asthma can be controlled in most of the cases. But even with the use of maximum pharmacological treatment, asthma still remains uncontrolled in some cases. For such cases of uncontrolled asthma, a novel therapy – Bronchial Thermoplasty - has been developed over the past few years.

It is a known fact that smooth muscle mass in airways increases in asthma. This increase in smooth muscle mass is associated with increase in severity of asthma[3]. Thus decreasing the airway smooth muscle mass has always been a possible target for treatment of asthma.

Bronchial Thermoplasty (BT) is application of controlled radiofrequency heat *via* catheter inserted through a flexible bronchoscope, to the bronchial walls. It reduces the smooth muscle mass in bronchial wall and thus results in decreased contractility.

METHOD

Bronchial Thermoplasy is done as an outpatient bronchoscopy procedure, in three sittings of about 30 minutes duration each. Alair® catheter is introduced *via* flexible bronchoscope. Distal end of Alair® catheter contains a flexible four pronged wire basket, which is then forwarded into the distal airway of up to 3mm diameter (Figures 1, 2 and 3). Radiofrequency energy is then delivered for 10 seconds *via* catheter to airway walls. Catheter is then retracted by 5mm and again the radiofrequency is delivered to airway walls. In this way, in one sitting, BT is done to whole one lower lobe. In next sitting,

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Figure 1: Alair® radiofrequency system

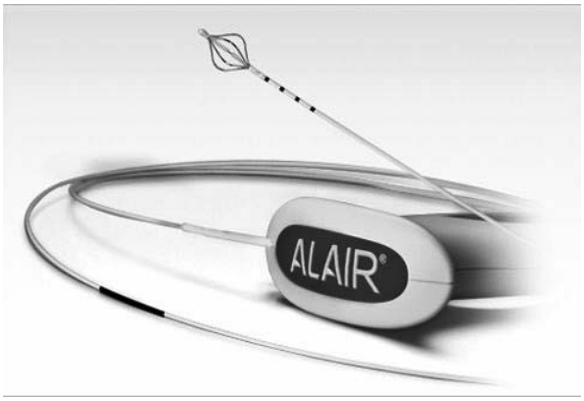

Figure 2: Alair® Catheter

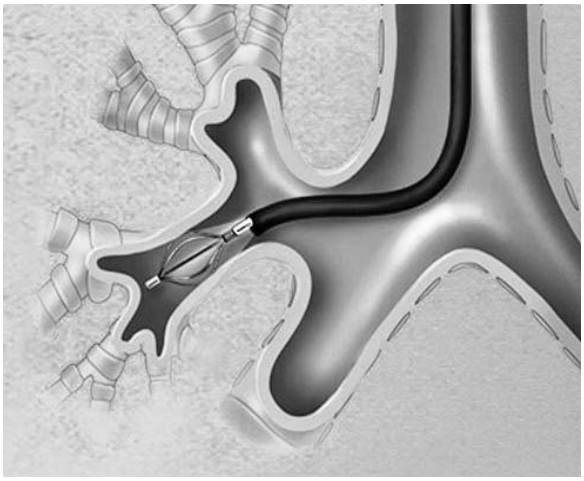

Figure 3: Bronchial thermoplasty catheter in Bronchus

BT is done to the other lower lobe and in third sitting, BT is delivered to both upper lobes. The radiofrequency energy delivered to airway wall, gets converted into heat energy and reduces the airway smooth muscle mass.

REVIEW OF BT RESEARCH TRIALS (Table 1)

Danek CJ *et al* in their initial experimental study in dogs, applied three different temperatures (55, 65 and 75 degree centigrade) to each of three different lung regions[4]. Fourth lung region was untreated and served as control. There was significant reduction in airways smooth muscle mass, airway contractility and airway hyper-responsiveness to methacholine in lung regions treated with 65 and 75 degree centigrade of radiofrequency energy. And this effect lasted up to three years in dogs. The results of this study were very promising and led to an idea of applying it in humans to control asthma.

Miller JD *et al* carried this experiment forward and studied the feasibility, safety and efficacy of BT in human airways[5]. They applied BT in nine patients of lung cancer scheduled to undergo lung resection surgery after three weeks. BT was well tolerated in all nine subjects with no new symptom or adverse effect. BT resulted in significant reduction in smooth muscle mass in the airways. This study provided further boost to the idea of applying this new technique in the treatment of bronchial asthma.

In a small study, Cox G et al offered BT to 16 patients with mild to moderate severe asthma[6]. BT was well tolerated in all patients with no major side effects. And it resulted in decreased airway hyper-responsiveness and increase in symptom free days. However, FEV1 values did not show any significant change from baseline. These positive effects lasted for a period of two years.

With correct application of current pharmacological management, asthma can be effectively controlled in most of the patients. So though BT showed a promise in management of asthma, its true role was needed to be tested in severe symptomatic asthma patients. Povard ID *et al* conducted a randomized controlled trial (RISA trial) of BT in patients of symptomatic severe asthma despite being on maximum

Table 1: Summary of research trials of bronchial thermoplasty

No.	BT Research trial	Subjects	Results	Adverse effects/ limitations	Conclusion
1	BT in Dogs[4]. Danek C.J. *J Appl Physiol* 2004.	11 Healthy Mongreal Dogs	Airway responsiveness significantly decreased after BT.	No deaths. Mucous plugs in two cases.	BT deceases airway responsiveness
2	BT in Humans – 1st feasibility study[5]. Miller JD *et al. Chest* 2005	Nine Lung Cancer patients posted for surgery	BT caused a significant reduction in Airway smooth muscle mass	Mucous plugs in two patients.	BT was safe, might benefit in patients with Asthma
3	BT in mild to moderate asthma[6]. Cox G *et al. Am J Respir Crit Care Med* 2006	16 patients with mild to moderate asthma	BT significantly reduced the airway responsiveness, and increased the number of symptom free days	Transient and related to bronchoscopy	BT was well - tolerated and decreased airway responsiveness for up to two years
4	BT in Severe Asthma[7] (RISA). RCT. Poward ID *et al. Am J Respir Crit Care Med* 2007	32 patients with uncontrolled severe asthma (15 in BT group, 17 patients in control group)	Significant decreases in Asthma symptoms, rescue medication use and improvement in lung function in BT group	Seven hospitalizations in four patients of BT group.	BT provided benefits in Asthma control in patients with severe asthma, but at the cost of significant short term adverse events
5	Asthma control during year after BT[8]. RCT. (AIR1 trial)Cox G *et al. N Engl J Med 2007*.	112 patients(56 in BT group and 56 in Control group) with uncontrolled severe asthma	Significant improvement in AQLQ, ACQ, decrease in rescue medication use, less exacerbations in BT group	Six hospitalisations in four patients in BT group. Increase in dyspnea and cough in first week post BT	BT provided benefits in Asthma control in patients with severe asthma, but at the cost of significant short term adverse events
6	BT in severe asthma – RCT with Sham control[9] (AIR2). Castro M *et al. Am J Respir Crit Care Med* 2010	288 Patients (190 in BT group and 98 in SHAM group) with severe asthma	Significant improvement in AQLQ and decrease in exacerbations, Emergency room visits in BT patients. But there was improvement in SHAM group also.	6% more hospitalization in BT patients during initial six weeks post BT.	BT provided benefits in Asthma control in patients with severe asthma, but at the cost of significant short term adverse events
7	Long term safety of BT (5 year follow up of AIR 1 trial)[10]. Thomson NC *et al. BMC Pulm Med* 2011	Five year follow up of AIR 1 trial patients (45 of BT group and 24 of Control group)	No significant increase in asthma symptoms, Exacerbations or hospitalizations in both BT and control group	No difference in Asthma control in BT and Control group during two to five year post BT	Improved Asthma control was maintained up to five years. No significant long term adverse event of BT.
8	Five year follow up of RISA trial[11]. Pavord ID *et al.* ATS 2011(Abstract)	12 of 15 patients of RISA trial were followed up for five years	Gradual decrease in hospitalization and emergency room visits for Respiratory symptoms. FEV1 remained stable	Small sample size. No control group.	No significant complication observed in BT group over five years
9	Two year follow up of BT patients of AIR2 trial[12]. Castro M. *et al. Ann Allergy Asthma Immunol* 2011.	166 of 181 patients of AIR2 trial completed the two year follow up	No increase in Asthma exacerbations, Emergency rooms visits for respiratory symptoms over two years post BT	SHAM group patients were not followed up in second year.	No significant complication in BT group over two years

(Abbreviations: AIR: Asthma Intervention research, ACQ: Asthma control questionnaire, AQLQ: Asthma quality of life questionnaire, BT: Bronchial thermoplasty, RISA: Research in severe asthma)

treatment (Fluticasone 750 microgram or more)[7]. Among 15 patients who received BT, four patients required seven hospitalizations for increase in respiratory symptoms, two patients developed lobar collapse and one patient needed bronchoscopy to clear mucous plugs after BT. While patients in controlled arm did not need any hospitalization during treatment period. However, after 22 weeks, patients with BT had significant decrease in rescue medication use and improvement in asthma control questionnaire score. And this effect lasted up to one year. For first time this study showed that BT is associated with transient but significant worsening of asthma symptoms.

In a randomized controlled trial (AIR1 trial) including 112 patients of asthma, Cox G *et al* examined the effect of BT on control of moderate to severe persistent asthma[8]. Patients receiving BT had significantly more adverse events than patients in control arm. However, majority of these adverse events occurred one day after the BT and resolved within seven days. Most common adverse events were increase in dyspnea, wheeze, cough and chest discomfort. In BT group, four patients required six admissions for increase in respiratory symptoms. But at the end of 12 months follow up, BT group showed significantly greater improvement in PEFR, Asthma quality of life questionnaire, Asthma control questionnaire, more symptom free days, less use of rescue medication and had fewer exacerbations.

All these above mentioned studies showed that BT plays some significant role in controlling the symptoms of asthma. But still in none of these trials, BT was compared with sham bronchoscopy in control group. This deficit in methodology in research trials certainly leaves room for a possibility that all the improvement in symptoms of asthma and related quality of life may be just a result of placebo effects of bronchoscopy.

To rule out this doubt of placebo effect, Castro M *et al* conducted a multi-centre, randomized, double blind, sham controlled trial (AIR2) to assess the effectiveness and safety of BT in the treatment of severe asthma[9]. In this trial, 190 patients in treatment arm received BT while 98 patients in control arm also underwent bronchoscopy without actual BT. Patients in sham group without receiving BT also showed significant improvement in Asthma Quality of Life Questionnaire (AQLQ) score. This reflects the placebo effect of bronchoscopy on AQLQ scores. Thus, it also raises questions over the validity of results of previous BT trials, which were conducted without sham group. But authors of AIR2 trial concluded that the improvement in AQLQ score in patients who received BT was more than the improvement in AQLQ score in sham group (5.7 *vs* 5.5 respectively). Though this difference is statistically significant, but it is not big enough to be clinically relevant. Similarly, there was statistically significant decrease in severe asthma exacerbations (0.70 exacerbations/subject/year in sham group *vs* 0.48 exacerbations/subject/year in BT group) as well as emergency hospital visits (0.45 visits/subject/year in sham group vs 0.10 visits/subject/year in BT group) in BT patients over one year follow up period. But these figures indicate that for a given patient, BT will reduce one severe exacerbation over the period of six years, and four emergency room visits over the period of 10 years, in comparison to a sham group patient. And all this benefit will come at the cost of increased risk of hospitalization during initial six weeks after BT. Results of AIR2 trial indicate that BT perhaps modifies the host response and thus results in lesser bronchoconstriction on exposure to the trigger factors of asthma exacerbation. Apart from reducing bronchial smooth muscle mass, whether BT has any effect on airway inflammation in asthma, is still not clearly known and should be included in the future research trials of BT. There was no significant change in PEFR, FEV1, and use of rescue medications.

Regarding safety of BT, two to five years follow up results of all three major trials of BT are available now[10-12]. There was no increase in asthma symptoms, exacerbations, emergency hospital visits, and fall in FEV1 or any other significant adverse event observed in BT patients on follow up.

Cost of BT radiofrequency system and BT catheter is about Rs. 14 Lakhs and Rs. 67,000 respectively. So the cost of BT per patient will be about Rs. 3 to 4 Lakhs. This high cost will also be another limiting factor for its use in developing countries like India.

All the BT trials (one in Dogs and five in humans) were supported by Industry (Asthmatx Inc.), who is manufacturer of Alair® Bronchial thermoplasty system and catheter. So though BT appears to have found some niche in the management of uncontrolled severe asthma, further independent large randomized controlled trials and results of application of BT in real hospital settings are awaited to define its true role in asthma management.

CONCLUSION

Bronchial thermoplasty is a new therapeutic bronchoscopy procedure, which has been used in research trials in cases of uncontrolled severe asthma, in addition to pharmacological therapy. BT causes statistically significant improvement in the quality of life and decreases the future exacerbations and emergency hospital visits. But clinical utility of this improvement in asthma control is little. It does not improve the FEV1. However, no significant adverse effect was found in five year follow up of BT patients.

In view of high cost of procedure and increased risk of significant short term transient bronchoscopy related complications, at this point of time, Bronchial thermoplasty cannot be recommended for routine use in patients of uncontrolled severe asthma.

However, as all the six BT trials were industry-funded, further independent trials are needed to define its true role in management of Asthma.

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Original Article

A PILOT STUDY OF SAME DAY SPUTUM SMEAR EXAMINATION, ITS FEASIBILITY AND USEFULNESS IN DIAGNOSIS OF PULMONARY TB

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Summary

Introduction: A large number of tuberculosis cases are continuously being reported from India and other developing countries leading to high morbidity and mortality. In spite of many newer tests available for diagnosing a case of tuberculosis, smear microscopy of sputum is still the preferred test under programmatic conditions. The current national and international guidelines recommend two sputum smear examinations in two days for diagnosing cases of tuberculosis, which is time-consuming, tedious, needs multiple visits, leading to high dropout of infectious cases. In the background of existing limitations of smear microscopy, we attempted to complete the diagnosis of tuberculosis on same day by serial collection of the spot sputum specimen and analyze its advantages, feasibility and viability.

Material & Methods: The study was undertaken by the Department of Microbiology, Lala Ram Sarup Institute of Tuberculosis and Respiratory Diseases during May 2010 to April 2011. Sputum specimens were collected from 330 randomly selected tuberculosis suspects who attended OPD of hospital, patients submitted spot and home collected morning sputum sample in a standard method and spot and additional spot sputum(X- spot) collected one hour after the first spot sample as per the proposed front loading method. All the samples received were stained by acid fast Ziehl-Neelsen (ZN) stain and examined on the same day. The sputum sample was pooled and cultured in Lowenstein Jensen (LJ) media in duplicate set of bottles. The results of two different microscopic methods were compared with the gold standard culture test.

Results: Out of the total 330 TB suspects, 70.60% were males and 29.39% females. The most common complaint was of cough with sputum (88.18%), chest pain (70.21%), fever (55.15%) and loss of appetite (43.03%). Upon examining the total sputum slides, 18.48 % were positive for acid fast bacilli. The smear positivity was 61/330(18.48%) by standard methods and in proposed new method 43/330(13.03%). Sensitivity of the standard and proposed new method smear microscopy was 58.25% and 40.07% respectively and specificity was 99.55% in both the methods.

Conclusion: Same day smear microscopy for diagnosing tuberculosis by a proposed new method of smear examination in the case of suspected tuberculosis seems not a promising step towards improving the quality of sputum smear examination. The results of sensitivity and specificity of the two approaches were not similar. More than eighty per cent responded in favour of same day sputum delivery system and getting result on same day. This study can be confirmed on larger scale and preference of patients can be examined in peripheral laboratory also before taking it up for consideration in the national tuberculosis programme. **[*Indian J Tuberc 2011; 58:* 160-167]**

Key words: Tuberculosis, Sputum smear examination, Acid fast bacilli.

INTRODUCTION

Direct sputum smear examination by Ziehl Neelsen (ZN) stain is a simple, economical and reliable tool used widely for identifying acid fast bacilli for diagnosis and treatment of tuberculosis (TB) cases under national tuberculosis control programme in several developing nations[1]. It is a key component of directly observed therapy shortcourse (DOTS) and DOTS plus strategies for diagnosing tuberculosis, initiating antituberculous drugs, monitoring progress of disease and a valid document to declare the cure in designated microscopic centers (DMCs) situated in far flung areas[2].

Newer diagnostic techniques for tuberculosis are operational in urban laboratories while in rural areas at primary health centers (PHCs)/ designated microscopic centers (DMCs) level, direct sputum smear examination is preferred tool being simple, rapid and most reliable[3]. Tuberculosis is an important reflector of slow economic growth of developing nations, rendering loss of productive manpower and adverse economy. Despite the implementation of

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DOTS and DOTS plus programme throughout the country on war footing thereby providing access to diagnostic and treatment facilities free of cost, TB is spreading fast[4].

In the national tuberculosis control programme, the passive case finding method requires tuberculosis suspects to visit the health care facilities many times, i.e. for submitting the spot sputum sample on the first day, submit early morning sputum samples on second day and for collecting the report on subsequent days[5]. This accentuates the costs and discomfort of diagnostic compliances and delay in treatment which in turn dissuade the poor patients from seriously following the existing norms of tedious tuberculosis control programme, thereby finally resulting in high dropouts, who further spread tuberculosis[6-8].

In the backdrop of high dropouts, increase in tuberculosis cases and higher morbidity, the accepted belief that two day sputum specimen examination for spotting acid fast bacilli requires a review now. Recent studies for the diagnosis of tuberculosis reveal that yield of acid fast bacilli(AFB) increases during serial sputum examination on the same day, i.e. in first sputum smear examination it is 85.8%, increase in yield of second sputum specimen by 11.9% and increase in yield of third sputum is by 3%[9].

Worldwide some studies have been undertaken to analyze the feasibility, usage and advantages of two serial sputum examinations on the same day in comparison to existing TB control protocol. Our study is an attempt to assess the use, feasibility and advantages of two serial sputum smear examinations on the same day and compare their outcomes with conventional smear microscopy and gold standard TB culture for diagnosis.

MATERIAL AND METHODS

This study was undertaken at the Department of Microbiology of Lala Ram Sarup Institute of TB and Respiratory Diseases, New Delhi during May 2010 to April 2011. It is a national reference laboratory for the diagnosis of tuberculosis and is a internationally accredited laboratory. The Microbiology Department on an average examines 200 pulmonary samples daily.

The protocol was approved by the Institutional Research Committee chaired by the Director of the institute. In this study, we have enrolled patients who agreed for voluntary participation and were ready to give written consent after understanding the objects and other details of the study. Patients were not compensated for participating in the trial and underwent the same routine procedures undertaken under operational conditions. Patients were screened using the routine procedures of the outpatient clinics and were examined by a large number of clinicians. At the time of enrolment, patient details are filled in the prescribed patient proforma.

The proforma includes details of age, sex, registration number, lab number, history of cough and fever for more than two weeks, past history of tuberculosis, family history of tuberculosis, preference for sputum submission and other relevant information of patients. The patients were provided with sputum container and were asked to submit sputum specimens as per RNTCP guidelines i.e one on-the-spot specimen at the time of the first visit, and second specimen collected at home the next very day morning, and bring the sample to the laboratory. In the newer scheme, the same patient deposited one on-the-spot specimen collected at the time of the first visit, a second on-the-spot specimen collected one hour later[10,11]. In this study, the slides were examined on daily basis, given a separate study number and routine laboratory numbers, which were covered with plane stickers for blinding. All smears were then mixed before examination and graded by laboratory technicians following the RNTCP guidelines and rechecked by senior microbiologist[11]. Quality control of the ZN smear was maintained by systematic and effective internal quality control scheme as per RNTCP guidelines in order to maintain the error wthin the acceptable limits[11].

All the samples collected from the patients were pooled and culture was done on two Lowenstein Jensen (LJ) media after decontaminating the sample by petroffs' method[11]. Culture is considered as 'gold standard' in order to validate and compare the results of standard and front loading smear microscopy

methods as also for calculation of their sensitivity, specificity, positive predictive value and negative predictive value.

In this study, patients were considered as 'smear positive' as the single bacillus is seen in any o the samples[12].

RESULTS

A total of 330 TB suspects were inducted into the study during May 2010 to April 2011. The enrolled subjects submitted the sputum samples as per predetermined protocol. From 330 suspected cases of tuberculosis, sputum specimens were collected for re-evaluation of diagnostic test microscopy by standard method as well as newer approach, a front loading method of sputum collection. The demographic data showed that number of male patients in the study was 233(70.60%) and females 97(29.39%). The mean age of male patients was 43.5 years and female 40.5 years (Table-1). The clinical records showed that most of the patients complained of cough with sputum for >2 weeks (88.18%), chest pain (71.21%), and fever >2 weeks (55.15%), preference of sputum submission on same day (93.03%) and loss of appetite (43.03%) (Table1). Amongst the total identified 61/330 smear positive cases, 96% (59/61) patients had initially recorded the cough for >2 weeks complaints, followed by 95% (58/61) giving history of blood with sputum, while 93% (57/61) cases had history of breathlessness,

Table 1: Demographic and Clinical profile of participants

Demographic/Clinical features		No. (%)	Smear Positivity (%)
Total No. of Pulmonary suspects		330	61(18.48)
Sex	Male patients	233 (70.60)	53 (86.88)
	Female patients	97 (29.4)	08 (13.11)
Mean age	Male patients	43.5	
	Female patients	40.5	
Cough	>2 weeks	291 (88.18)	59 (96.72)
	<2 weeks	39(11.2)	-
Fever for	>2 weeks	182(55.15)	56 (91.80)
	< 2weeks	48(14.54)	-
Chest pain		235(71.21)	55 (90.16)
Breathlessness		73(22.12)	57 (93.44)
Hemoptysis		106(32.12)	58 (95.08)
History of contact		93(28.18)	32 (52.45)
Preference of sputum submission on same day		307(93.03)	53 (86.88)
Loss of appetite		142(43.03)	59 (96.72)

Note: Figure in parenthesis indicates percentage.

91% (56/61) patients were suffering from fever >2 weeks, 90% (55/61) patients complained of chest pains, 86% (53/61) patients had preference of submitting sputum same day and 52% (32/61) had history of TB contacts.

In the standard method of smear microscopic examination, first sputum sample collected immediately in the vicinity of laboraty under our vigilance, showed smear positivity in four (12.72%) stained slides. The second sample of the same suspects being the morning home collected sputum sample brought by the patient on the following day showed 61 (18.48%) positive smears (which include all the 42, first smear positive samples). Finally, a total of 61/330 (18.48%) ZN stained slides positive for acid fast bacilli by standard method of smear microscopic examination were identified.

In the new proposed method, smear positivity for acid fast bacilli was 43/330 (13.03%), first sample showed 42(12.72%) smear positives only, the second sputum collected one hour after the first sample showed 39(11.8%) positive smears. Among the first sputum samples, one sample that was negative was identified as 'smear positive' in second sputum sample for acid fast bacilli. With

Table 2: Comparison of two different approaches of ZN smear examination in clinical samples

Approach		Standard approach			Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
		Positive	negative		68.85	99.62	97.67	99.62
New attempted method	Positive	42	1	43				
	Negative	19	268	287				
Total		61	269	330				

Table 3: ZN smear microscopy and its grading of new attempted method (one pot second spot after one hour) of same sample

Approach	Samples	Smears grading			
		Scanty	1+	2+	3+
Standard method	1st Spot(330)	-	12 (3.63)	08 (2.42%)	23 (6.96%)
	Morning(330)	1 (0.3%)	27 (8.18%)	18 (5.45%)	16 (4.84%)
New attempted method	1st Spot (330)	-	12 (3.63%)	08 (2.42%)	23 (6.96%)
	2nd spot (330)	-	12 (3.63%)	05 (1.51%)	22 (6.66%)

this, in the new proposed method, the total positive samples 43(13.03%) included 38 samples with positive smear identified in first and second sputum samples and one additional positive sample identified in second sputum sample only, among the suspected TB cases (Tables 2).

When we observed the grading of positive smears in standard method, 12 smears were graded as 1+, 08 smears as 2+, 22 smears as 3+ among the 42 positive first spot smear. Among the total 61, second morning positive sputum smears, 27 smears were graded as 1+, 18 smears as 2+, and 16 smears as 3+.

While in newer proposed smear microscopic method, 12 positive smears were graded as 1+, 08 positive smears as 2+, 22 positive smears as 3+ in 42 positive first spot smears same as the first sputum smear results of standard methods and the second sputum which was collected one hour after first sputum under the vigilance of the laboratory staff, 12 positive smears were graded as 1+, 05 positive smears as 2+ and 22 positive slides as 3+ in 39 positive slides. The maximum percentage (7%) of 3+ positive smears were seen in first spot samples which showed that chances of getting sputum positivity is comparatively higher among first samples (Table 3).

Table 4: Diagnostic comparison of standard sputum smear microscopy, new smear microscopy with gold standard culture test

Approach	ZN Smear	Culture		Sensitivity (%)	Specificity (%)	PPV	NPV
		Positive	Negative				
Standard method	Positive	60	1	58.25	99.55	96.77	83.70
	Negative	43	226				
New attempted method	Positive	42	1	40.07	99.55	97.67	78.74
	Negative	61	226				

Table 5: Comparison between attempted new sputum smear microscopy with standard sputum smear microscopy examination

		Conventional Approach					
		Positive smear	Negative smear	Sensitivity	Specificity	PPV	NPV
New attempted method (1st spot & 2nd spot sputum sample after 1 hour)	Positive	42	1	68.85	99.62	97.67	93.37
	Negative	19	268				
Total		62	269				

There was an increased yield of 6% of smear positivity observed in the standard method of sputum smear examination in comparison to proposed new method of sputum smear microscopic examination (Table 2). The result showed that 86.96% and 81.51 % specimens were negative for AFB respectively in standard sputum smear examination (first spot and morning sputum samples), where as 87% and 88.2% of negative smear were found in first and second sputum smear examination respectively in the proposed new method of same day smear microscopic examination.

In the proposed new method of same day smear microscopic examination, 92.87% smears were positive in first and second stained slides as well as one additional case identified during second slide examination (Table 5).

The sputum culture result on LJ medium of 330 TB suspects showed that 103(31.21%) were found positive for growth of *Mycobacterium tuberculosis* .The results showed that 60(18.18%) sputum samples were found to be culture positive when the sputum was collected by standard method (first spot and second morning sample) and 42(12.72%) sputum specimens came out to be culture positive when samples were collected according to the new proposed method(first spot and second spot sputum after one hour of first spot on same day). In this result, sputum culture was positive in 42 for Mycobacterium in both the methods of smear examination (Table 4).

Sensitivity of the standard method and new proposed method was 58.25% and 40.07% respectively whereas specificity was similar i.e 99.55% in both the methods (Table-4).The positive predictive value in standard and new proposed methods was almost similar i.e. 96% and 97% respectively. The negative predictive value in standard method and new proposed methods was 83.70% and 78.74% respectively (Table 4). Though the new proposed method is a less sensitive (68.85) method in comparison to standard method of smear examination, but specificity (99%) was comparable to standard method and was found to be patient's friendly and less cumbersome smear microscopic examination procedure (Table 5).

DISCUSSION

Accurate diagnosis followed by prompt and effective treatment is the prerogative of tuberculosis care and control programme. Smear microscopic examination because of its simplicity, low cost and high specificity is still the main test for diagnosis of tuberculosis in most of the developing countries.

This systematically carried out study showed that symptoms like chronic cough for more than two weeks, fever for more than two weeks, chest pain and haemoptysis were observed in more than 90% of patients who were smear positive. These symptoms associated with tuberculosis patients had been observed by Daley *et al* also[13].

The overall smear positivity rate in our study came out to be 18.48% which is almost similar to other studies conducted in high prevalent countries, i.e. Nigeria and Ethiopia : 21%, Yemen:24% Nepal : 25%[14] where sputa were examined for diagnosis of tuberculosis. A study from Malawi by Harries *et al* had shown that percentage of positive cases using two sputum strategy was 16.1% which was lesser in comparison to our results[15].

In our study, significant difference was observed in the positivity rate in standard method of smear examination and the proposed new method of same day smear examination (98% *vs*. 70%). In contrast to our study, Ramsay *et al* in his study showed that the spot - x spot, proposed new method of same day smear microscopic examination identified 95% smear positive patients and spot – morning - spot (standard method) scheme identified 97% of smear positive patients[14]. A study from Ethiopia states that out of the total TB diagnosed cases, 94% were identified by the same day smear microscopy and 98% were identified by routine spot-morning–spot smear microscopy method but the study also emphasized that improvement in patient care can be done by reducing the number of patients' drop-out by examining the sputum sample on same day[16].

The previous report from LRS Institute of TB and Respiratory Diseases by Sarin *et al* and from TRC Chennai by Gopi *et al* showed that two spot specimens identified 92.2% of the total TB cases[17,18].

In our study, the result of the proposed new method of same day smear examination was almost same as Hirao *et al* where they studied that there was no difference in the number of positive smear between extra spot and the first spot samples[7]. Studies from Ethiopia, Nepal, Nigeria and Yemen showed slight increase in yield of extra spot sample, i.e. 8%, 9%, 4% and 12% respectively[14].

Our finding confirms that 3+ positive specimens are more common in first sputum samples (43.47%), with a significant difference seen in 3+ grading of morning samples (25%) and second spot (33.33%). This result is in contrast to the findings of earlier studies wherein higher bacillary load has been documented in the morning specimen which would have been the basis of multiple sputum collection procedure for diagnosing TB [7,19].

In the proposed new method of smear microscopy, 6% less bacilli were identified in comparison to the standard smear microscopic examination but brief patient interaction at the time of sputum collection showed that they were most comfortable with proposed sputum smear microscopic examination and its results within same-day. Simultaneously, the same-day sputum smear microscopic examination and its results are extremely useful for clinicians who can start the treatment immediately. This has reduced the turnaround time in the diagnosis and treatment of TB patients.

The available limited data on the yield of smear positivity by examining morning *versus* spot sputum suggest that yield of single morning specimen is approximately higher by 12% over the yield of single spot specimen[9]. Higher yield in morning samples similar to our study has been documented by Ramsay *et al* in his research publication[14]. These approaches are costly to the patients and programmes often experience high dropout rates from the diagnostic process due to multiple visits of patients[20].

The earlier study showed that the two spot smear strategy would miss about 3% - 5% of the positive cases[10,21], whereas in the present proposed new method of same day sputum examination, we have missed 6% of TB suspects.

In India, 13% of dropout cases has been observed amongst the tuberculosis suspects whereas report from Malawi is said to be 15%[22,23]. Failing to complete the diagnosis is a major obstacle to provide treatment in the developing part of the globe. At the first hand, this obstacle can be minimized by following the two specimen approach and by improving the quality of services.

Our findings confirm that culture positive result was 13% more than the result of smear microscopy. In comparison to total culture positive cases (103), sensitivity and specificity of smear examination in standard method and front loading method were 58.25%, 99.55% and 40.07%, 99.55% respectively. Hirao *et al* showed that sensitivity and specificity in routine method were 57.7% and 98.5% and in front loading method, it was 56.40% and 98.50% respectively. In their study, culture positive sputum samples (37%), were almost double of smear positive cases[7]. In view of the above, we may conclude that the front loading method is of low sensitivity in comparison to standard method of smear examination. However, in view of feasibility of the technique and convenience of patients, the method deserves to be considered for a larger study encompassing wide range of set-up like rural areas, semi-urban areas where TB suspects have to travel long distances to reach health care facilities.

A policy decision must be taken after thorough and more extensive approach towards study results. This is relevant in tuberculosis world of developing nations. This study highlights the utility of same day sample collection and smear examination, the discussion about which is already going on.

CONCLUSION

In contrast to other studies, this study showed that the two spot sputum specimen examination had a sensitivity inferior to the two

sputum specimens collected in standard method i.e spot and morning samples collected from the same patients. In this study, the patients' drop-out has not been taken into consideration which may make the result more relevant in present scenario. Otherwise, more than eighty percent patients responded in favour of same day sputum delivery system and getting result the same day. The sensitivity of the standard smear microscopy test was found to be higher in comparison to proposed new strategy of same smear microscopy but specificity of the two approaches was almost similar. This study indicates that it can be confirmed on a larger scale and preference of patients can be examined in peripheral laboratories also before implementing it in a national tuberculosis programme.

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Original Article

A COMPARATIVE ASSESSMENT OF KAP REGARDING TUBERCULOSIS AND RNTCP AMONG GOVERNMENT AND PRIVATE PRACTITIONERS IN DISTRICT GWALIOR, INDIA: AN OPERATIONAL RESEARCH

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Summary

Background: Tuberculosis is one of the oldest diseases known to mankind. However, still practitioners are unaware of various facts associated with it.

Objectives:

(1) To assess the knowledge, attitude and practices adopted by practitioners of both government and private sectors in diagnosis and management of TB patients.

(2) To assess the views of practitioners in strengthening the RNTCP programme.

Methodology: 200 allopathic practitioners from both government and private sectors providing their services in Gwalior District were interviewed using pre-designed pre-tested structured questionnaire.

Results: The mean score of knowledge related to tuberculosis and RNTCP was higher among government practitioners (9.8) compared to private practitioners (6.1). All practitioners were having positive attitude towards regular up gradation of knowledge while statistically significant differences were noted on issues related to management of TB patients as per RNTCP guidelines. X-ray was the most preferred modality for diagnosis and follow up among private practitioners compared to sputum examination among government practitioners. Referral of poor and serious patients was also very low among private practitioners.

Conclusion: The present study hereby concludes that there is a large gap in Knowledge, Attitude and Practices on TB and RNTCP among the practitioners of both the sectors. There is an urgent need for upgrading the knowledge on various issues and regular Continuing Medical Education (CME) involving various professional bodies. **[*Indian J Tuberc 2011; 58:* 168-177]**

Key words: Tuberculosis, RNTCP, KAP studies

INTRODUCTION

Tuberculosis is one of the oldest diseases known to mankind. Its description can be traced back even up to 377BC[1]. However, still practitioners are unaware of various facts associated with it[2,3]. Various governmental and non- governmental organizations have been involved in upgrading the knowledge of practitioners. Till date, around 2500 NGOs have been involved in various sectors of Revised National Tuberculosis Control Programme (RNTCP) like Evaluation, Community Monitoring, Advocacy, Communication and Social Mobilization (ACSM), etc. Government of India, under its Revised National Tuberculosis Control Programme (RNTCP) through its RNTCP PPM IMA project with support of GAFTM has also made sincere efforts to upgrade the knowledge of practitioners working not only in government sectors but also in private sector[4].

However, continuous evaluations of such strategies are the need of time as it helps policy makers and programme managers to frame and re-frame their future plans. Although studies have been carried out by different researchers, in India and abroad[5-7], to assess knowledge, attitude and practices of practitioners working in private sectors on various aspects of tuberculosis, but there are limited

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researches on comparative assessment of knowledge, attitude and practices of practitioners working in government and private sectors. Keeping this in mind, the present study was planned with the following objectives:

- To assess the knowledge, attitude and practices adopted by practitioners of both government and private sectors in diagnosis and management of TB patients.
- To assess the views of practitioners in strengthening the RNTCP programme.

METHODOLOGY

Study Area

The present study was a field-based Cross Sectional study carried out in both Rural and Urban areas of Gwalior District between July 2008 to June 2009 by students and staff of Department of Community Medicine, G.R Medical College, Gwalior. The study was presented in front of Institutional Review Board and prior approval was sorted before the start of study.

Study Participants

The present study was carried out among the registered allopathic practitioners who were providing their services in Gwalior District during the study period. A total of 200 allopathic registered practitioners (100 government and 100 private practitioners) were included in the study. The number was kept limited to 200 keeping in mind the resources allocated and the availability of government practitioners in Gwalior District. All the participants were selected using purposive sampling technique.

A list of all the practitioners from both private and government sectors was made with the help of Indian Medical Association, Gwalior branch and office of Chief Medical and Health Officer, Gwalior District respectively. The list was sorted to locate the area of the practitioners. A prior contact was made with the selected practitioner to explain the aims and objectives of the study and to get verbal consent for active participation in the study. An appropriate time for an indepth interview was also sorted from those who gave the verbal consent for the participation in study.

Exclusion Criteria

Practitioners not willing to treat TB patients from both the sectors were not enrolled in the study. This criterion was included in the study methodology because practitioners will not take keen interest in the studies on topics which are not related to them or in which they are not interested. This will affect the quality of the study.

Indepth Interviews

A pre-designed and pre-tested structured questionnaire was developed for a face-to-face indepth interview with the study participants. The information was collected about the general profile of the participants, knowledge about the signs, symptoms and management of TB patients, Attitude towards the TB patients, their practices in the management of TB patients and their views to further strengthen the RNTCP programme.

The study proforma was divided into three parts. The first part was related to the knowledge. All the questions were allocated one point for correct response and thus a total correct response was calculated. The part two of the proforma was related to the attitude of the practitioners towards TB patients. Five point Likert scale was used to assess the attitude of the practitioners towards TB patients. Those who showed agreement or strong agreement to a statement was rated to have a positive attitude and those who showed undecided, disagreement or strong disagreement was rated to have a negative attitude. The third part was related to the practices common among the practitioners in the management of TB patients and their views for further strengthening of RNTCP programme. All the practitioners were asked about the strategies commonly adopted by them in the management of TB patients. Views on issues of most preferred modalities to upgrade the knowledge of practitioners, creating awareness in the community and ways to enhance the participation of private practitioners in the programme was asked from

Table 1: Knowledge of Tuberculosis

S. No	Knowledge on TB	Correct Response	Incorrect and No response	$\chi 2$	df	p- value
1	TB is a leading cause of death among children in developing countries					
	Government	88	12	1.87	1	0.171
	Private	81	19			
2	Pulmonary TB is the most common TB in India					
	Government	94	6	1.161	1	0.204
	Private	84	16			
3	Cough is the most common symptom of TB					
	Government	96	4	1.33	1	0.24
	Private	87	13			
4	Cough of three weeks' duration should be subjected to sputum examination					
	Government	89	11	38.45	1	0.00
	Private	48	52			
5	X-ray has a supportive role in the diagnosis of Pulmonary TB					
	Government	81	19	29.21	1	0.0000
	Private	44	56			
6	In RNTCP, there are three treatment categories					
	Government	94	6	109.03	1	0.00001
	Private	21	79			
7	A new case of Pulmonary TB of CAT-I requires treatment for six-seven months					
	Government	84	16	72.46	1	0.000001
	Private	24	76			
8	During pregnancy, streptomycin should be avoided					
	Government	74	26	0.87	1	0.349
	Private	68	32			
9	Steroid is required in the management of TB meningitis					
	Government	92	8	0.31	1	0.579
	Private	94	6			
10	INH prophylaxis should be given to breast feeding babies whose mother has active TB					
	Government	74	26	22.28	1	0.00003
	Private	41	59			
11	TB is most common in the age group of 15-60 years					
	Government	74	24	0.44	1	0.577
	Private	78	22			
12	X-ray finding of Pulmonary TB persists for many years					
	Government	65	35	5.40	1	0.0201
	Private	54	56			
13	Resistance to Rifampacin and Isoniazid is required to label a patient with TB as MDR-TB					
	Government	35	65	9.50	1	0.0.00205
	Private	16	84			
14	ATT treatment should be stopped if a patient develops signs of Hepatitis during the course of treatment					
	Government	78	22	0.28	1	0.599
	Private	81	19			

- Number of Government practitioners : 100
- Number of private practitioners : 100

practitioners of both the sectors. These were the structured questions and participants were provided with a list of options and multiple responses were recorded.

Statistical Analysis

Descriptive statistics was presented to evaluate the knowledge of the practitioners regarding TB. The Chi square test was used to compare different proportions and to test the association between good Knowledge, Attitude and Practices of practitioners from both government and private sectors.

Limitation of the study

The study design involved '5 point Likert Scale' which ranged from 'Strong Agreement' to 'Strong Disagreement'. There was no provision to assess the reasons for the differential response due to limitation of time and resources and this can be considered as the limitation of the study.

RESULTS

In the present study, 200 allopathic practitioners were interviewed, 100 were from

Table 2: Attitude of practitioners towards TB patients

S. No	Attitude towards TB patients	Positive attitude	Negative attitude	$\chi 2$	df	P value
1	RNTCP training should be given to all practitioners • Government • Private	 98 94	 2 4	2.08	1	0.148
2	All TB patients should be referred to the nearest DOTS centre • Government • Private	 85 34	 15 66	53.97	1	0.00000
3	Sputum of suspected TB patients should be examined only at government accredited laboratories or DMCs • Government • Private	 81 23	 19 77	67.39	1	0.000001
4	Standard treatment regimen mentioned under RNTCP should be adopted in the management of TB patients • Government • Private	 87 26	 13 74	75.70	1	0.000001
5	There is a need for spreading awareness on TB in community • Government • Private	 98 100	 2 0	2.02	1	0.155
6	There is a need for continuous upgradation of practitioners on recent advances in the field of Tuberculosis • Government • Private	 98 99	 2 1	0.34	1	0.560

- Number of Government practitioners : 100
- Number of private practitioners : 100

Table 3: Practices common in management of TB patients

S. No	Practices common in management of TB	Government practitioners (N=100)	Private Practitioners (N=100)	$\chi 2$	df	P value
1	Modality used for the diagnosis of Pulmonary TB patients • Sputum Examination • X-rays • Elisa/Blood Examination • Others	 64 28 6 2	 36 47 12 5	15.94	3	0.00116
2	For follow up of Pulmonary TB patients • Sputum Examination • X rays • Elisa/ Blood Examination • Others	 54 36 7 3	 25 49 19 7	19.17	3	0.000190
3	Type of regime prescribed • Alternate • Daily	 92 8	 16 84	116.26	1	0.000001
4	Do you refer poor patients suffering from TB to the nearest DOTS centre ? • Yes • No	 89 11	 45 55	43.78	1	0.000001
5	Do you refer serious patients to the nearest DOTS centre ? • Yes • No	 91 9	 65 35	19.70	1	0.000001
6	Places to get the investigation done • Government accredited Government or Private laboratories • Non-accredited Private laboratories	 95 5	 15 85	129.29	1	0.000001
7	Do you have records of patients already treated or are under treatment ? • Yes • No	 95 2	 2 98	173.14	1	0.000002
8	Average duration of treatment required by the practitioners to treat a new smear positive case • <4 mths • 4-6 mths • 6-8 mths • >8 mths	 0 11 85 4	 4 18 63 15	15.33	3	0.001557
9	Do you treat / Have you treated TB with HIV co-infection ? • Yes • No	 48 52	 11 89	32.31	1	0.000000
10	Which ATT drug you avoid in patients having liver dysfunction • All ATT • Rifampicin • Isoniazid • Others	 78 12 6 4	 82 13 3 2	1.81	3	0.613

government sector and 100 were from private sector. Of this, 48 government and 38 private practitioners were providing their services in rural and peri-urban areas. On sex wise distribution, it was noted that 52 government and 64 private practitioners were males. 34 government and 37 private practitioners had received two years of Post Graduate training. Similarly, 28 government and 41 private practitioners had received three years of Post Graduate training.

The mean duration of practising for government practitioners was 19.7 years and that of private practitioners 15.7 years. However, 24 government and 35 private practitioners had been practising for about five years or less .

92 government practitioners had received some form of training on RNTCP ranging from one to seven days and only 58 private practitioners had received some orientation training on RNTCP of one day only.

Table 4: Views of Practitioners for strengthening of RNTCP

S. No	Views for strengthening RNTCP	Government practitioners	Private practitioners
1	Most effective way by which knowledge of practitioners can be regularly upgraded		
	• CME	58	62
	• Books	32	22
	• Journals	24	32
	• Pamplets /hand notes	18	31
	• Newspapers	12	25
	• Others	22	27
2	Most effective way of creating awareness in the community		
	• TV	91	93
	• Radio	83	86
	• Newspapers	42	58
	• Wall paintings	48	41
	• Street shows	32	24
	• Others	25	19
3	Most effective ways to enhance the participation of private practitioners in RNTCP		
	• Providing incentive for referring patients.	64	82
	• Inviting representative of private professional bodies in running the programme at least at district level	46	61
	• Providing basic infrastructure facilities for routine investigations related to tuberculosis at their clinics	26	31
	• other	51	42

- Number of Government practitioners : 100
- Number of private practitioners : 100

The average number of chest symptomatic patients who were attended by government practitioners was 9.4 compared to 5.2 of private practitioners.

In the present study, all correct responses regarding the knowledge were given one point each and all incorrect or non-responses were allotted zero points. Thus, of the maximum 14, government practitioners scored an average of 9.8 compared to 6.1 of private practitioners.

It was observed in the present study that most of the practitioners were aware of the current status of tuberculosis in India. However, there was statistically significant difference in the knowledge of the two groups in relation to the signs and symptoms, diagnosis, management and operational aspects of RNTCP (Table-1).

On question-by-question analysis, it was noted that most of the private practitioners were unaware of the correct diagnostic modalities. There were statistically significant differences in the knowledge related to the role of X-ray, drugs and prophylaxis between the two groups. It was also observed that there was little awareness between the two groups on the issue related to MDR-TB (35 and 16).

It was noted that there was statistically significant variation in the attitude of two groups of practitioners towards TB patients. While the government practitioners were having a positive attitude towards the fact that a TB patient should be managed as per the guidelines of RNTCP but the private practitioners were against this opinion. However, both were having a positive attitude towards the fact that there is a need for spreading awareness on TB in community (Table-2).

On detailed analysis of question related to the practices common among practitioners of both the groups, it was noted that there was statistically significant difference in the approach of two groups. While the government practitioners followed the guidelines described under RNTCP/WHO, the private practitioners did not follow them (Table-3).

Practitioners of both the groups believe that Continuing Medical Education (CME) is the most effective way of upgrading the knowledge of practitioners on the recent advances made in the field of tuberculosis. Similarly, consensus was also noted on the question of creating awareness among the community. Both the groups were of opinion that television is the most effective way of creating awareness in the community (Table-4).

DISCUSSION

Knowledge of practitioners on TB and RNTCP

It is clear from the present study that government practitioners are more knowledgeable on TB and its management as per Revised National Tuberculosis Control Programme (RNTCP) guidelines compared to private practitioners. The mean score of government practitioners was 9.8 compared to 6.1 of private practitioners. This is similar to the findings reported by Vandana N *et al*[5], Dosumu EA[6] and Ayaya SO *et al*[7] in Lucknow (India), Nigeria and Eldoret Kenya respectively. This is probably because government practitioners had received more indepth training and regular updates from programme managers.

Most of the practitioners were aware of the current situation of Tuberculosis in India. But there was a statistically significant difference in the knowledge about the sputum examination, role of X-ray, treatment categories and treatment duration of new smear positive TB cases. Most of the private practitioners were unaware of the fact that a cough of three weeks' duration should be subjected to sputum examination and that X-ray has only a supportive role in the diagnosis of pulmonary TB[8].

Similar differences in the knowledge were noted between the two groups on the issues related to the operational aspects of the programme. Most of the private practitioners were unaware of the number of treatment categories. However, there was little awareness among both the groups on the issue related to the MDR tuberculosis. Only 35% of government and 16% of private practitioners were aware of the operational definition of MDR tuberculosis[8]. Ayaya SO *et al*[7] also noted similar finding in their study in Eldoret Kenya.

It was noted in the study that most of the practitioners were aware about the pharmacological aspects of TB management. Practitioners were aware about the role of steroids and streptomycin in the management of TB[9]. Similarly, majority of practitioners were aware of the fact that ATT should be stopped in persons who have developed hepatitis while on treatment[8].

Attitude towards TB patients

Most of the practitioners, irrespective of the sectors under which they were providing services, were having a strong positive attitude towards the fact that RNTCP training and regular upgradation of knowledge (recent advances) on TB should be provided to all the practitioners. Similar consensus was also noted on issues related to spreading awareness on TB in community. Swamy RK[10] in his baseline KAP study under RNTCP project had also noted similar consensus among their study participants.

However, statistically significant differences in attitude were noted on issues related to management of TB patients. While the government practitioners were of the opinion that a TB patient should be diagnosed and managed as per the guidelines of RNTCP, private practitioners were against this opinion. There can be various reasons for this differential attitude between the practitioners of both the groups. One of the reasons could be that, TB patient contributes a large bulk of patients reporting to private clinics that too for a long time. Their treatment in government sector will cause huge monetary loss to private practitioners. Other reasons could be that, private practitioners may believe that the alternate day ATT may be less effective or that the quality of drugs provided under RNTCP may be poor resulting in lower cure and higher relapse rate. Besides this, there can be other causes also, thus authors are of the opinion that a separate study should be carried out to assess the causes of this differential approach between the practitioners of both the groups.

Practices common among practitioners for management of TB Patients

The present study has found that there is a statistically significant difference in the approach for the management of TB patients between the two groups. While the government practitioners (64% and 54%) relied on sputum examination for diagnosis and follow up of TB patients, private practitioners prefer X-ray as the most common modality for diagnosis and follow up. Studies carried out by other researchers among private practitioners had also reported similar trends in their studies[2, 3, 11, 12]. Similarly, the government practitioners prefer alternate day regimen (92%) recommended under RNTCP, private practitioners prefer daily regimen. However, the researchers would like to say that the respondents may have reported what they believed to be acceptable, instead of what they actually practised in their clinic. Swamy RK[10] had also shown similar finding in his report.

On the question of referral to DOTS centre, government practitioners do frequent referral of poor and serious patients to the nearest DOTS centre compared to private practitioners. This difference in approach of two groups can be attributed to the fact that there can be huge monetary loss of private practitioners if frequent referral is made by them. Besides this, some patients reporting to private practitioners do not want to be referred to a government hospital. The referral rate found in the present study is similar to rates reported by other researchers like Bhalla A[13], Murthy KJ *et al*[14] and Krishnan A *et al*[15].

It was noted in the present study that most of the private practitioners (85%) preferred non-accredited private laboratories as the most common place for sputum examination compared to government practitioners (5%). Non-accredited laboratories do not have any internal or external quality monitoring system which leads to frequent incorrect reporting, thus leading to false diagnosis by the practitioners. This approach of private practitioners can be assigned to either the lack of awareness about the accredited private laboratories or government laboratories in their locality or to the monetary gain received from these laboratories on referring such patients to them.

The study has also found that practically none of the private practitioners have any record of TB patients they have treated or are under their treatment.

This can be because of a lack of understanding of the Public Health dimension of TB or that they find the RNTCP recording stipulation time-consuming and burdensome. However, this is a potentially dangerous situation where such patients default from treatment and become sources of TB in community. Aryay SO[7] had also made similar observation in their studies.

The present study has found that most of the practitioners (85% and 63%) prescribe ATT for a period of six to eight months to a newly diagnosed smear positive TB case. Similarly, most of the practitioners prefer to stop all ATT if a patient develops liver dysfunction while on ATT. This is similar to the guidelines made under RNTCP programme[8]. Studies carried out by Uplekar M[3] *et al* and Singla N *et al*[2] in two major states of India had also shown similar trends.

It was found that majority of private practitioners do not prefer to treat TB patients who are also suffering from HIV infection. This could probably be due to lack of knowledge about the management of HIV-TB co infection. This is similar to the finding of Kermode M *et al*[16] on health care workers in rural India. However, the researchers are of the opinion that a separate study involving a larger study population should be undertaken to find out the exact reasons behind this differential attitude.

Strengthening of RNTCP programme

Practitioners of both the groups were of the opinion that short Continuing Medical Education (CME) programmes are the most effective way of upgrading the knowledge of practitioners. This is followed by books, journals, etc. Continuing Medical Education (CME) programmes provide valuable opportunities for practitioners to directly listen and interact with specialists and programme managers and get their querries solved in a very short time. Continuing Medical Education (CME) programmes also provide valuable opportunities for private practitioners to upgrade their knowledge on recent advances in the field of TB management.

Similar consensus was also observed on issues of spreading awareness on TB and RNTCP among the members of community. Most of the practitioners were of the opinion that Television and Radio are the most effective way of spreading awareness at a very faster rate in a large section of population.

On the question of increasing the involvement of private practitioners in the programme, most of the practitioners of both the sectors were of the opinion that some monitory support should be provided to private practitioners for making frequent referral to DOTS centres. This will not only encourage the private practitioners to make frequent referrals but it also takes care of the financial losses incurred due to frequent referrals.

CONCLUSION

The present study hereby concludes that there is a large gap in Knowledge, Attitude and Practices on TB and RNTCP among the practitioners of both the sectors. There is an urgent need for upgrading the knowledge, especially of private practitioners on various issues including management of TB in HIV positive patients, guidelines under RNTCP, etc. Regular Continuing Medical Education (CME) programme involving various professional bodies like Indian Medical Association (IMA), Indian Academy of Pediatrics (IAP), etc., can help in fulfilling this job. Regular upgradation of knowledge can also help in changing the negative attitude and practices among the practitioners. The programme managers should also rethink on their strategies so that more and more involvement of private sector can be utilized under the programme. This may also include providing some additional benefits to private practitioners if they make regular referral of TB patients.

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Case Report

SCROFULODERMA - A CASE SERIES FROM RURAL INDIA

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Summary: Cutaneous tuberculosis is the rarest presentation of all the forms of tuberculosis. Scrofuloderma is a frequent manifestation of cutaneous tuberculosis in Indian scenario. Males are affected one and half times more than females. The most common affected age group showing clinical infection is within the first three decades of life. A series of cases mostly malnourished children attending a tertiary care centre in a rural area of central India is being reported. They have presented with a wide spectrum of clinical features, forcing us to establish the final diagnosis by Mantoux test, fine needle aspiration cytology and histopathological examination. The mainstay of treatment remains medical therapy but the underlying cause for severe immunosuppression needs to be ruled out and treated. **[*Indian J Tuberc 2011; 58:* 189-195]**

***Key words*:** Cutaneous Tuberculosis, Scrofuloderma, Rural India

INTRODUCTION

Amongst the infectious diseases, tuberculosis is a leading cause of death in the developing and underdeveloped nations as well as the developed nations. Though improved hygiene, better living conditions, introduction of BCG vaccine and effective chemotherapy, have greatly been responsible for the reduction of prevalence and incidence of tuberculosis, World Health Organisation (WHO) estimates that the incidence of tuberculosis is going to increase in the next five years due to the emergence of multi drug resistant (MDR) *Mycobacterium tuberculosis*. The emergence of HIV has changed the scenario of tuberculosis. Tuberculosis is an important cause of mortality among people infected with HIV. According to WHO, one third of the world's population is infected with tuberculosis bacilli[1].

Cutaneous tuberculosis (TB) constitutes about 1.5% of tuberculosis patients[2]. *M. tuberculosis* is the major causative organism for cutaneous tuberculosis and rarely *M. bovis* can also lead to the condition. It accounts for 0.1-0.9% of the total dermatology out-patients in India[2,3].

The emergence of an immunocompromised host along with an increased use of immunosuppressants like anticancer agents and corticosteroids have given rise to diverse presentations of cutaneous tuberculosis. Cutaneous tuberculosis was classified in 1981 by Beyt *et al* and is widely accepted with some modifications as follows[4]:

Exogenous source:

- Tuberculous chancre
- Warty Tuberculosis or Tuberculosis verrucosa cutis
- Lupus vulgaris

Endogenous source:

- Contiguous spread - Scrofuloderma
- Auto-inoculation - Orificial Tuberculosis
- Hematogenous - Miliary Tuberculosis
  - Lupus vulgaris
  - Tuberculous gumma

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Tuberculides:

- Micropapular - Lichen scrofulosorum
- Papular -Papular or papulonecrotic tuberculide
- Nodular - Erythema nodosum
  - Erythema induratum

Lupus vulgaris (LV) is the most common clinical type of cutaneous TB in adults and scrofuloderma is the most common type seen in children[3,5,6]. A lack of awareness among the common man and clinicians inexperienced about the varied manifestations of cutaneous tuberculosis makes the disease still prevalent in our country.

Case Series

We present a series of cases of scrofuloderma seen in the dermatology outpatient department of Mahatma Gandhi Institute of Medical Sciences situated in a rural area of central India.

Sl.No:	Case history	Investigations
1)	40-year-old male with lesions around left shoulder region, (Fig. 1) gradually progressing over three months. Matted lymph nodes present.	1) Histopathology revealed central necrosis with typical granulomatous inflammation at the periphery. Tissue stained for AFB negative. 2)FNAC from the nodes showed no AFB. 3) Chest X-ray showed pulmonary nodules in hilar area and pleural scarring.
2)	10-year-old boy with an ulcerated lesion with undermined edges over the upper chest (Fig. 2) for two months. Axillary lymph nodes present.	1) Histopathology showed dermal abscess with ill defined histiocytes. AFB staining of the tissue was positive. 2) FNAC stained for AFB was positive. 3) Chest X ray showed infiltrations and cavities. 4)Mantoux test was positive.
3)	12-year-old girl with multiple pustular lesions over the right post auricular region, right supra-clavicular region and near the right anterior axillary region (Fig. 3) for three months.	1)Skin biopsy showed epithelioid cell granuloma with central caseation necrosis. Biopsy specimen stained for AFB positivity. 2)Pus for AFB staining was positive. 3)Chest X ray showed no changes. 4)Mantoux test was positive.
4)	9-year-old boy with cystic lesions over the right infra-mandibular region and the right axillary region. (Fig. 4) for four months.	1)Biopsy showed granulomas with central necrosis. Tissue stained positive for AFB. (Fig. 9) 2)FNAC from the cystic lesions for AFB was positive. 3)Chest X ray showed no changes. 4)Mantoux test was positive
5)	40-year-old male with purulent discharging lesion with scarring over the upper half of the chest (Fig. 5) for two and half a months.	1)Skin biopsy showed granulomas with caseation necrosis in the centre. Tissue stained positive for AFB. (Fig. 10) 2)Discharging fluid stained for AFB was positive. 3)Chest X ray suggestive of pulmonary involvement.
6)	25-year-old unmarried male with enlarged inguinal lymph nodes (Fig. 6) which were associated with pus discharge for three months. No history of any high risk behavior.	1)Skin biopsy showed tubercular granulomas. Tissue stained positive for AFB. 2)FNAC of the nodes was positive for AFB. 3)Chest X ray showed no changes. 4) VDRL was negative.
7)	30-year-old male with lesions over the right infra auricular and supra clavicular region with serous discharge (Fig. 7) for four months.	1) Skin biopsy showed tubercular granulomas with caseation necrosis. Tissue stained for AFB was negative 2) Discharge stained for AFB was positive. 3)Chest X ray showed no changes of tuberculosis.
8)	20-year-old male with lesions over the lower region of the chest with darkening of the surrounding areas (Fig. 8).	1. Skin biopsy showed granulomas with central necrosis. Tissue stained for AFB was negative. 2. Chest X ray was suggestive of old healed tuberculosis.

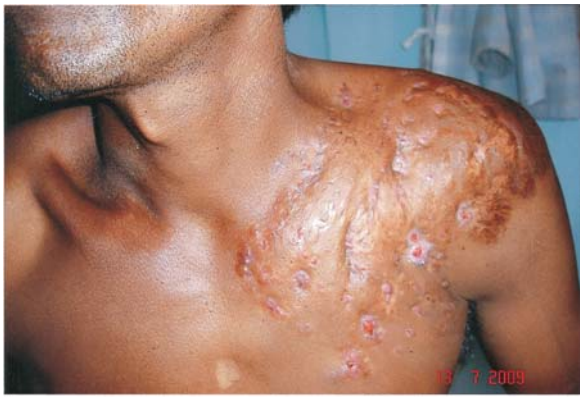

Figure 1: 40-year-old male with lesions around left shoulder region, gradually progressing over three months. Matted lymph nodes present.

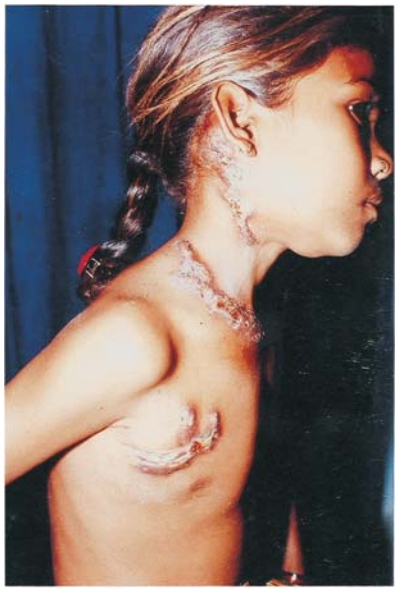

Figure 3: 12-year-old girl with multiple pustular lesions over the right post auricular region, right supra-clavicular region and near the right anterior axillary region for three months.

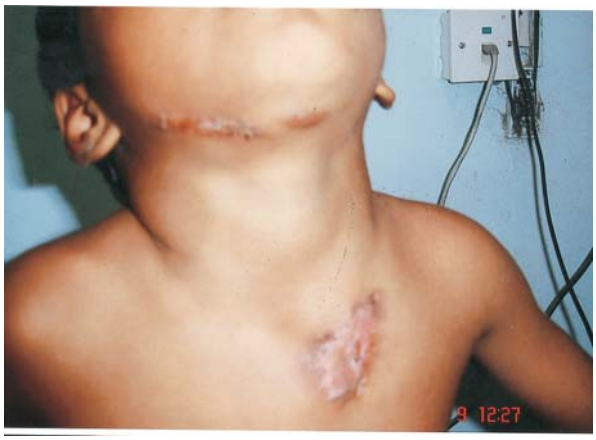

Figure 2: 10-year-old boy with an ulcerated lesion with undermined edges over the upper chest for two months. Axillary lymph nodes present.

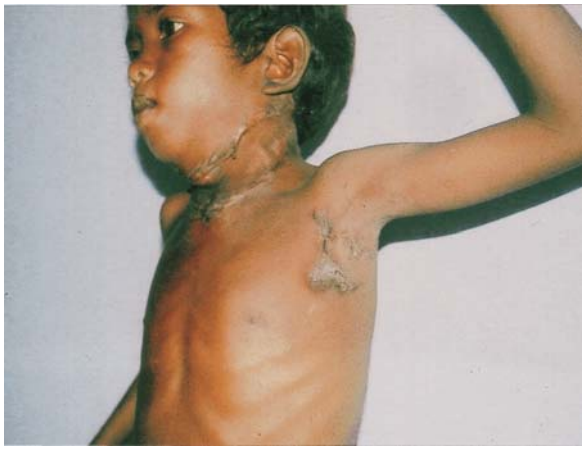

Figure 4: 9-year-old boy with cystic lesions over the right infra-mandibular region and the right axillary region for four months.

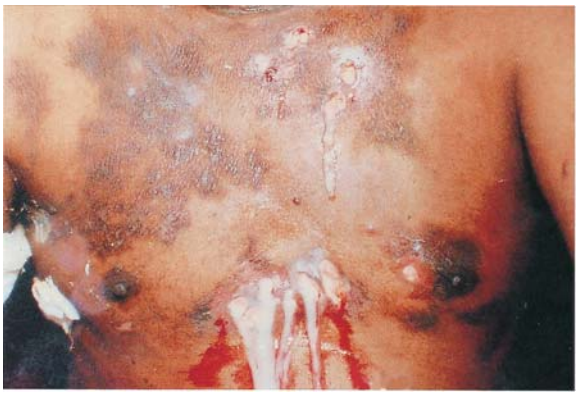

Figure 5: 40-year-old male with purulent discharging lesion with scarring over the upper half of the chest for two and half months.

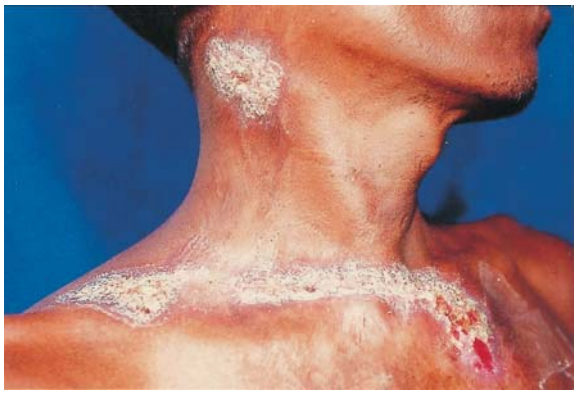

Figure 7: 30-yr-old male with lesions over the right infra auricular and supra-clavicular region with serous discharge for four months.

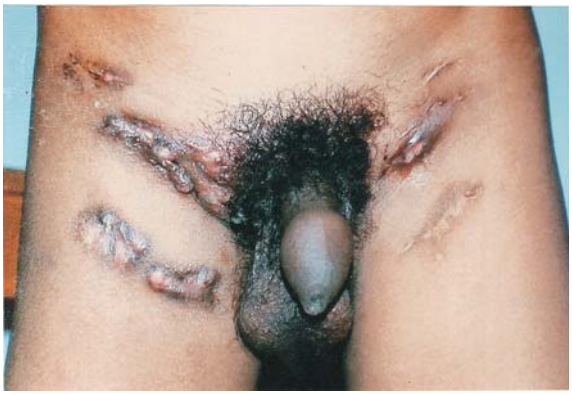

Figure 6: 25-year-old unmarried male with enlarged inguinal lymph nodes which were associated with pus discharge for three months. No history of any high risk behaviour.

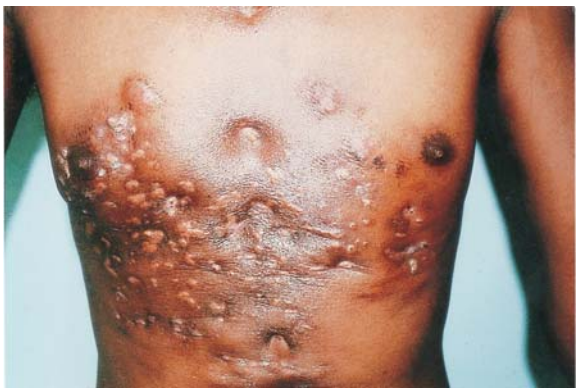

Figure 8: 20-year-old male with lesions over the lower region of the chest with darkening of the surrounding areas.

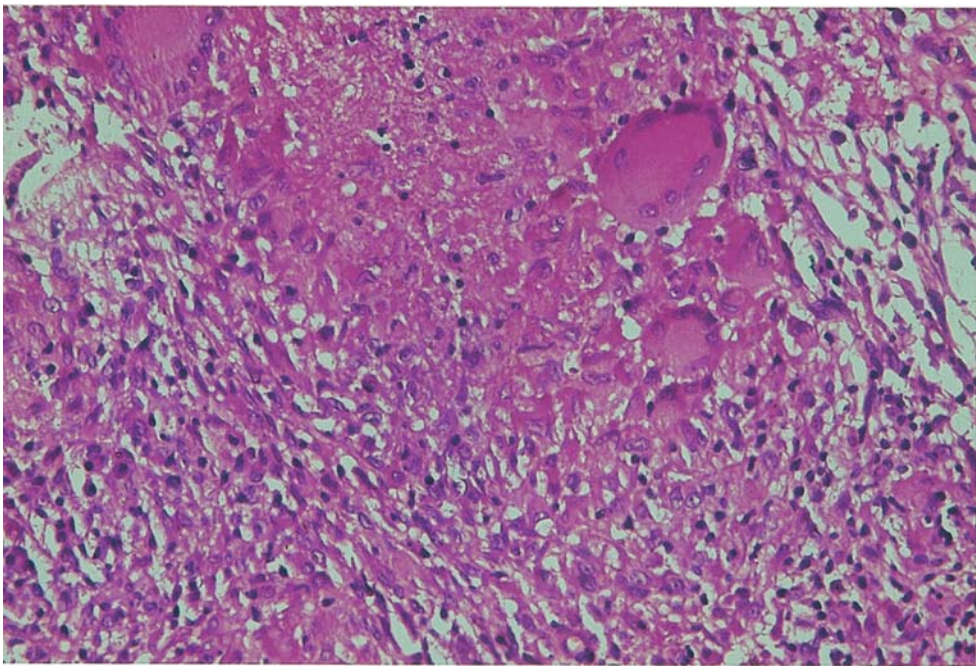

Figure 9: Hematoxylin and Eosin stained biopsy specimen at 400X showing tubercular granuloma.

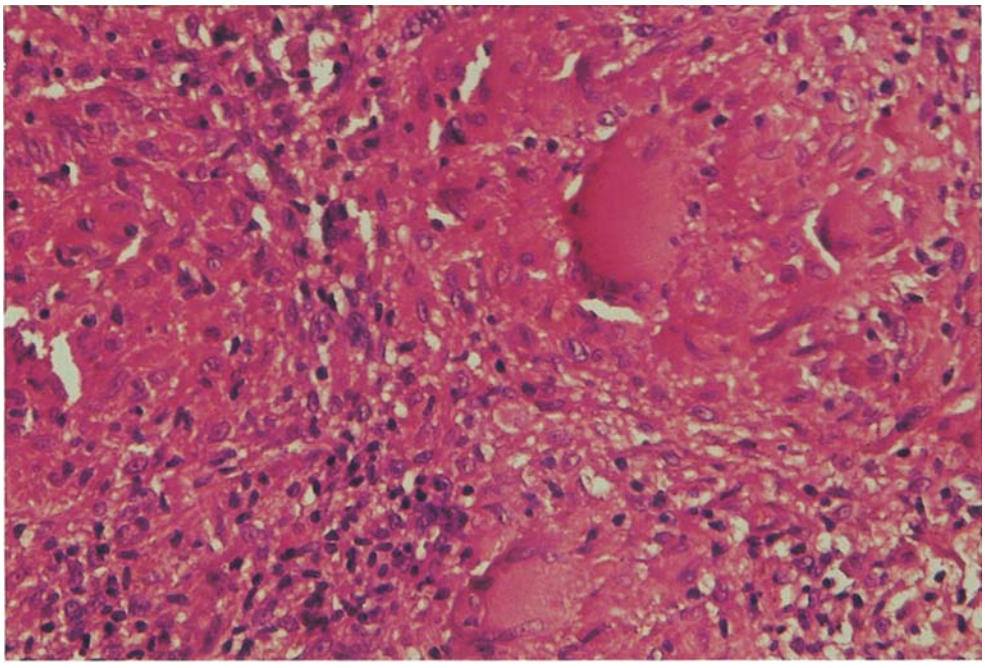

Figure 10: Hematoxylin and Eosin stained biopsy specimen at 400X showing tubercular granuloma.

DISCUSSION

Scrofuloderma occurs as a result of spread of infection to the skin from an underlying tuberculosis focus, usually a lymph node but also infected bones or joints. The lesions start as firm, painless and subcutaneous nodules that gradually enlarge and suppurate and then, form ulcers and sinus tracts in the overlying skin. Typical ulcers have undermined edges and a floor of granulation tissue. Scrofuloderma lesions show presence of acid fast bacilli (AFB) from stained cytology smears or biopsy samples as well as positive cultures for mycobacteria compared with other types of cutaneous tuberculosis[7,8]. Tuberculin sensitivity usually is marked. But it has a very low specificity.

Histopathological examination is very important in the diagnosis of cutaneous tuberculosis. Histopathology reveals the presence of characteristic tubercular granulomas with epithelioid cells, Langhan's giant cells and lymphocytes. Features like distribution of granulomas in the dermis, nature of cellular infiltrate, presence of necrosis and certain specific epidermal changes aid in the classification and diagnosis of the variants of cutaneous tuberculosis. Histopathology of cutaneous tuberculosis can mimic many other diseases which produce tuberculoid granuloma[6].

The diagnosis of scrofuloderma in our cases was confirmed by histopathology, staining of the biopsy and fine needle aspiration cytology (FNAC) specimens and Mantoux test. Pus discharge from the lesions was stained for AFB. Chest X ray was done in all our patients to look for any foci of pulmonary tuberculosis and four out of eight cases had positive findings. All our patients were also screened for HIV and none was found to be reactive.

Cutaneous tuberculosis can be confused with cutaneous leishmaniasis, leprosy, atypical mycobacterial infections, chromomycosis, sporotrichosis and sarcoidosis. Many of these like sarcoidosis shows granulomas, but in sarcoidosis the granulomas are naked tubercles with a small focus of necrosis in the centre with inclusion bodies. Moreover, steroids are the mode of treatment in sarcoidosis, but in our cases, all of them started responding to anti- tubercular treatment.

An increased number of farmer deaths in this part of rural India, in the recent times have gained quite awareness amongst all of us. Such incidents are due to a reduction in the per capita income of the family, thereby affecting the nutrition, especially of growing children in such areas. Most of the patients in our case series belong to families of low socio-economic status with poor living conditions. Various studies have shown that childhood cutaneous TB patients were residing in overcrowded dwellings with severe malnutrition[7,9]. Malnutrition, in turn, reduces the immunity of the individual making him/her more susceptible to cutaneous tuberculosis.

The general measures taken should be to treat the malnutrition, treat any concomitant illness causing immunosuppression, and giving anti-tuberculosis treatment as per the recommendations of therapy for extrapulmonary TB. WHO recommends (2009) treatment of cutaneous tuberculosis in HIV negative individuals (both adults and children) using directly observed treatment short course (DOTS) chemotherapy consisting of four drugs, isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) given for two months (intensive phase), followed by isoniazid and rifampicin given for the next four months (continuation phase)[10]. The drugs are administered daily or three times weekly. This regimen was followed in our patients. Alternatively, daily intensive phase followed by three-times weekly continuation phase [2HRZE/4(HR)3] or three-times weekly dosing throughout therapy [2(HRZE)3/4(HR)3] may also be used.

TB patients with known positive HIV status or living in an HIV-prevalent setting should receive daily doses of antitubercular drugs, at least during the intensive phase. For the continuation phase, the optimal dosing frequency for such patients is also daily, although the three-times weekly dosing is an acceptable alternative.

Most of the cases discussed above are of malnourished individuals, most of them being PEM. **Hence, Scrofuloderma needs to be diagnosed early**

in children and has to be treated promptly in addition to taking care of the nutrition, thereby improving the immunological status.

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Original Article

DETERMINANTS FOR THE RETREATMENT GROUPS OF PULMONARY TUBERCULOSIS PATIENTS TREATED IN A DOTS PROGRAMME IN SIKKIM, INDIA

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Summary

Objective: To assess knowledge, attitude and different health-seeking behaviours among 250 cured and 250 category-II tuberculosis patients.

Methods: A case-control study was conducted in different health settings in Sikkim, a part of the Indian continent. A questionnaire was filled for the purpose.

Results: Results showed significant differences in overcrowding, smoking and alcohol intake. There was a general unawareness with the disease and its treatment between the two groups. 45% of the respondents reported that tuberculosis is caused by germs. 81.4% stated that tuberculosis presents only as cough. 94.8% of the case group and 90.8% of the control group stated that it is a transmissible disease. Sharing food with tuberculosis patients (64% of case group, 55% of the control group; $p<0.05$), inadequate diet (16.4% of case group, 9.6% of the control group; $p<0.03$) were mentioned as modes of transmission. Sixty six per cent of the case group and 56.8% of the control group mentioned the use of DOTS for prevention and control ($p<0.05$). Sixty three per cent of the control group regarded tuberculosis as a life threatening condition ($p<0.00$) [(adjusted OR=2.04, (95%CI: 1.43, 2.93)]. Tuberculosis was considered as a completely curable disease by 96.4% of the case group ($p<0.05$). 40.6% of the respondents agreed to be in contact with a tuberculosis infected person. 64% of the retreatment group discontinued their treatment due to frequent travelling for work.

Conclusion: The study revealed lack of knowledge, positive attitude and inappropriate health seeking behaviours among of the tuberculosis patients, irrespective of their categorization. **[*Indian J Tuberc 2011; 58: 178-188*]**

Key words: Default, Failure, Relapse, Tuberculosis, Knowledge, Attitude, Practice

INTRODUCTION

Tuberculosis (TB) is one of the leading causes of morbidity and mortality resulting in huge economical loss in low income countries. The South East Asia Region accounts for 34% of the global TB burden. India ranks among the first five countries, out of the 22 high burden countries which contributes 80% of global load[1]. Directly Observed Treatment Short-course (DOTS) is providing medical care and treatment to the TB patients in a manner that is convenient and accessible. However, guaranteed compliance to treatment by the patient and health care providers are the key to the success of DOTS. Sikkim, the 22nd state of India, has faced several impediments with regard to the treatment of tuberculosis. The retreatment category represents the more serious groups in the Revise National Tuberculosis Control Programme (RNTCP) where outcome of anti-tubercular therapy is often not satisfactory. According to the RNTCP annual report of 2008, the cure rate of new cases in Sikkim stood at 87.2% but the cure rate of the retreatment group was found to be only 49.1%. Similarly, the failure rate of new cases was 8.3% but the failure rate of the retreatment group was 21.4%[2]. A study in Egypt revealed that the significant risk factors for treatment failure were non-compliance to treatment, due to deficient health education and poor patient knowledge about the disease[3]. The purpose of this research is to determine to what extent the cured tuberculosis patients and retreatment tuberculosis patients were educated about tuberculosis and its treatment, their outlook, approach in addition to practices regarding DOTS, RNTCP and to assess the factors regarding their

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role in influencing the outcome of the anti-tubercular treatment. Moreover, very little is known about healthcare-seeking behaviour of the tuberculosis infected people in Sikkim with regard to TB. To tackle this huge problem, it is important to address all the issues. Studies in different countries have reported that knowledge about and stigma towards TB is affected by socio-economic variables[4,5]. Low awareness[6], stigma[7,8], illiteracy[9] and gender[10]. We carried out this study with the objectives (i) to determine the factors responsible for default, failure and relapse; (ii) to gain a clearer perspective into the health assumptions and beliefs surrounding tuberculosis; its treatment and prevention; (iii) Role of KAP in influencing the treatment outcome as an end point indicator.

MATERIAL AND METHODS

Study Area

The study was carried out in Sikkim, a Himalayan state of India. Large tracts of the state are covered by snow-clad peaks, glaciers of higher Himalaya in the north and with dense forest cover of mid-Himalaya. It shares its borders with the plateau of Tibet, China in the north, Bhutan in the east, Nepal in the west and contiguous with the West Bengal in the south. Five potential health facilities in the state were selected from different geographical locations for the data collection on the basis of population distribution, namely Mangan district government hospital (North), Sir Thutob Namgyal Memorial hospital and Central Referral Hospital, Manipal (East), Geyzing district government hospital (West) and Namchi district government hospital (South).

Study Population and Study Design

The data was collected by carrying out a survey in all the four districts of Sikkim to identify default, failure and relapse cases. The analysis of data was carried out by case-control study design. The default, failure and relapse cases were taken as cases and those who received treatment and cured were taken as controls. We matched cases and controls by age and gender, keeping the ratio of cases and controls 1:1. The study was carried out during January 2009 to June 2010.

Case definition

Patients who were enrolled under category II regimen of Directly Observed Treatment Short-course (DOTS) were considered as "**Cases**".

A patient, who had not taken anti-tubercular drugs for two months or more and is sputum smear positive, was considered as a case of "**default**". The patient, who was smear positive at five months or more was taken as a case of "**failure**" and those patients who had been declared cured of pulmonary tuberculosis by a physician but reported back to the health service as smear positive was taken as "**relapse**" .

Control definition

Patients, who had pulmonary tuberculosis in the past, but got completely cured by using either category I or completed category III of DOTS regimens. Theirs sputum samples having remained negative for acid fast bacilli at the end of completion of category I or category III of DOTS regimen and they continue to remain sputum negative till the end of this study period.

Inclusion criteria for selection of cases and controls

Individuals in the age group of 18 years and above of either sexes of indigenous population, diagnosed and treated in the five different health facilities in Sikkim.

Relapse cases were recruited from retrospective record and the cases were registered only after they fulfilled the criteria of relapse at treating DOTS centre.

Exclusion criteria for selection of cases and controls

Those patients who refused to give informed written consent to participate in this study or if he/she

could not be contacted after three attempts on separate occasions, was excluded from this study.

Non-respondent criteria for selection of cases and controls

If a designated respondent was found to be having severe behavioural problems or cognitive impairment or if he/she was suffering from severe hearing impairment or articulation disorder or any terminal illness then he/she was considered as a non-respondent.

Data Collection

A pre-tested semi-structured, open-ended questionnaire form was designed which was completed by face-to-face interview by a trained data collector after obtaining written consent from the participant. The questionnaire consisted of two sections: Section one, dealing with patient background (age, sex, ethnicity, educational level, financial status, marital status, presence of overcrowding, TB unit, habit of smoking/drinking and previous history of treatment with anti-TB chemotherapy). Section two, probing patient's knowledge, attitude and practice through several basic questions on tuberculosis (source of information, causative agent, mode of transmission, food habits and addiction habits, symptoms, seriousness of the disease, diagnostic investigations, their compliance to drugs, side effects of anti-tuberculosis therapy, disturbance of regular activities by anti-tubercular regimen, practice of follow-up, preventive measures taken by the patient, BCG vaccination, their suggestions to other TB symptomatic cases, quality of service provided by DOTS and adherence to treatment).

HIV testing was carried out in all the patients who gave consent for the test and was performed following NACO guidelines.

Data analysis

Data were entered in EpiInfo 3.5.1 version by the process of double entry and analyzed by using the EpiInfo 3.5.1 version and SPSS-version 13. Association of potential socio-demographic and treatment related risk factors among defaulters, failures and relapse was initially studied through univariate analysis. Chi--square test was applied to compare the relationship between different variables against "cases" and "controls". To determine the independent effect of various factors on "cases" and "controls", multiple logistic regression was performed and their significance was estimated in terms of adjusted OR and their 95% confidence intervals. *P* value less than 0.05 was considered as significant. Some 15% of all the cases were randomly selected and re-interviewed by the study supervisor within a week of the original interview.

Ethical statement

Ethical permission for the study was obtained from the State TB Cell, Government of Sikkim, state task force (RNTCP) and PhD review committees of Sikkim Manipal University. These questionnaires were translated into the local language Nepali & Hindi and tested for its consistency, clarity and cultural acceptance. The data generated through the pre-test was not included for analysis at the end of the final study. Written consent was obtained from the study participants.

RESULTS

The study was carried out from Jan'09-June'10, in which 250 of each cases (25-defaulters, 134- failures and 91- relapse) and matched controls were taken.

Socio-Demographic Profile (Table 1)

A large number of respondents (75.8%) belonged to the age- group of 18-35 years. Sixty three per cent of the respondents were males and 37% were females. Regarding the ethnic status, 65% were of Nepali origin, 23.2% of Bhutia origin and 7.6% of Lepcha origin and 4% were non-locals. About 70% of the respondents were from the east district. Forty eight percent were unemployed, 12.8% were professionally employed, 27.8% were skilled and 11% were unskilled labourers. Sixty two percent and 65.4% of respondents were of single status and financially dependent on some other members of the family respectively.

Table 1: Factors associated with Demography, Knowledge, Attitude and Practice among the TB patients in the four districts of Sikkim

Category		Total	X^2	P-value	OR	95% C.I	
						Low	High
Overcrowding	Absent	326(65.2)	6.43	0.01	1.64	1.13	2.38
	Present	174(34.8)					
Financially	Dependent	327(65.4)	0.32	0.57	1.13	0.78	1.64
	Independent	173(34.6)					
H/O T.B in family	Yes	130(26.0)	1.76	0.18	1.34	0.89	2.00
Smoking	Regular	190(38.0)	3.74	0.05	0.69	0.48	0.99
	Non Smoker	310(62.0)					
Alcohol	Regular	211(42.2)	7.38	0.00	0.59	0.42	0.86
	Non-alcohol	289(57.8)					
Main causes of TB:	Infection by germs	225(45.0)	0.29	0.58	1.11	0.78	1.59
Condition that	Inadequate diet	65(13.0)	4.52	0.03	0.54	0.31	0.92
favours the spread:	Sharing food with TB pts	298(59.6)	3.66	0.05	0.69	0.48	0.99
Ways to prevent the occurrence:	Starting DOTS at the earliest	306(61.2)	3.71	0.05	0.68	0.48	0.98
Source of information on DOTS:	Doctor	232(46.4)	12.23	0.00	0.52	0.36	0.74
Have you taken BCG injection?		168(33.6)	5.60	0.01	0.62	0.43	0.90
Is TB a life threatening condition ?		272(54.4)	14.90	0.00	2.04	1.43	2.93
Is TB completely curable?		471(94.2)	3.66	0.05	0.42	0.19	0.96
What will you do if family/friends show symptoms of TB:	Advise him to go to the hospital	311(62.2)	7.65	0.00	1.70	1.18	2.45
Will you motivate your relatives to take a complete course of DOTS regimen		486(97.2)	3.60	0.05	0.26	0.07	0.95
Have you done sputum culture?	Yes	171(34.2)	205.33	0.00	0.02	0.00	0.04
Close contact with any person who had cough		203(40.6)	11.55	0.02			
Was there any :	No	363(72.6)	11.12	0.00			
	Memory loss	29(5.8)					
	Depression	108(21.6)					
Experienced any problem in taking the drugs	Loss in appetite	5.72	0.01	0.39	0.19	0.82	

Table 2: Knowledge about TB among TB patients in the four districts of Sikkim.

Category		Case group n (%)	Control group n (%)
Main causes of TB of lungs:	Infection by germs	109(43.6)	116(46.4)
	Curse of God	3(1.2)	5(2.0)
	Bad habits	123(49.2)	106(42.4)
	Inadequate diet	95(38.0)	78(31.2)
Common symptoms:	Cough for=> 2 wks	209(83.6)	198(79.2)
	Chest pain	58(23.2)	59(23.6)
	Blood in sputum	49(19.6)	51(20.4)
	Difficulty in breathing	27(10.8)	32(12.8)
	Evening rise of temperature	93(37.2)	79(31.6)
	Prolonged fever	103(41.2)	88(35.2)
	Loss of appetite	57(22.8)	60(24.0)
	Weight loss	37(14.8)	31(12.4)
	Weakness	95(38.0)	91(36.4)
Is TB transmissible from one person to another?		237(94.8)	227(90.8)
Perceptions about the mode and spread of TB	Contaminated water	9(3.6)	6(2.4)
	Air pollution	23(9.2)	15(6.0)
	Contaminated food	9(3.6)	4(1.6)
	Inadequate diet	41(16.4)	24(9.6)
	Overcrowded conditions	15(6.0)	9(3.6)
	Ill-ventilated/Ill-luminated rooms	3(1.2)	1(0.4)
	Damp and moist conditions	9(3.6)	8(3.2)
	Sneezing and coughing without covering face	72(28.8)	98(39.2)
	Spitting out on floors and walls	27(10.8)	28(11.2)
	Indiscriminate dumping of garbage	10(4.0)	19(7.6)
	Sharing food with TB pts	160(64.0)	138(55.2)
Prevention and control	Avoid residing in overcrowded conditions	7(2.8)	13(5.2)
	Avoid residing in ill-ventilated/luminated	4(1.6)	6(2.4)
	rooms	74(29.6)	77(30.8)
	Covering with hanky while coughing	35(14.0)	35(14.0)
	Avoid spitting on floors and walls	164(65.6)	142(56.8)
	Starting DOTS at the earliest		
Source of information on DOTS:	Family	13(5.2)	13(5.2)
	Friend	8(3.2)	14(5.6)
	Health worker	67(26.8)	54(21.6)
	Doctor	136(54.4)	96(38.4)
	Radio/TV	27(10.8)	31(12.4)
	Posters	15(6.0)	23(9.2)
	School	1(0.4)	1(0.4)
Have you taken BCG injection?		97(38.8)	71(28.4)
If yes, do you know for what reasons	Protection from TB	8(3.2)	7(2.8)

Illiteracy was found to be more (30%) in the case group though statistically insignificant. Overcrowding [40.4% in cases and 29.2% in control group (adjusted OR=1.64, (95%CI: 1.13, 2.38)], smoking [42.4% in cases and 33.6% in control group] and regular alcohol intake [48.4% in cases and 36.0% in control group] was found to be significantly higher in the case group.

Knowledge of respondents on tuberculosis (Table 2)

Among the 500 patients who were taken into the study, only 45% of respondents knew that tuberculosis was caused by germs. There were no significant differences in their knowledge on the cause of tuberculosis in the two groups. Knowledge on various symptoms of tuberculosis was very poor in the respondents ranging from 11.8% to 38.2% except 81.4% of the respondents knew cough for> 3 weeks is a symptom of tuberculosis. No significant difference was seen on the symptoms of tuberculosis in the two groups. However, 92.8% respondents knew tuberculosis could be transmitted from person to person, though significant difference was not seen in the two groups. Knowledge on the modes of transmission like air pollution (7.6%), overcrowding (4.8%), residing in ill-ventilated and ill-luminated rooms (0.8%), damp and moist conditions (3.4%), sneezing and coughing without covering face (34%) and spitting on floors and walls (11%) was found to be inadequate in both the groups. Regarding knowledge about the various methods of prevention and control of tuberculosis, 61.2% and 30.2% of respondents knew tuberculosis could be prevented by starting DOTS at the earliest and by covering the mouth while coughing. Significant number of case group knew tuberculosis could be prevented by starting DOTS at the earliest. Knowledge regarding other preventive aspects was poor ranging from 2%-14% in both the groups. Doctors (46.4%) and health workers (24.2%) is the main source of information on DOTS to the respondents. Other sources like radio/TV and schools imparted information on DOTS only in 11.6% and 0.4% of the respondents respectively. Significant number of respondents in the case group received information on DOTS from doctors. Only 33.6% of the respondents knew that they had received BCG vaccination during

Table 3: Attitude of TB patients towards TB in the four districts of Sikkim.

Category		Case group n (%)	Control group n (%)
Is TB a life threatening condition?		114(45.6)	158(63.2)
Is TB completely curable?		241(96.4)	230(92.0)
What will you do if	Avoid him	5(2.0)	2(0.8)
family/friends show	Stop sharing food, clothes or room with him	11(4.4)	10(4.0)
symptoms of TB:	Advise him to go to the hospital	140(56.0)	171(68.4)
	Advise him to go to the DOTS centre	79(31.7)	47(18.8)
	You take him to the nearest DOTS centre	31(12.4)	40(16.0)
	Report the case to the nearest DOTS centre	13(5.2)	8(3.2)
	Discuss this matter with health personnel.	1(0.4)	7(2.8)
Complete course of DOTS regime can cure TB?		235(94.0)	235(94.0)
Any need to complete the course even after symptoms subside?		145(58.0)	126(50.4)
Any need to stop alcohol intake while on DOTS regimen?		243(97.2)	234(93.6)
Is it essential to isolate a patient till the completion of DOTS regimen?			
If any relatives get diagnosed with tuberculosis will you motivate him to take a		217(86.8)	201(80.4)
complete course of DOTS regimen?		247(98.8)	239(95.6)

childhood, but only 3% of the respondents knew it is a vaccine for tuberculosis.

Attitude of respondents on tuberculosis (Table 3)

Significant number of the respondents in the control group (63.2%) [Adjusted OR=2.04, (95%CI:1.43,2.93)] regarded tuberculosis as a life threatening condition and significant number of respondents in the case group (96.4%) believed that tuberculosis is a curable disease. Majority of the respondents (62.2%) [Adjusted OR=1.70, (95% CI:1.18,2.45)] advised other tuberculosis patients to go to the hospital, whereas only 25.3% of the respondents advised them to go to the DOTS centre. Their other attitude towards tuberculosis patients like taking a tuberculosis patient to a DOTS centre, reporting a case of tuberculosis to a DOTS centre and discussing about tuberculosis case with health personnel was poor ranging from 1.6%-14.2%. Majority of the respondents (98.6%) said that they would not like to avoid tuberculosis infected patients. Ninety five percent and 97.2% of the respondents said they would not take alcohol during DOTS regimen and would motivate other tuberculosis patients to take a complete course of DOTS regimen. Only 54.2% of

Table 4: Practice of TB patients towards TB in the four districts of Sikkim.

Category		Case group n (%)	Control group n (%)
Have you done sputum culture?		162(64.8)	9(3.6)
Did you ever come in close contact with any person who had TB	Yes	106(42.4)	97(38.8)
	Lived together	35(33.3)	51(51.5)
	Worked together	6(5.7)	10(10.1)
	Regularly met	19(18.1)	8(8.1)
	Occasionally met	42(40.0)	27(27.3)
	Rarely met	3(2.9)	3(3.0)
Regular follow up sputum examination during last DOTS treatment	Yes	237(94.8)	225(90.0)
Discontinued DOTS state reasons:	Yes	25(10.0)	0(0)
	Chest symptoms subsided early	1(4.0)	
	Lost motivation to continue for 6-8 months	1(4.0)	
	Due to work, have to frequently travel around	16(64.0)	
	Do not want to visit centre due to stigma	4(16.0)	
	Medicines are too strong, feels weak	3(12.0)	
Was there any :	Memory loss	17(6.8)	12(4.8)
	Depression	68(27.2)	40(16.0)
Any inconvenience in taking the treatment under supervision	Yes	50(20.0)	54(21.6)
Ever lost wages while taking treatment	Yes	42(16.8)	50(20.0)
Ever needed an escort to reach the DOTS Centre	Yes	50(20.0)	55(22.0)
Experienced any problem in taking the drugs	Yes	129(51.6)	124(49.6)
	Difficulty in swallowing	38(15.2)	47(18.8)
	Vomiting	46(18.4)	55(22.0)
	Headache	14(5.6)	15(6.0)
	Nauseous	37(14.8)	33(13.2)
	Giddiness	16(6.4)	20(8.0)
	Weakness	18(7.2)	14(5.6)
	Loss in appetite	26(10.4)	11(4.4)

the respondents said that they would need to take DOTS treatment even after symptoms subside.

Practice of respondents on tuberculosis (Table 4)

Majority of the respondents (92.4%) came for regular follow-up of sputum examination during the treatment course; though significant difference was not seen in the two groups. Significant number of respondents (42.4%) gave history of close contact with persons who had cough. Significant number of respondents (64.8%) underwent sputum culture during investigations. Only 25% of the case group discontinued DOTS treatment, the most common cause for the discontinuation of DOTS was frequent travel due to one's work (64%). Only 18.4% of respondents lost wages during the course of treatment, significant difference was not seen in the two groups. Though vomiting was the most common side effect experienced by the respondents, significant number of case group experienced loss of appetite as side effect to the drugs.

Practice profile of the case group

About 80% of the case group knew that they were undergoing the treatment twice ($p<0.005$), 68.8% knew that they were given Cat-I treatment on the initial infection ($p<0.005$) and 53.6% correctly said that they were not cured initially and hence were on further treatment.

DISCUSSION

In this study, we identified some important gaps in their knowledge, attitude and practice of respondents on tuberculosis. We observed overcrowding, smoking habits and regular alcohol intake to be significantly higher in the case group. Other studies also support significant role of overcrowding [16], Smoking[12, 13] and alcohol consumption[14,15] in tuberculosis. Respondents in the case group were more illiterate compared to control group, though not significant statistically.

Our study showed that only 45% of the respondents recognized infection by germs to be the main cause of tuberculosis, though significant difference was not noted in the two groups. Similar to our findings, studies in India[17] and rural part of China[18], also reported inadequate knowledge of the participants on the causative agents of tuberculosis. Generally, it has been found that patients with symptoms usually recognize the severity of the disease and have a higher chance of compliance[19]. Though cough> 3 weeks, fever and hemoptysis are the most well known symptoms of pulmonary tuberculosis, majority of the respondents knew (81.4%) only cough >3 weeks as the common symptom of pulmonary tuberculosis. Knowledge on other symptoms of pulmonary tuberculosis was very poor in our respondents. Studies in South India[20] and Bangladesh[21]have also reported cough and fever as symptoms in tuberculosis. Although the germ theory was not well- known, majority (92.8%) of the respondents knew that tuberculosis is a communicable disease; it is an uplifting feeling that the greater awareness of this knowledge in the present study is encouraging as ignorance of this fact has the consequences of increasing transmission of the disease. However, majority of them lacked to have correct knowledge on the mode of transmission. Wrong perceptions, like tuberculosis is spread by sharing food with tuberculosis patients (59.6%) and inadequate diet (13%) observed in the respondents needs to be addressed to remove misconception and stigma attached with the disease. As a result of this ignorance, patients will not adopt the correct preventive and the control measures in their household and /or workplace. In our study, significant number of respondents believed in starting DOTS at the earliest to prevent the spread of tuberculosis, these findings indicated that DOTS, if implemented effectively, can achieve and maintain its target of case detection and cure rate of tuberculosis among the symptomatics and their treatment. Since overcrowding was found to be significant in our demographic finding, only 4% of the respondents had the knowledge to avoid staying in overcrowded conditions, thus implying that the patients by and large do not seem to be well-known with the enormous role of crowded and poorly ventilated places in spreading tuberculosis[23]; certain measures have to be taken to understand its importance in transmission of the disease. Preventive measures in other studies have included keeping body and house clean, avoiding infected people, eating clean food, water, eating healthy food, dusty air and stop smoking[22,29]. Our study shows that majority of the respondents had acquired

knowledge regarding DOTS from the hospital workers; however, communications through mass media including TV/radio and posters, health education for school and public was seen deficient which points to overall lack of community awareness and need of public education. It is known that most countries use BCG vaccines as a part of their TB-control programmes. Vaccination of BCG as a protective means against tuberculosis was mentioned by only 3% of the respondents however; only 33.6% of the respondents had the knowledge that they were vaccinated. Overall, certain information like tuberculosis being caused by tubercle bacilli, the disease infectivity and the implications of BCG vaccination, is highly specialized and specific information, not understood by most patients; furthermore, the health care providers may not go in-depth and profoundly in explaining these facts to majority of the patients. Another reason could be that generally, hospitals are crowded health setting so in most cases the interaction between the healthcare providers and the patients may be insufficient for the initiation of a complete and satisfactory educational dialogue.

In this study we found that 63.2% of the control group perceived tuberculosis to be a life threatening disease ($p<0.05$). This attitude or belief of theirs may have played some role in taking tuberculosis treatment seriously and adhering to the treatment better than the case group. However, it is also of great importance for the patients to know that tuberculosis is curable but with regular treatment. The majority of (94.2%) respondents in this study also believed that tuberculosis is a curable disease ($p<0.05$). On one hand, the attitude of casually believing that tuberculosis is curable may have landed the case group on Cat-II regimen or it can be explained by the fact that most of the respondents were interviewed after having treatment for a long period of time after which they felt free of symptoms. Awareness designed to create adequate knowledge should impart proper knowledge as well as should teach the individual to implement their knowledge in their regular life correcting their wrong attitude to right. We also observed a genuine concern among the respondents towards other tuberculosis patients, however, the extra effort or going out of one's way to inform others about DOTS seems to be lacking in both the groups. Hence, efforts can be diverted towards the patients by actively involving them in the programme. This study also highlights serious deficiencies in the attitude of the respondents about their disease. About 46% were of the view that treatment can be stopped after symptoms subside. Poor drug compliance could contribute to multi drug resistance in the country.

The health care seeking behaviour of the respondents was good in terms of regular follow-up of sputum examination, though some of them discontinued their treatment as a result of wrong perceptions and work related financial resources. Similar reasons were mentioned in other studies[25, 31]. Considerable number of respondents had reported side effects to the drugs which were seen in other studies[24,30]. It has also been documented that when patients know about the natural history of TB, its complications and the importance of complying with drug therapy, their adherence to the prescribed regimen is improved [28]. Studies in central India[26] and in Malawi[27] have shown that, patients who completed treatment had a better understanding of the duration of TB treatment than patients who interrupted treatment. Majority of the respondents (79.2% of case group and 85.6% of controls group) did not give consent for HIV testing. Tuberculosis patients may deliberately conceal their HIV status to avoid further isolation or stigma. They may try to live with it for as long as possible, being the source of infection to others. All the participants who had undergone HIV testing, were found to be non-reactive. HIV/AIDS is known to play a major role in increasing the burden of TB, but it was not seen in our study. It was seen that 42.2% of the case group and 38.8% of the control group had come in close contact with people suffering from cough, it was observed that only a small per cent of people actually demonstrated sufficient knowledge or had proper health care seeking practice of TB which shows overall poor practice in health care.

In the practice profile of the case group, it was seen that significant number of them had better practice in knowing about the categories they were given, number of treatment they had undergone and also about the outcome of their previous treatment. Nonetheless, it would be hard to ignore the fact that since this particular group had been in the regimen

twice or even thrice, a majority of these patients can end up being multi-drug resistant or even extensive drug resistant, if proper and constant guidance, monitoring and counselling are not given to this delicate group as the world is already bearing the brunt of the negligence and inattention to the TB control programmes in the initial years of the operation. Hence, there is a need to emphasize the need to understand the reasons for the misconceptions about TB and address it properly. Lack of motivation and training of health care providers can also affect the patient's knowledge about the disease as knowledge is known to be associated with health care practice and actions based one's attitude. TB control could improve significantly if more consideration were given to knowledge, attitude and practice towards tuberculosis and related healthcare seeking pattern among the people[11].

CONCLUSION

We observed poor knowledge, inappropriate health care seeking behaviour and non-participative attitude towards tuberculosis among the cured and retreatment patients. Demographic factors like smoking, consuming alcohol, overcrowding were found to be significant, nonetheless, no difference was observed in the knowledge, attitude and practice between the two groups. This clearly shows the kind of information that is being forwarded to these two categories of patients, irrespective of their categorization of the regimen. To begin with, this may be an obstacle in effective cure, prevention and control of the disease. Hence, there must be a persistent exercise of the health care providers to advance their scientific knowledge, learning booths to be set up in the waiting rooms which provide counselling and advisory sessions with the involvement of other cured patients as examples, public awareness programmes using electronic and print media, such programmes should particularly deal with the myths and various misconceptions and lastly setting up of health education programmes in school and higher educational facilities.

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Case Report

OPHTHALMIC MANIFESTATIONS OF CENTRAL NERVOUS SYSTEM TUBERCULOSIS- TWO CASE REPORTS

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***Summary*:** In this report, we present two unusual ocular manifestations due to CNS tuberculosis. One of the cases is a 7 years' old boy with brain stem tuberculoma who presented with horizontal gaze palsy. The other is a 14 years' old girl with temporal lobe tuberculoma who presented with unilateral sixth nerve paresis and papilledema. Both responded well to treatment with antitubercular drugs. It highlights the importance of gaze palsy as a rare manifestation of CNS tuberculosis. **[*Indian J Tuberc 2011; 58:* 196-198]**

Key words: CNS Tuberculoma, Gaze palsy, Sixth nerve paresis.

INTRODUCTION

In developing countries, tuberculomas account for 5-30% of intracranial space occupying lesions[1].Most published reports highlight a greater frequency in children and young adults. In the absence of obvious pulmonary or disseminated tuberculosis, central nervous system tuberculosis with ocular manifestations represents a diagnostic dilemma due to diverse systemic findings, inconclusive laboratory results and protean neuro-radiological features[2,3]. Patients present to ophthalmology department with neuro-ophthalmic manifestations like eye movement disorders and optic nerve abnormalities that are palsies of third and other cranial nerves, medial longitudinal fasciculus involvement like one and a half syndrome and eight and a half syndrome, vertical gaze dysfunctions, convergence nystagmus, internuclear ophthalmoplegia or total ophthalmoplegia[4,5].

We describe the rare entity of horizontal gaze palsy without diplopia as the only neurologic manifestation of presumed pontine tuberculoma in a child. The second child we describe had unilateral sixth nerve paresis and papilledema, which again is a rare occurrence.

CLINICAL RECORDS

Case I

A 6 years' boy presented in the Ophthalmology out patient department with inability to move his eyes to left since two days.

Best corrected visual acuity was 20/20 in both eyes. There was left horizontal gaze palsy for both saccadic and pursuit movements without vertical and rotary nystagmus (Figure 1a-e). Dolls eye movement and convergence were preserved. Diplopia was absent in primary gaze and other gaze positions. Vertical eye movements were normal. Rest of anterior segment and fundus showed no abnormality.

Systemic examination revealed an underweight (14 kg) child with stunted growth. Investigations showed elevated ESR (42 mm) and leukocyte count of 8900/cmm. Mantoux was negative and serum Adenodeaminase level was 36 U/L. Chest X-ray was normal. CSF study revealed mononuclear pleocytosis, increased protein and negative PCR for *mycobacterium tuberculosis*. A brain MRI revealed a well-defined 25mmX 15 mm T1W hypointense and T2W hyperintense solid nodular intensely enhancing

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lesion in left paramedian Pons. The surrounding dense perilesional edema spread along to middle cerebellar peduncle (Figure 2a).

Based upon serum Adenosine-deaminase levels & MRI findings, presumptive diagnosis of tuberculosis was made. Keeping in mind the deteriorating condition of patient and need for urgent medical intervention, he was started on WHO regimen for neurotuberculosis[6] along with prednisolone (2mg/kg/day for six weeks and tapered over two weeks).

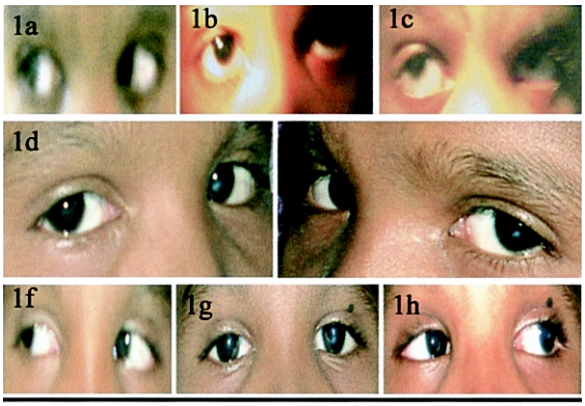

Figure 1: Ocular motility examination showing
a-c left horizontal gaze palsy.
d-e preservation of dolls eye movements.
f-g full recovery of leftward gaze

One week after therapy, ocular movements recovered completely with nystagmus only in extremes of gaze (Figure1f-g). Six months later, he developed left seventh nerve palsy. Visual acuity at one year follow-up was 20/20 N6 in B/E. Serial non-contrast CT scan at three monthly intervals showed gradual decrease in perilesional edema and by one year there was complete resolution of the lesion with only residual foci of calcification (Figure 2b). The child was under observation for six more months and no relapse was observed.

Case II

A 14-year-old girl presented with defective vision, headache and vomiting for 15 days. She had intermittent fever, headache for nine months. Ocular examination revealed left sixth nerve paresis. Bilateral anterior segments were normal. Fundoscopy revealed florid papilledema. Visual acuity was 20/40 in R/E and 20/120 in L/E. MRI brain and orbit showed right temporal lobe large variegated irregularly outlined lobulated rim enhancing lesion with central necrosis and extensive perifocal white matter edema (Figure 3). Chest X-ray finding was normal. The space occupying lesion was completely excised.

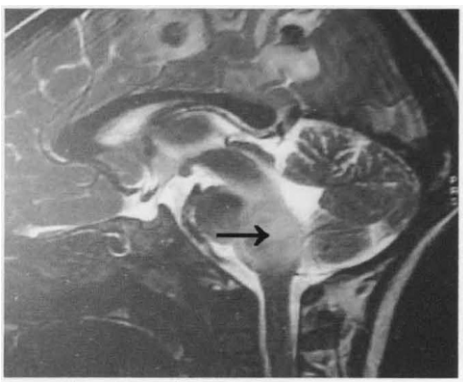

Figure 2a: Saggital T2 weighted MRI revealing pontine lesion with patchy hypointense core with perifocal hyperintensity (edema) before treatment.

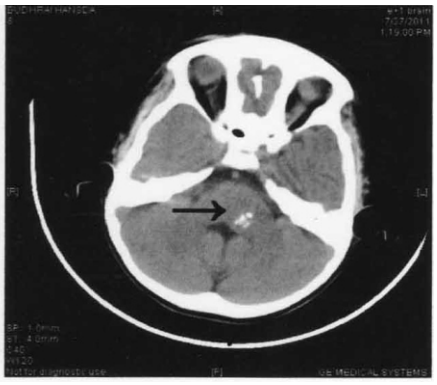

Figure 2b: CT scan showing complete resolution of pontine lesion with speckled area of calcification.

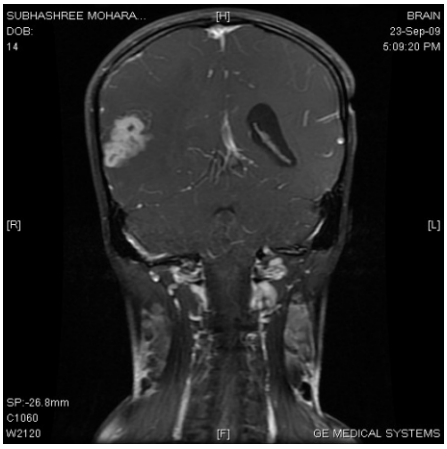

Figure 3: T1C coronal image showing a thick walled lobulated irregularly outlined intensely enhancing lesion in right temporal lobe

Histopathology report revealed multiple caseating granulomas with Langerhan's type giant cells consistent with tuberculosis. She was advised WHO anti-tubercular regimen[6] for one year.

Six months later, visual acuity was 20/120 N36 in R/E and counting finger at one foot in L/E. There were gliotic changes in the right temporal lobe suggestive of complete excision and no recurrence.

DISCUSSION

There are few reports of gaze palsy in children as a presenting feature of tuberculoma[4,7]. Our case no.1 was unique as inspite of having multiple lesions in the brain, he had symptoms of pontine involvement only.

The lesion lies in left pontine paramedian reticular formation which houses innervations to the ipsilateral lateral rectus and contralateral medial rectus[8]. To the best of our knowledge, there has been only one report of a right gaze palsy without diplopia as the only neurologic manifestation in a 38-year-old man[9]. The gaze palsy in their case recovered after one month of therapy whereas in our case the recovery period was only one week This was inspite of the fact that the pontine lesion was larger in our case. Even if the diagnosis was presumptive, the response to ATT made the diagnosis appropriate in first case. Apart from the seventh nerve palsy considered a paradoxical response[10], child had 7kg weight gain and enjoyed asymptomatic life within one year.

In second case, the diminution of vision of both eyes was attributed to secondary optic atrophy **following papilloedema. This particular case is remarkable due to the rare association of unilateral sixth nerve paresis and papilledema in a tuberculoma case.**

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Indian J Tuberc 2011; 58: 199-203

STATUS REPORT ON RNTCP*

RNTCP has continued to achieve the twin objectives of NSP case detection and treatment success rate at the national level during the second quarter, 2011 (Figure). With this, it is evident that the programme, while sustaining its past achievements, is progressing satisfactorily towards achieving the TB related Millennium Development Goals, in terms of achieving the programme objectives.

RNTCP performance in second quarter 2011

During the quarter, over 1.9 million suspects were examined, 260,896 sputum positive cases were diagnosed, and 406,442 TB cases were registered for treatment. The annualized total case detection rate is 136 cases per 100,000 population. With a total of 174,845 new smear positive cases being registered for treatment, the new smear positive TB case notification rate (annualized) for the second quarter 2011 is 59 per lakh population. In addition to this, 89,468 new smear negative cases, 62,892 new extra pulmonary cases, 53,611 smear positive re-treatment cases and 25,132 re-treatment Others' were also registered for treatment in this quarter. The treatment success rate amongst the new smear positive Pulmonary TB cases registered in the second quarter 2010 is 87.7% and the sputum conversion rate of patients registered during the first quarter 2011 is 90.3%. The default rates among NSP (5.6%), NSN (6.7%) and re-treatment cases (14.3%) continue to show the declining trend over the past several quarters.

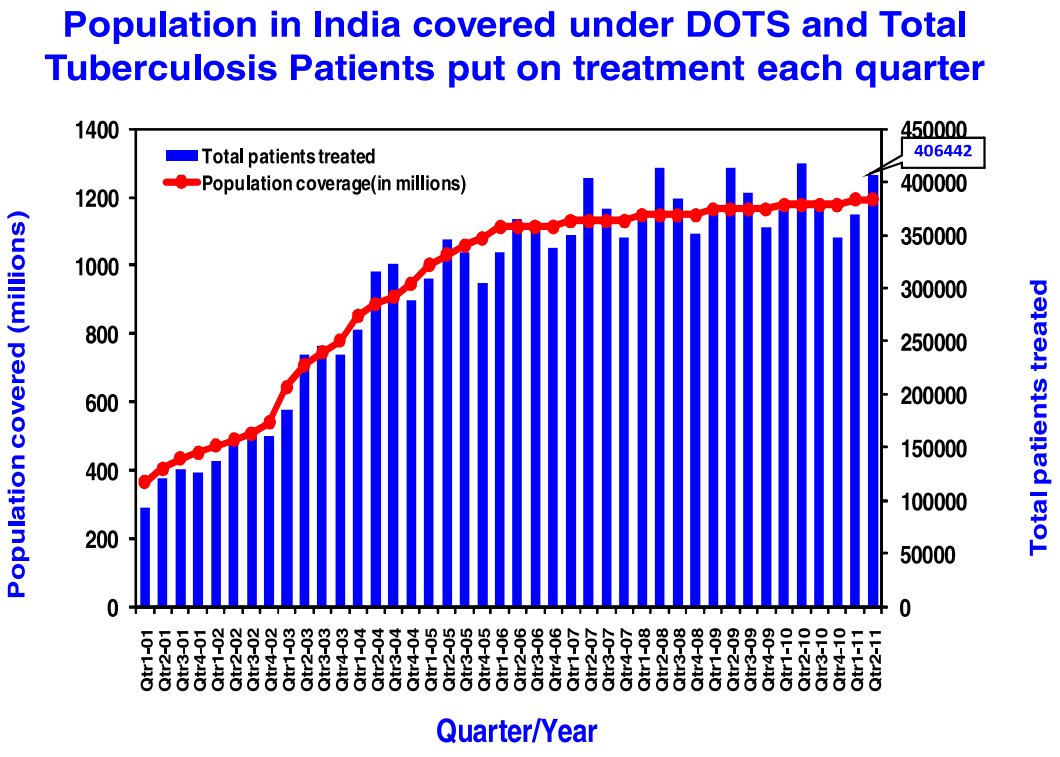

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Table: Performance of RNTCP Case Detection (2011, second quarter), Smear Conversion (2011, first quarter), and Treatment Outcomes (2010, second quarter)

State	Population (in lakh) covered by RNTCP[1]	No. of suspects examined	Suspects examined per lakh population	Rate of change in suspects examined per lakh population (compared to same quarter in previous year)	No of Smear positive patients diagnosed[2]	Suspects examined per smear positive case diagnosed	Rate of change in suspects examined per s+ case diagnosed (compared to same quarter in previous year)	Annualized smear positive case notification rate (reported by RNTCP DMCs)	Annualized smear positive case notification rate [from CFR: sm + cases (NSP + Rel + TAD) * 4 / Pop]	Total patients registered for treatment[3]	Annualized total case notification rate	Annualized new smear positive case notification rate	Annualized new smear negative case notification rate	Annualized new extra pulmonary case notification rate	Annualized previously treated case notification rate
Andaman & Nicobar	5	1081	219	-7%	95	11	14%	77	69	218	177	57	44	54	21
Andhra Pradesh	847	131912	156	-7%	19791	7	-17%	93	77	28046	132	60	30	17	26
Arunachal Pradesh	12	2924	236	11%	431	7	-32%	139	109	661	213	82	38	39	52
Assam	306	39361	129	11%	6277	6	-10%	82	70	10624	139	58	36	20	25
Bihar	977	96502	99	0%	12222	8	-1%	50	44	20226	83	37	25	6	16
Chandigarh	14	4720	328	3%	629	8	-17%	175	86	683	190	61	18	73	38
Chhattisgarh	243	25886	107	-3%	3468	7	-17%	57	52	7018	116	45	41	16	13
D & N Haveli	4	593	168	9%	87	7	-3%	98	70	114	129	49	19	25	36
Daman & Diu	3	667	247	-5%	56	12	-26%	83	46	80	119	34	40	18	27
Delhi	195	40157	206	-13%	6388	6	-21%	131	112	15014	309	79	55	111	63
Goa	18	2977	168	-16%	323	9	-16%	73	50	468	106	38	15	30	22
Gujarat	590	95470	162	-11%	16103	6	-26%	109	87	19111	130	61	13	18	37
Haryana	254	52363	206	20%	7582	7	-14%	119	95	11040	174	65	31	31	46
Himachal Pradesh	68	19838	292	30%	2373	8	-7%	140	121	4106	242	87	38	60	57
Jammu & Kashmir	117	27604	236	56%	2604	11	6%	89	83	3975	136	67	19	28	21
Jharkhand	315	39574	126	15%	6330	6	-11%	80	74	10427	133	64	38	9	22
Karnataka	594	123072	207	6%	12005	10	3%	81	65	17793	120	51	25	22	23
Kerala	346	71460	207	-16%	3617	20	-14%	42	38	6495	75	33	16	17	9
Lakshadweep	1	274	361	305%	3	91		16	16	3	16	11	0	0	5
Madhya Pradesh	722	91167	126	12%	14851	6	-12%	82	69	23086	128	53	36	14	25
Maharashtra	1127	152834	136	-12%	19153	8	-11%	68	60	33536	119	47	25	22	25
Manipur	24	3342	136	7%	397	8	-16%	65	62	871	142	53	39	26	23
Meghalaya	26	6235	238	25%	759	8	3%	116	92	1372	209	73	46	49	41
Mizoram	10	2109	210	15%	205	10	14%	82	74	604	241	56	67	70	48
Nagaland	22	3612	161	6%	494	7	-19%	88	80	966	172	60	37	34	40
Orissa	408	51568	127	-6%	8021	6	-20%	79	70	13305	131	59	29	24	18
Puducherry	14	5305	381	-9%	715	7	-7%	206	68	435	125	51	19	31	24
Punjab	277	51406	186	18%	7211	7	-11%	104	96	11936	172	70	29	37	36
Rajasthan	678	108347	160	18%	21981	5	-18%	130	107	31169	184	74	43	24	43
Sikkim	6	1838	300	17%	178	10	3%	116	103	439	287	77	66	81	63
Tamil Nadu	674	148701	220	-16%	11748	13	-21%	70	63	20639	122	49	30	24	19
Tripura	36	4798	133	-2%	496	10	-12%	55	49	730	81	44	16	13	9
Uttar Pradesh	2008	333835	166	12%	52928	6	-10%	105	95	78837	157	75	35	18	28
Uttarakhand	99	20033	201	22%	3036	7	-18%	122	90	4338	175	63	40	30	42
West Bengal	895	147352	165	-1%	18339	8	-20%	82	73	28077	125	59	22	21	24
Grand Total	**11935**	**1908917**	**160**	**1%**	**260896**	**7**	**-19%**	**87**	**75**	**406442**	**136**	**59**	**30**	**21**	**26**

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, data from DMCs

3 Total patients registered for treatment, include new sputum smear positive cases, new smear negative cases, new extra-pulmonary cases, new others ,relapse,failure,TAD and retreatment others

State	Annualized previously treated smear positive case notification rate	No (%) of pediatric cases out of all New cases		3 month conversion rate of new smear positive patients	3 month conversion rate of retreatme nt patients	No (%) of all Smear Positive cases started RNTCP DOTS within 7 days of diagnosis		No (%) of all Smear Positive cases registered within one month of starting RNTCP DOTS treatment		No (%) of all cured Smear Positive cases having end of treatment follow- up sputum done within 7 days of last dose		No (%) of cases (all forms of TB) registered receiving DOT through a community volunteer		Proportion of all registered TB cases with known status	Proportion of TB patients known to be HIV infected among tested	Proportion of TB patients known to be HIV infected among registered	Proportion of HIV infected TB patients put on CPT (RT report)	Proportion of HIV infected TB patients put on ART (RT report)
Andaman & Nicobar	15	14	7%	100%	70%	79	88%	73	81%	56	81%	49	22%	13%	0%	0%		
Andhra Pradesh	19	1107	5%	92%	75%	15063	90%	16376	98%	11718	83%	23225	83%	83%	13%	11%	92%	41%
Arunachal Pradesh	29	57	11%	91%	73%	274	80%	339	99%	247	92%	198	30%	57%	1%	0%		
Assam	13	460	5%	88%	65%	4697	86%	5000	92%	3246	76%	3495	33%	25%	1%	0%	33%	107%
Bihar	8	1204	7%	88%	74%	9374	87%	10601	98%	7459	81%	12602	62%	8%	3%	0%	0%	69%
Chandigarh	26	59	11%	87%	76%	294	94%	313	100%	312	99%	153	22%	98%	1%	1%	0%	100%
Chhattisgarh	7	364	6%	89%	72%	2671	84%	3103	98%	2058	79%	3592	51%	14%	3%	0%	0%	0%
D & N Haveli	26	5	6%	95%	73%	63	95%	66	100%	33	97%	19	17%	14%	0%	0%		
Daman & Diu	13	3	5%	95%	67%	31	97%	32	100%	22	100%	19	24%	91%	3%	3%	0%	0%
Delhi	36	1868	16%	89%	73%	5021	90%	5469	98%	4454	97%	1267	8%	64%	1%	1%	84%	78%
Goa	14	30	8%	85%	65%	207	90%	205	89%	192	95%	55	12%	96%	6%	6%	100%	74%
Gujarat	27	866	6%	91%	68%	12076	92%	12851	98%	10146	90%	10759	56%	90%	5%	5%	95%	70%
Haryana	33	497	6%	90%	74%	5568	89%	5802	93%	3853	83%	2937	27%	55%	2%	1%	6%	29%
Himachal Pradesh	38	187	6%	91%	77%	2050	97%	2062	98%	1686	93%	474	12%	30%	2%	1%	0%	100%
Jammu & Kashmir	17	249	7%	92%	80%	2426	98%	2449	99%	1903	97%	397	10%	11%	2%	0%	0%	50%
Jharkhand	11	530	6%	92%	77%	4970	84%	5815	99%	3063	64%	6557	63%	14%	4%	1%	3%	22%
Karnataka	16	958	7%	88%	62%	8348	85%	9455	96%	5857	82%	8885	50%	92%	15%	13%	99%	72%
Kerala	7	710	12%	84%	69%	3017	89%	3098	91%	2183	81%	4162	64%	55%	3%	2%	53%	75%
Lakshadweep	5	0	0%		0%	3	100%	3	100%	3	0%	3	100%	0%		0%		
Madhya Pradesh	17	2101	11%	91%	72%	11340	89%	12524	99%	7695	78%	14328	62%	14%	3%	0%	33%	100%
Maharashtra	14	1806	7%	90%	68%	15105	88%	16766	97%	10905	82%	10393	31%	79%	11%	8%	94%	59%
Manipur	11	57	8%	91%	71%	378	95%	375	95%	271	87%	462	53%	49%	8%	4%	54%	46%
Meghalaya	25	185	17%	83%	63%	566	89%	606	95%	384	84%	765	56%	13%	2%	0%		
Mizoram	20	95	20%	95%	66%	186	98%	189	99%	119	92%	113	19%	65%	9%	6%	100%	58%
Nagaland	24	118	16%	91%	81%	359	76%	385	82%	311	72%	416	43%	49%	10%	5%	87%	68%
Orissa	11	641	6%	88%	64%	6029	84%	6980	97%	4212	73%	9552	72%	11%	2%	0%	0%	50%
Puducherry	22	25	7%	90%	83%	209	82%	223	88%	170	96%	0	0%	55%	2%	1%	100%	67%
Punjab	27	705	7%	90%	73%	6352	94%	6627	98%	5201	93%	2944	25%	65%	2%	1%	52%	66%
Rajasthan	35	1288	5%	92%	76%	15030	82%	17061	93%	12185	80%	4391	14%	25%	1%	0%	36%	36%
Sikkim	33	36	12%	91%	76%	162	96%	166	99%	150	97%	159	36%	0%		0%		
Tamil Nadu	14	1264	7%	91%	70%	9147	85%	10394	97%	7565	85%	5098	25%	89%	8%	7%	87%	57%
Tripura	6	12	2%	91%	68%	368	81%	449	99%	326	79%	345	47%	37%	2%	1%	50%	25%
Uttar Pradesh	20	3956	6%	92%	79%	43271	90%	47290	99%	32028	87%	56614	72%	8%	2%	0%	27%	40%
Uttarakhand	29	290	9%	89%	74%	2018	88%	2238	98%	1702	87%	2596	60%	36%	1%	0%	0%	50%
West Bengal	15	1154	5%	88%	64%	13565	81%	15687	94%	10574	80%	7095	25%	46%	2%	1%	71%	69%
Grand Total	**18**	**22901**	**7%**	**90%**	**72%**	**200317**	**88%**	**221072**	**97%**	**152289**	**83%**	**194119**	**48%**	**43%**	**7%**	**3%**	**91%**	**58%**

Major activities during the Quarter

Programme review

The Biannual National Review Meeting for the State TB Officers and RNTCP Medical-Consultants was held from 18th to 20th May 2011 at Surajkund, Delhi NCR. The meeting was convened with the underlying theme of **National scale up of DOTS plus (PMDT) services under RNTCP in India** with the objectives of reviewing the performance and quality of RNTCP services, the progress and challenges in the expansion of DOTS Plus (PMDT) services in the country and to update the STOs and Consultants on newer initiatives, policy changes etc.

The inaugural session of the meeting on 18th May 2011 was chaired by Sh.P.K.Pradhan, Special Secretary and Mission Director NRHM, Government of India and Dr.R.K.Srivastava, Director General Health Services, Government of India. The inaugural session was also attended by Dr.Sangay Thinley, Director (CDS), WHO-SEARO.

Progress in Supervision, Monitoring and Training

Central Internal Evaluation of Meghalaya was conducted by Central TB Division (CTD) and a few state internal evaluations of various districts were also undertaken.

Joint Donor Review Mission

A mission to review the Revised National Tuberculosis Control Programme (RNTCP) was undertaken between May 30 and June 9, 2011. The Joint Review Mission, coordinated by CTD and the World Bank, included representatives of WHO, USAID, NIH, DFID, GFATM, the Bill and Melinda Gates Foundation, and the Clinton Health Access Initiative (CHAI) with emphasis on National Strategic Plan for RNTCP for next five year plan (2012-17); "Universal Access" to high-quality diagnosis and patient-friendly treatment under DOTS, including by expanding treatment and diagnosis of HIV-associated TB and MDR-TB; long term financing of RNTCP; distribution and quality assurance of anti-TB drugs; and human resource development. The mission conducted detailed discussions at CTD and also visited the states of Bihar, Madhya Pradesh, Karnataka and Maharashtra and has provided recommendations for the National Strategic Plan for 2012-17.

Progress in accreditation of Intermediate Reference Laboratories (IRL)

RNTCP has accredited 29 Culture and DST laboratories in the country which includes four National reference laboratories, 15 Intermediate Reference laboratories and 10 laboratories from other sectors like Medical Colleges, NGOs and Private sectors, the other laboratories are in different stages of accreditation. The Line Probe Assay (LPA) has been introduced in the programme and two NRLs, three IRLs and three Medical College Laboratories have been accredited and one laboratory in private sector with Liquid culture diagnostics has been accredited to deliver the services.

Progress in the DOTS- Plus services for MDR TB cases

DOTS Plus services for management of MDR TB are now available in 165 districts covering a population of 352 million in 17 states. Till date, a total of around 4858 MDR-TB patients are on treatment at 28 DOTS Plus Sites functional in these states. Other states are in various stages of preparatory activities for rolling out DOTS-Plus services.

Progress in PPM & ACSM activities

Regional ACSM Workshop was held in Jaipur from 12th to 14th May, 2011 with participants from States of Rajasthan, Gujarat, and Haryana. The group comprised STO Rajasthan, DTOs, Consultants, and Communication Facilitators. The workshop focused on field activities and the participants prepared their sample district plans which listed strategic interventions to overcome the challenges faced by them in the field. Till second Quarter 2011 under RNTCP, 1963

NGOs and 10230 PPs are involved under various NGO PP Schemes.

Progress in TB HIV Collaborative Activities

Scale-up of Joint TB/HIV collaborative activities continues to progress impressively. As per the National Technical Working Group's decision to roll out Intensified TB/HIV package of services to the remaining six states and UTs, training of master trainers has been planned in the month of October 2011 by CTD and NACO; this will take us a step closer to achieving nationwide coverage by the end of 2011. Though the performance is improving overall at national level and in selected high HIV prevalent states, the same is not true for low HIV prevalence states with gross mismatch at service delivery level between RNTCP and NACP. Addressing this would require a major scale-up of integration of NACP services in the general health system and this is being planned jointly by RNTCP and NACP in the next five years (2012-17). In addition, several new initiatives are being tested to enable early and improved diagnosis of HIV-infected TB patients - like 'HIV testing among TB suspects' and use of improved, rapid diagnostics to diagnose TB among PLHIV. These would be crucial to achieving universal access to TB/HIV care – All TB patients with known HIV status and all HIV-infected TB patients linked to CPT and ART – and thereby achieving the goal of reduced mortality and morbidity due to HIV-associated TB.

Short Communication

DETERMINANTS OF CHILDHOOD TUBERCULOSIS - A CASE CONTROL STUDY AMONG CHILDREN REGISTERED UNDER REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAMME IN A DISTRICT OF SOUTH INDIA

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Summary

Aim: To study the determinants of Tuberculosis (TB) in children between the age group of 0-14 years receiving treatment under Revised National TB Control Programme (RNTCP) .

Methods: A case (registered under RNTCP) control study was undertaken with 41 cases and 82 controls.

Results: Factors found to have significance according to binary logistic regression were low-birth weight (LBW) [Odd's ratio=3.56],Malnutrition [Odd's ratio=3.96], Passive smoking [Odd's ratio=6.28] and exposure to fire-wood smoke [Odd's ratio=6.91].

Conclusion: LBW, malnutrition, passive smoking and fire-wood smoke are the risk factors to be addressed to prevent pediatric TB. **[*Indian J Tuberc 2011; 58:* 204-207]**

***Key words*:** Tuberculosis in children, Risk factors of tuberculosis in children, Determinants of pediatric tuberculosis.

INTRODUCTION

Globally, there were an estimated 14 million prevalent cases of TB in 2009.[1] Of the 1 million estimated cases of TB in children worldwide, 75% occur in the 22 high-burden countries where the proportion attributable to children ranges from 15% to 20% of all cases.[2] Studies on determinants of TB in pediatric population is scarce. Risk factors of TB in children in developing countries are probably poor socio-economic conditions, malnutrition, overcrowding, the overall younger population, HIV co-infection and a high prevalence of TB in adults acting as contacts.[3] On realizing the importance of childhood TB, initiative was taken for formulation of guidelines for diagnosis and treatment of cases under RNTCP in Aug 2003. Childhood TB is a thrust area of the programme since then. Factors contributing to the high burden of childhood TB in the country is not yet fully understood. Hence the present study was undertaken to determine the risk factors of TB (disease) in children between 0-14 yrs of age in Thiruvanathapuram (TVM) district of Kerala.

METHODOLOGY

The design of the study was case control and the case group constituted incident cases of TB in Children between the age group of 0-14 years residing in TVM district of Kerala. Address and details of the children registered under RNTCP during the third and fourth quarters of 2009 were taken from TB units (TU) in TVM. Data was collected using a questionnaire by house visits. Study period was between 1st Aug and 31st Dec 2009. Children between 0-14 years of age without any symptoms suggestive of TB (disease) residing in the neighborhood of the cases were taken as controls. Children with cough for more than two weeks duration (during the immediate weeks before the data collection), or any other

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symptoms or signs suggestive of extra-pulmonary TB like lymph node enlargement or pyrexia of unknown origin were excluded from control selection.

The overall sample size was 123 with control case ratio of 2:1 (41 cases and 82 controls). Some of the variables used in the study are defined as follows: A contact is defined as any person with a suspected or diagnosed case of active TB disease within the last two years.[4] Passive smoking is defined as inhalation of cigarette, cigar or pipe smoke produced by another individual, it is composed of second hand smoke (exhaled by smoker) and side stream smoke.[5] Housing indicators were also assessed by the investigators based on standard criteria.[6] The study protocol had been approved by the ethical committee of Government Medical College, TVM. Binary-logistic regression was used to find out independent predictors of the outcome.

RESULTS

The analysis included data of 123 children between 0-14 years of age, 41 cases and 82 controls. The diagnosis of TB was made by either a pediatrician (49%) or the medical officer of district TB centre (MO- DTC) (49%) in most cases. Pulmonary TB was found to be the most common type (78%). No case in this group was sputum positive. The most common

Table 1: Clinical parameters of the case group under study.

Factor	**Number (Percentage)**
1. The Doctor who diagnosed TB in the cases	
Pediatrician	20 (48.8%)
MO-DTC	20 (48.8%)
General Practitioner (not a pediatrician)	01 (2.4%)
Total	41
2.Type Of Tuberculosis	
Pulmonary	32 (78.0%)
Extra-Pulmonary	09 (22.0%)
Total	41
3. Sputum Status of Pulmonary Cases.	
Negative	32 (100%)
Positive	0
Total	32
Extra-pulmonary Site.	
4. Organ/system involved other than pulmonary.	
Central nervous system	5 (55.5%)
Bone	2 (22.2%)
Disseminated	1 (11.1%)
Abdomen	1 (11.1%)
Total	09

Table 2: Distribution of co-variates across the study groups.

Factor	Cases N (%)	Controls N (%)	Odd's ratio (95% CI)	P value (chi-square)
1. **Socio-demographic factors**				
Age between 0-6 yrs	26 (63.4)	43 (52.4)	1.57 (0.73-3.39)	0.240
Male gender	22 (53.6)	47 (57.3)	0.86 (0.40-1.83)	0.700
Father educated (High School and Above)*	23 (56.1)	65 (79.3)	2.99 (1.32-6.76)	0.007
Mother educated (High School and Above)*	25 (61.0)	65 (79.3)	2.44 (1.07-5.57)	0.031
Father engaged in High Income generating works*	14 (34.1)	52 (63.4)	3.34 (1.52-7.34)	0.002
Mother engaged in High Income generating works*	6 (14.6)	28 (34.1)	3.02 (1.13-8.05)	0.021
Family income Rs.10,001 and above per month*	7 (17.1)	47 (57.3)	6.52 (2.59-16.42)	< 0.001
2. **Biological Factors of The Study Subjects.**				
Low birth weight (<2500grams)*	24 (58.5)	17 (20.7)	5.39 (2.37-12.24)	< 0.001
Weight for age 70% and below of the expected*	16 (39)	10 (12.1)	4.60 (91.85 – 11.46)	0.001
Children who are not vaccinated for measles*	10 (24.3)	4 (4.8)	6.29 (1.83-21.56)	0.001
Children without BCG scar.	1	0		0.156
Children with h/o contact with TB patients*	19 (46.3)	13 (15.8)	4.58 (1.95-10.75)	< 0.001
3. **Environmental factors**				
Children residing in Kutcha houses*	26 (63.41)	23 (28.04)	4.446 (2.00-9.87)	<0.001
Children residing in overcrowded houses*	26 (63.41)	16 (19.5)	7.150 (3.09 -16.52)	<0.001
Children residing in houses with Inadequate ventilation*	24 (58.5)	14 (17.0)	6.857 (2.94 -15.99)	< 0.001
Children who were exposed to fire-wood smoke at their homes*	26 (63.4)	18 (21.9)	6.163 (2.706 -14.035)	< 0.001
Children with exposure to passive smoking*	19 (46.3)	13 (15.8)	6.677 (2.915 -15.292)	< 0.001
4. Multivariate analysis of the exposure factors				
Factor	**Adjusted OR* with 95% CI**			**P value**
Low Birth weight	3.561 (1.245-10.186)			0.018
Malnutrition	3.961 (1.298-12.082)			0.016
Passive Smoking Exposure	6.285 (2.317-17.047)			< 0.001
Exposure to fire-wood smoke	6.914 (2.529-18.905)			< 0.001

* p value significant
OR*= Odd's ratio.

extra-pulmonary site was CNS (55.5%) , (Table 1).

The median (standard deviation) age of the case group was five (3.62) years and that of control group was six (3.13) years. No statistically significant difference in the age and gender was found between the two groups (Table 2). Education of the parents, their occupation, housing, ventilation, overcrowding, monthly family income, measles vaccination and contact with active TB, were found to be significantly associated with TB in children on univariate analysis (Table 2). Prediction of occurrence of TB in children was tried using multivariate analysis . Low birth weight (LBW), under-nutrition, exposure to passive smoking and exposure to fire-wood smoke were found to be the determinants of childhood TB (Table 2).

DISCUSSION

All the participants in the case group were sputum negative. It is a known fact that 95% of cases in children below 12 years of age are smear negative.[2]

Education and occupation of the parents with monthly family income were used as a proxy for assessing the socio-economic status. We got a statistically significant difference which emphasises the role of these factors as distal determinants of TB. In low and middle income countries, childhood TB is closely associated with poverty, overcrowding, and malnutrition.[2] Exposure to fire-wood smoke was also found to be significantly associated with childhood TB, this finding was consistent with studies published elsewhere[7], but most studies were done among adults.

LBW was found to be significantly associated with childhood TB. There is no other indicator in human biology, which tells us so much about the past events and the future trajectory of life, as the weight of the infant at birth.[8] This association may be explained by the fact that in most cases, under weight children, if not properly cared for, are prone to mal-nourishment in later life , which in turn decreases their immunity . In the present study, weight for age (IAP criteria) of the study subjects were taken as a proxy for under nutrition. Significantly, higher proportion of children in the case group had their weights below or equal to 70% of the expected . Study by Vijaykumar *et al*[9] found significant association between severe malnutrition and severe forms of infection.

Passive smoking was also found to be a significant determinant of TB in the present study. There are numerous studies world wide which prove this association. One such study revealed that passive smoking was an important determinant of TB in children.[10] We acknowledge certain limitations of this study. Major limitation of the study is that all the cases may not have been diagnosed based on the standard diagnostic criteria. Another limitation of the study is that the control population was not evaluated for their infection status by Mantoux test.

CONCLUSION

LBW, malnutrition, passive smoking and fire-wood smoke exposure are the risk factors to be addressed to prevent childhood TB. Since this study could not quantify or measure the exposure level further, research in this area is called for.

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Short Communication

FACTORS ASSOCIATED WITH LOW UTILIZATION OF X-RAY FACILITIES AMONG THE SPUTUM NEGATIVE CHEST SYMPTOMATICS IN JALPAIGURI DISTRICT (WEST BENGAL) 2009

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***Summary*:** New sputum negative (NSN) tuberculosis case detection in Jalpaiguri district has been consistently low. Availability and accessibility of health facilities with chet x-rays is key for the diagnosis of NSN cases. To identify factors associated with utilisation of x-ray facilities in the district, we interviewed 4,875 chest symptomatics who were sputum negative on two occasions with an antibiotics course in between. Chest radiography was available in only three public health facilities in the district. Low income, long distance from the public health facilities with chest radiography and high cost of x-rays at private hospitals were key factors associated with symptomatics not undergoing X-ray. It is necessary to increase facilities for radiological diagnosis and provide mobility support for the symptomatics in Jalpaiguri. **[*Indian J Tuberc 2011; 58:* 208-211]**

Key words: Tuberculosis, Sputum negative, Jalpaiguri, India.

INTRODUCTION

Jalpaiguri district is situated in the Northern part of Indian state of West Bengal. The district has a large cover of tea plantation and forest and 67% of the population is Below Poverty Line (BPL) with a monthly income of less than Rs. 2000. Revised National Tuberculosis control Programme (RNTCP) is implemented in the district through nine Tuberculosis units (TU) and 44 Designated Microscopic Centres (DMC). The facilities for X-ray chest are available at Jalpaiguri district hospital, Alipurduar and Mal subdivision hospitals. The programme has been achieving the targets of 70% new smear-positive (NSP) TB case detection and 85% cure rate of such cases since 2004. The average NSP case detection and the cure rate during 2004-2009 were 76% and 88% respectively[1].

According to RNTCP guidelines in use in 2009, if a chest symptomatic is found to be negative on three sputum smear examinations, he/she is prescribed with a broad-spectrum antibiotic for 10-14 days and repeat sputum test is advised if symptoms persist[2]. Chest x-ray is advised to such patients whose sputum is still negative and if findings of the X-ray are consistent with active pulmonary TB, the patient is diagnosed as a case of new sputum smear negative tuberculosis (NSN-TB). During 2009, the NSN: NSP case detection ratio in the district was only 0.3 as against the recommended ratio of 1 (range 0.40- 1.2)[1]. Availability and accessibility of health facilities with chest x-rays as well as their affordability are key for the diagnosis of NSN TB cases. In view of the low NSN case detection in the district, we conducted a retrospective cohort study to identify the factors associated with utilization of x-ray facilities among the sputum negative chest symptomatics in Jalpaiguri.

METHODS

We identified a cohort of the chest symptomatics (n=5214) in the district whose

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sputum smears were negative for AFB on two occasions and had received antibiotics in between during the year 2009 from the laboratory registers at the DMCs. These registers contain information about the name, age, sex of the chest symptomatics, results of sputum examination, whether a course of antibiotics received or not, results of repeat sputum examination, whether the patient was advised chest x-ray, date of starting of anti-TB treatment and the treatment regimen. The chest symptomatics were advised chest x-rays by the concerned medical officers after the results of the repeat sputum examination were available.

After obtaining the informed consent, the trained health workers using the semi-structured questionnaire interviewed the cohort members in their homes to find whether the chest symptomatic was x-rayed and reasons for not doing the x-rays. For the symptomatics who underwent chest x-rays, we obtained the data about their diagnosis from the TB registers. We analysed the data using Epi-info software to identify factors associated with not undergoing chest X-rays. We conducted the stratified analysis to identify the confounding and effect modification. All the variables found to be significantly associated with not undergoing chest x-rays were included in the multiple logistic regression analysis. The study was approved by the Institutional Ethics Committee of North Bengal Medical College, West Bengal.

RESULTS

We interviewed 4,875 (93%) of the 5214 eligible symptomatic case patients (or parents in case of the minors). Most (4,677, 96%) of the symptomatics were aged more than 14 years while 2,926 (60%) were males. Of the 4875 symptomatics, 1,913 (39%) underwent chest X-rays and 1,101 (58%) were diagnosed as NSN TB cases. Compared to those who underwent x-rays, chest symptomatics, who did not undergo X-rays, were more likely to be from BPL families [Odds ratio (OR): 132.7, 95% confidence interval (CI): 103.7-168.5] and had their residences situated more than 30 Kms. away from the nearest public health facility with X-ray (OR: 37.7, 95% CI: 29.2-48.7). Such patients were more likely not to afford the cost of X- ray investigations from private hospitals (OR: 63.3, 95% CI: 42.8-93.5). Chest symptomatics who did not undergo X-rays, were also unaware about the need of X-rays for diagnosis of their illness (OR: 4.2, 95% CI: 2.9-6.1) (Table-1).

Table 1: Univariate analysis of the factors associated with not undergoing chest x-rays, Jalpaiguri (West Bengal) 2009.

Variables		Chest X-ray done		Odds Ratio (95% CI)
		No (n=2962)	Yes (n=1913)	
Income	APL	85	1523	1
	BPL	2877	390	132.7 (103.7-168.5)
Distance from the nearest public health facility with X-ray	<30Kms	69	906	1
	>30Kms	2893	1007	37.7 (29.2-48.7)
Knew that X-rays are needed for diagnosis	Yes	210	34	1
	No	2752	1879	4.2 (2.9-6.1)
Afford X-rays from private hospital	Yes	27	704	1
	No	2935	1209	63.3 (42.8-93.5)

Table 2: Multivariate analysis of the factors associated with not undergoing chest x-rays, Jalpaiguri (West Bengal) 2009.

Variables	Adjusted odds ratio (95% CI)
BPL *Distance from the nearest public health facility with X-ray >30 Km	82.9 (64.7- 106.3)
Did not know that X-rays are needed for diagnosis	22.7 (8.4-61)
Did not afford X-rays from private hospital	22.1 (13-37.7)

When stratified by the income level, we observed that the association between the distance from the nearest public health facility with X-Ray and undergoing X-rays was modified by the BPL status of the chest symptomatics (OR among BPL: 22.3, 95% CI=2.3-214.9, OR among APL: 0.4, 95% CI=0.2-0.6, Chi Square for differing odds ratio by stratum=11.9, p=0.005). On multiple logistic regression, interaction term income and distance [Adjusted Odds Ratio (AOR)=82.9, 95% CI=64.7-106.3), knowledge about the need for x rays for their diagnosis (AOR=22.7, 95% CI=8.4-61) and the cost of X-ray investigations at private hospitals (AOR=22.1, 95% CI=13-37.7) were significantly associated with chest symptomatics not undergoing x-rays (Table 2).

During 2004-2009, the average NSN: NSP ratio in the district was 0.3 (range: 0.12-0.51). The ratio was less than 0.3 in five blocks, 0.30-0.50 in four blocks range and >0.50 in the remaining four blocks.

DISCUSSION

Smear negative pulmonary tuberculosis constitutes about 50% of all new cases of pulmonary tuberculosis[3,4]. NSN TB cases have a low bacillary burden with minimal disease or cavitations and hence are associated with lower mortality than NSP cases. Human to human transmission rate of NSN TB cases is often lower than NSP cases[5]. Rouillon *et al* reviewed five studies comparing the bacteriological status of the source case with the prevalence of infection (as measured by tuberculin reactivity) among household contacts aged less than 15 years. The prevalence of infection among children exposed to smear-positive cases varied between 39%–65%, whereas the tuberculin reactivity rate was only 4.7%–26.8% among contacts of smear-negative patients, whose TB diagnoses were based on positive cultures or radiography[6]. A recent DNA fingerprinting study from San Francisco attributed 17% of tuberculosis transmission in this low-prevalence setting to patients with smear-negative culture-positive pulmonary TB. NSN TB cases, if left untreated, are also likely to progress to active disease[5]. In view of this, the detection and management of smear-negative pulmonary disease is an important component of any national TB control programme.[7]

In Jalpiguri, majority of the NSN cases remained undetected mainly on account of un-availability of adequate public health facilities with chest x-rays in the district. Facilities for x-rays were available only in three health facilities. Low detection of NSN cases was also observed during 2004-2009 with blocks away from district health facility showing lowest NSN: NSP ratio. High proportion of BPL families in the district, financial affordability in utilizing the x-ray facilities at the private hospitals and longer distance to the public health facilities having x-ray services further compounded the issue. The findings of the study also suggest a need to educate the chest symptomatics about the importance of undergoing chest X-rays.

Our study had one main limitation. We assessed the patient related factors associated with chest sympomatics not undergoing x-rays and did not evaluate the provider related factors.

In conclusion, the low detection of NSN cases in Jalpaiguri was mainly on account of shortage of public X-ray facilities in the district. **It is therefore necessary to increase the facilities for radiological diagnosis in the district by providing X-ray facilities at the block primary health centres. Providing mobility support to the chest symptomatics and subsidizing the cost of X-rays in private health facilities through public private partnership would also increase the detection of NSN TB cases in the district**.

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ABSTRACTS

Evaluating PCR, culture & histopathology in the diagnosis of female genital tuberculosis

R. B. P. Thangappah, C. N. Paramasivan and Sujatha Narayanan. *Indian J Med Res* 2011; **134(1)**: 40-6

Genital tuberculosis (GTB) is one of the major causes for severe tubal disease leading to infertility. Unlike pulmonary tuberculosis, the clinical diagnosis of GTB is difficult because in majority of cases the disease is either asymptomatic or has varied clinical presentation. Routine laboratory values are of little value in the diagnosis. An absolute diagnosis cannot be made from characteristic features in hysterosalpingogram (HSG) or laparoscopy. Due to the paucibacillary nature of GTB, diagnosis by mycobacterial culture and histopathological examination (HPE) have limitations and low detection rate. The objective of this study was to evaluate the efficacy of PCR technique, culture and histopathological examination in the diagnosis of GTB in female infertility. This study included 72 infertile women who met the inclusion and exclusion criteria. After a .detailed history and clinical examination all patients were subjected to investigations including pelvic sonogram, HSG and laparoscopy. Endometrial samples were allocated for AFB smear, culture and HPE examination. Only 49 samples were available for PCR using IS 6110 and TRC4 primers. In seven patients peritoneal fluid was also taken for culture and PCR. Based on the clinical profile and laparoscopic findings, a diagnostic criteria was derived to suspect GTB. Specific diagnostic tests were evaluated against this diagnostic criterion. Laparoscopy was suggestive of tuberculosis in 59.7 per cent of cases, AFB smear was positive in 8.3 per cent, culture was positive in 5.6 per cent, HPE positive in 6.9 per cent and PCR was positive in 36.7 per cent of cases. Based on the diagnostic criteria, GTB was suspected in 28 of the 49 cases. On evaluating against the diagnostic criteria, the sensitivity of PCR, HPE and culture were 57.1, 10.7, 7.14 per cent respectively. The concordance of results between the clinical criteria and specific diagnostic tests were analysed by Kappa measure of agreement. The culture and HPE showed mild agreement with the clinical criteria, whereas PCR showed a moderate agreement. PCR was-positive in two of the 21 cases in whom GTB was not suspected. False positive PCR in these two cases were ruled out by multiple areas of sampling and re-sampling in one case. The PCR results were negative in 12 of the 28 cases. PCR using TRC4primers had a higher sensitivity (46.4%) than IS 6110 primers (25%) in detecting clinically suspected GTB. Our results showed that conventional methods of diagnosis namely, HPE, AFB smear and culture have low sensitivity. PCR was found to be useful in diagnosing early disease as well as confirming diagnosis in clinically suspected cases. False negative PCR was an important limitation in this study.

A retrospective study of seasonal variation in the number of cases diagnosed at a tertiary care tuberculosis hospital

D. Behera and P. P. Sharma. *Indian J Chest Dis Allied Sci* 2011; **53**: 145-52

To study the seasonality of tuberculosis (TB), data from a tertiary care respiratory hospital in south Delhi over a six years' period from April 2002 to March 2008 were analysed. A total of 192,863 patients were registered newly in the hospital during this period. Maximum number of symptomatic patients reported to the out-patient department during April-June and the minimum during October-December. An increase of about 25% in symptomatics was observed ($p<0.05$) in the period from April to June in comparison to October to December. The amplitude of seasonal variation was estimated as 11% of the annual mean symptomatics. The maximum sputum-positive TB cases were diagnosed during the period from April to June and the number was least during October to December. There was an increase of about 34% in sputum-positive cases ($p<0.001$) during the period from April to June against October to

December. The amplitude of seasonal variation was estimated as 14.4% of the annual mean smear-positives per quarter. The extra-pulmonary TB (EPTB) cases were the maximum during April-June. Chest symptomatics of all types of TB cases were the lowest in January. A seasonal pattern of TB was observed for pulmonary TB and EPTB cases. This information would be useful for administration and managers to take extra care to arrange and provide extra facilities during the peak seasons.

Clinical response of newly diagnosed HIV seropositive and seronegative pulmonary tuberculosis patients with the RNTCP Short Course regimen in Pune, India

S. Tripathy, A. Anand, V. Inamdar, M. M. Manoj, K.M. Khillare, A.S. Datye, R. Iyer, D. M. Kanoj, M. Thakar, V. Kale, M. Pereira and A.R. Risbud. *Indian J Med Res* 2011; **133(5)**: 521-8

In the Revised National Tuberculosis Control Programme (RNTCP) in India prior to 2005, TB patients were offered standard DOTS regimens without knowledge of HIV status. Consequently such patients did not receive anti-retroviral therapy (ART) and the influence of concomitant HIV infection on the outcome of anti-tuberculosis treatment remained undetermined. This study was conducted to determine the results of treatment of HIV seropositive pulmonary tuberculosis patients with the RNTCP (DOTS) regimens under the programme in comparison with HIV negative patients prior to the availability of free ART in India. Between September 2000 and July 2006, 283 newly diagnosed pulmonary TB patients were enrolled in the study at the TB Outpatient Department at the Talera Hospital in the Pimpri Chinchwad Municipal Corporation area at Pune (Maharashtra): they included 121 HIV seropositive and 162 HIV seronegative patients. They were treated for tuberculosis as per the RNTCP in India. This study was predominantly conducted in the period before the free ART become available in Pune. At the end of six months of anti- TB treatment, 62 per cent of the HIV seropositive and 92 per cent of the HIV negative smear negative patients completed treatment and were asymptomatic; among smear positive patients, 70 per cent of the HIV-seropositive and 81 per cent of HIV seronegative pulmonary TB patients were cured. Considering the results in the smear positive and smear negative cases together, treatment success rates were substantially lower in HIV positive patients than in HIV negative patients, (66% vs 85%). Further, 29 per cent of HIV seropositive and one per cent of the HIV seronegative patients expired during treatment. During the entire period of 30 months, including six months of treatment and 24 months of follow up, 61 (51 %) of 121 HIV positive patients died; correspondingly there were 6 (4%) deaths among HIV negative patients. The HIV seropositive TB patients responded poorly to the RNTCP regimens as evidenced by lower success rates with chemotherapy and high mortality rates during treatment and follow up. There is a need to streamline the identification and management of HIV associated TB patients in the programme with provision of ART to achieve high cure rates for TB, reducing mortality rates and ensuring a better quality of life.

Outcome of standardized treatment for patients with MDR-TB from Tamil Nadu, India

Pauline Joseph, Vijaya Bhaskara Rao Desai, Nalini Sunder Mohan, Jemima Sheila Fredrick, Rajeswari Ramachandran, Balambal Raman, Fraser Wares, Ranjani Ramachandran and Aleyamma Thomas. *Indian J Med Res* 2011; **133(5)**: 2011; 529-34

Programmatic management of MDR- TB using a standardized treatment regimen (STR) is being implemented under the Revised National Tuberculosis Control Programme (RNTCP) in India. This study was undertaken to analyse the outcomes of MDR- TB patients treated at the Tuberculosis Research Centre, Chennai, with the RNTCP recommended 24 months STR, under programmatic conditions. Patients failed to the category II re-treatment regimen and confirmed to have MDR-TB, were treated with the RNTCP's STR in a prospective field trial on a predominantly ambulatory basis. Thirty eight patients were enrolled to the trial from June 2006 to September 2007. Time to culture conversion was two months or less for 82 per cent of patients. Culture conversion rates at three and six months were 84 and 87 per cent respectively. At the end of treatment, 25 (66%) were cured, five defaulted, three died and five failed. At 24 months, 30 (79%) patients, including five defaulters, remained

culture negative for more than 18 months. Twenty two (58%) patients reported adverse drug reactions (ADRs) which required dose reduction or termination of the offending drug. No patient had XDR-TB initially, but two failure cases emerged as XDR- TB during treatment. Outcomes of this small group of MDR- TB patients treated with the RNTCP's STR is encouraging in this setting. Close attention needs to be paid to ensure adherence, and to the timely recognition and treatment of ADRs.

Effect of efflux pump inhibitors on drug susceptibility of ofloxacin resistant *Mycobacterium tuberculosis* isolates

Mradula Singh, G. P. S. Jadaun, Ramdas, K. Srivastava, Vipin Chauhan, Ritu Mishra, Kavita Gupta, Surya Nair, D. S. Chauhan, V. D. Sharma, K. Venkatesan and V.M. Katoch. *Indian J Med Res* 2011; **133(5)**: 535-40.

In drug resistant, especially multi-drug resistant (MDR) tuberculosis, fluoroquinolones (FQs) are used as second line drugs. However, the incidence of FQ-resistant *Mycobacterium tuberculosis* is rapidly increasing which may be due to extensive use of FQs in the treatment of various other diseases. The most important known mechanism *i.e., gyrA* mutation in FQ resistance is not observed in a significant proportion of FQ resistant *M. tuberculosis* isolates suggesting that the resistance may be because of other mechanisms such as an active drug efflux pump. In this study, we evaluated the role of the efflux pumps in quinolone resistance by using various inhibitors such as carbonyl cyanide m-chlorophenyl hydrazone (CCCP), 2,4-dinitrophenol (DNP) and verapamil, in clinical isolates of *M. tuberculosis.* A total of 55 *M. tuberculosis* clinical isolates [45 ofloxacin (OFL) resistant and 10 ofloxacin sensitive) were tested by Resazurin microtitre assay (REMA) to observe the changes in ofloxacin minimum inhibitory concentration (MIC) levels in presence of efflux inhibitors as compared to control (without efflux inhibitor). The MIC levels of OFL showed 2-8 folds reduction in presence of CCCP (16/45; 35.5%), verapamil (24/45; 53.3%) and DNP (21/45; 46.6%) while in case of isolates identified as OFL sensitive these did not show any effect on ofloxacin MICs. In 11 of 45 (24.5%) isolates change in MIC levels was observed with all the three inhibitors. Overall, 30 (66.6%) isolates had reduction in OFL MIC after treatment with these inhibitors. A total of eight isolates were sequenced for *gyrA* gene, of which, seven (87.5%) showed known mutations. Of the eight sequenced isolates, seven (87.5%) showed two to eight fold change in MIC in presence of efflux inhibitors. Our findings suggest the involvement of active efflux pumps of both Major Facilitator Super Family (MFS) family (inhibited by CCCP and DNP) and ATP Binding Cassette (ABC) transporters (inhibited by verapamil) in the development of OFL resistance in *M. tuberculosis* isolates. Epidemiological significance of these findings needs to be determined in prospective studies with appropriate number of samples / isolates.

Pulmonary tuberculosis among health care workers at two designated DOTS Centres in urban city of Ibadan, Nigeria

A. O. Kehinde, A. Baba, R. A. Bakare, O. M. Ige, C. F. Gbadeyanka and O. E. Adebiyi. *Indian J Med Res* 12011; **133(5)**: 613-7.

Tuberculosis (TB) infection control interventions are not routinely implemented in many Sub-Saharan African countries including Nigeria. This study was carried out to ascertain the magnitude of occupationally-acquired pulmonary TB (PTB) among health care workers (HCWs) at two designated DOTS centres in Ibadan, Nigeria. One year descriptive study (January-December 2008) was carried out at the University College Hospital and Jericho Chest Hospital, both located in Ibadan, Nigeria. A pre-tested questionnaire was used to obtain socio-demographic data and other relevant information from the subjects. Three sputum samples were collected from each subject. This was processed using Ziehl-Neelsen (Z-N) stains. One of the sputum samples was cultured on modified Ogawa egg medium incubated at 37°C for six weeks. *Mycobacterium tuberculosis* was confirmed by repeat Z-N staining and biochemical tests. A total of 271 subjects, 117 (43.2%) males and 154 (56.8%) females were studied. Nine (3.3%) had their sputum positive for acid fast bacilli (AFB) while six (2.2%) were positive for culture. The culture contamination rate was 1.8 per cent. Significantly, all

the six culture positive samples were from males while none was obtained from their female counterparts. About half of the AFB positive samples were from subjects who had spent five years in their working units. Eight AFB positive cases were from 21-50-year-age-group while students accounted for seven AFB positive cases. The study showed that occupationally-acquired PTB is real in Ibadan. Further studies are needed to ascertain and address the magnitude of the problem.

A systematic review of risk factors for death in adults during and after tuberculosis treatment

C. J. Waitt and S. B. Squire. *Int J Tuberc Lung Dis* 2011; **15(7)**: 871-85.

Despite effective anti-tuberculosis chemotherapy, case-fatality rates of up to 25% are described in both industrialised and resource-poor settings. An understanding of the factors predisposing to poor outcome may allow the development of adjunctive treatment strategies or closer clinical monitoring in high-risk individuals. The objective was to describe the definitions and timing of deaths due to tuberculosis (TB), and the reported range of risk factors for death. All electronically available studies investigating risk factors for death in TB patients from 1966 to 2010 were analysed. Included were peer-reviewed reports of cohort, case control or cross-sectional studies with the primary objective of determination of quantitative effect estimates of the relationship between risk factors and death in adults treated for TB. Many studies were limited by their retrospective design, reliance on data from registries and charts, and risk of reporting bias. Most studies reported risk factors for all- cause mortality throughout anti-tuberculosis treatment. In the context of high TB incidence and human immuno-deficiency virus (HIV) prevalence, risk factors for death are HIV positivity, advancing immunosuppression, smear-negative disease and malnutrition. In regions of low TB incidence and HIV prevalence, risk factors include non- infective comorbidities, sputum smear-positive disease and alcohol and substance misuse. There remains a need for prospective clinical studies, particularly with a focus on deaths occurring during the first months of anti-tuberculosis treatment. Qualitative research should be used to further explore the relationship between sex and health- seeking behaviour, and to optimise delivery of health care to socially marginalised groups.

Hydrochloric *vs* sulphuric acid in water for Ziehl-Neelsen staining of acid-fast bacilli

K. J. M. Aung, P. Nandi, A. Hamid Salim, A. Hossain and A. Van Deunt. *Int J Tuberc Lung Dis* 2011; **15(7)**: 955-8.

The objective of the study was to compare 25% sulphuric acid in water (H_2SO_4) with hydrochloric acid in water (HCI) to differentiate acid-fast bacilli in sputum smears stained with 1% carbolfuchsin. For one year, all 158 microscopy laboratories used either H_2SO_4 or 3%/6%/10% HCI for their routine work, alternating monthly between H_2SO_4 and HCI. Each month, a sample of five smears per laboratory was rechecked blind. After recording qualitative staining aspects, all sample smears were restained before rechecking, using H_2SO_4 for destaining. A total of 368059 H_2SO_4 and 335436 HCI smears were routinely read, yielding 7.2% positive or scanty results in both groups. Of these, 9492 were re-checked. There was no difference in false-negatives detected (0.66%, 95%CI 0.44-0.95 for H_2SO_4 *vs* 0.68%, 95%CI 0.46-0.98 for HCI), but apparently there were more false-positives with H_2SO_4 (2.12%, 95%CI 0.92- 4.14 *vs* 0.28%, 95%CI 0.00-1.54, P = 0.05). Qualitatively, only 3% HCI yielded significantly inferior differentiation results. HCI 6-10% in water can be recommended for Ziehl Neelsen destaining above H_2SO_4. Diluting is easier and safer, and it may cause less confusion with false positives during rechecking, including a restaining step.

Xpert MTB/RIF®, a novel automated polymerase chain reaction-based tool for the diagnosis of tuberculosis

E. C. Bowles, B. Freyee, J. van Ingen, B. Mulder, M. J. Boeree and D. van Soolingen. *Int J Tuberc Lung Dis* 2011; **15(7)**: 988-9.

There is an urgent need for new point of care tests for tuberculosis (TB). Xpert MTB/RIF® is a real-

time polymerase chain reaction-based system that detects *Mycobacterium tuberculosis* DNA and rifampicin (RMP) resistance modulating mutations directly from clinical samples in two hours. The sensitivity for detecting *M. tuberculosis* in culture-positive samples was 93.8% (60/64) and exceeded smear microscopy (40/64, 62.5%). The specificity for detecting *M. tuberculosis* was 92.0% (23/25) and for RMP resistance it was 100% (8/8). The test is simple to conduct and requires basic sputum handling facilities only. These characteristics render it a promising close-to-patient test for TB in various settings.

LIST OF REVIWERS, 2011

Agarwal, Nishi, *Delhi*
Agarwal, Upasna, *Delhi*
Alladi Mohan, Tirupati
Amitava Chakrabarti, *Chandigarh*
Arora, V.K *Delhi*
Bedi, R.S. *Patiala*
Behera, D. *Delhi*
Chadha, V.K. *Bangalore*
Chopra, K.K. *Delhi*
Dewan, R.K. *Delhi*
Gopi, P.G. *Chennai*
Guleria, Randeep, *Delhi*
Gupta, Dheeraj, *Chandigarh*
Gupta, K.B. *Rohtak*
Gupta, Kumud, *Delhi*
Hanif, M. *Delhi*
Jagat Ram, *Chandigarh,*
Jaikishan, *Patiala*
Jawahar, M.S. *Chennai*
Janmeja, A.K. *Chandigarh*
Kandala Venu, Visakhapatnam
Kannan, *Delhi*
Khalid Umer Khayyam, *Delhi*
Kumar, Prahlad, *Bangalore*
Myneedu, V.P., Delhi
Mohapatra, Prasanta, *Chandigarh*
Narang, P. *Wardha*
Puri, M.M, *Delhi*
Raghunath, D. *Bangalore*
Rajasekaran, S. *Chennai*
Rajendra Prasad, *Lucknow*
Rajkumar, *Delhi*
Rajwanshi, *Chandigarh*
Ritu Kulshrestha, *Delhi,*
Ravindran, C. *Calicut*
Samantray, J.C., *Delhi*
Sarin, Rohit, *Delhi*
Selvakumar, N. *Chennai*
Shah, Ashok, *Delhi*
Sharma, Meera , *Chandigarh*
Sharma, S.K. *Delhi*
Sharma, Sangeeta, *Delhi*
Sharma, V.K., *Delhi*
Singla, Rupak, *Delhi,*
Vanaja Kumar, Chennai
Varinder Singh, Delhi
Vinod Kumar, Pondicherry

(Names are in alphabetical order)

Obituary

(1936 – 2011)

Dr. R.C. Jain was born on 10th October, 1936 at Dhampur in Bijnor District of Uttar Pradesh. He passed his M.B.B.S. and M.D. from King George's Medical College, Lucknow.

Dr. Jain belonged to a family of freedom fighters as both his parents were renowned freedom fighters.

After completing his studies, he went to United Kingdom and worked with renowned Thoracic Surgeons there.

After returning to India, he joined Rajen Babu TB Hospital, Delhi as Senior Thoracic Surgeon. Dr. Jain later joined the Lala Ram Sarup Institute for TB & Respiratory Diseases as Medical Superintendent. It was in his tenure there that LRS Institute was taken over by the Government of India. Being the Founder Director of this Institute, he initiated this organization to become a famous centre of excellence for Tuberculosis and Chest Diseases as this is today.

Dr. Jain was associated with the Tuberculosis Association of India for over four decades. Presently, he was Vice Chairman, TAI, and Vice President of Delhi TB Association, Chairman, New Delhi TB Centre. Besides, he was Chairman elect of the Scientific Committee of the SEAR.

Dr. Jain, being one of the top Thoracic Surgeons in the capital, was very down to earth. He lived life as a saint. Dr. Jain's humble nature and good deeds will always be remembered by one and all who came in his contact. He was always very kind to poor and needy.

The void created by Dr. Jain's passing away is difficult