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Editorial

CHANGING ROLE OF TUBERCULOSIS ASSOCIATION OF INDIA IN 75 YEARS

[*Indian J Tuberc 2014; 61:* 1-4]

Early Ayurvedic texts leave no doubt in anybody's mind that TB existed in India during ancient times. 'Open Air Treatment' (in sanatoria) was the model adopted by the philanthropic societies and individuals who initiated the movement against this crusade of humanity. The first such institution for isolation and treatment of such patients was founded in 1906 at Tilaunia, near Ajmer, by a Christian Missionary. In 1908, Dr. Louisa Hart, a missionary working in Madanapalle Town (A.P) started a movement for treating such patients in temporary building. The first sanatorium outside missionary auspices was opened in 1909 at Dharampore (Shimla Hills) under the name of Hardinge Sanatorium. In 1912, the first Government run Sanatorium was started at Bhowali in U.P. It was named King Edward Sanatorium to commemorate the reign of King Edward VII. These individual efforts culminated in the establishment of Tuberculosis Association of India (TAI) in 1939 as a voluntary Organization. This was established as a registered society by incorporating the King Emperor's Anti TB Fund and King George Thanks Giving Anti TB Fund.

Primarily, the main functions of TAI were to act as an advisory body on the prevention, control, treatment and relief of TB. It used to be a coordinating agency for standardizing methods for TB control, establishing model demonstration centres, undertaking research and investigation on subjects concerning TB and training health workers of the community and professionals.

In the pre-chemotherapy era, when no anti TB drugs were available, the emphasis was laid on early diagnosis and prevention of the disease. Use of collapse therapy, nutritional support as the treatment and BCG vaccination for prevention of disease were practised and advocated. TAI used to propagate these policies through workshops and conferences.

During the Chemotherapy era, Dr. B.K. Sikand a pioneer in the field of TB was appointed as the first secretary of TAI. He realized that the traditional approach to the TB problem i.e. the sanatorium was beyond the means of our country with the limited resources and hence worked out the scheme of domiciliary treatment (then known as the Organised Home Treatment - OHT). This was later adopted as domiciliary treatment in National TB Control Programme. To demonstrate OHT, a model clinic, New Delhi TB Clinic was established, where in addition to treatment, patients were given advice regarding sputum hygiene, contact examination and other prevention measures.

The Model TB Clinic was established by an agreement between Tuberculosis Association of India and Government of India. This was later known as New Delhi TB Centre (NDTBC) and is a pioneer institute involved in research in the field of tuberculosis since its establishment in 1940. In addition to providing quality treatment services, it has to its credit a number of landmark research studies which have guided Government of India in framing and revising TB control programme. Important among the studies in past include : Relative merits of various schedules in domiciliary treatment of pulmonary tuberculosis [1] (the study paved the way for concept of domiciliary treatment, at that time known as organized home treatment, as basis of NTP); The place of isolation in treatment and management of tuberculosis patients in

India[2] (The study showed that greater emphasis should be given on regular treatment rather than "Isolation". The 'Isolation' has even doubtful value compared to pre-antibiotic era. Isolation should no more be an argument for building beds or admitting patients to TB Institutes only); Disease among household contacts of tuberculosis patients at first and subsequent examination[3] (4.5% contacts were found to have pulmonary tuberculosis and this percentage did not vary according to the sputum status of the index case. The prevalence of non-pulmonary disease however was higher among child contacts of 'Sputum Positive' Index Cases compared to the 'Sputum Negative' group); A trial of relatively inexpensive regimens in the domiciliary treatment of pulmonary tuberculosis[4] (Sputum conversion at six months appeared to be a little less in TH regimen, 67% as compared to 94% and 81% in STH/SHZ and STH/TH regimen respectively. Though by nine months there was hardly any difference. Cavity closure was exactly similar in three regimens at six months); A critical appraisal of relative merits of radiology and bacteriology in case finding[5] (Limiting case finding to 'symptomatic' by radiology, followed by bacteriology of abnormal x-ray is least wasteful and constitutes rational utilization of the facilities.); A study to evaluate the contribution of an additional third drug as an initial supplement in treatment to pulmonary tuberculosis[6] (Conclusion was drawn after 24 weeks of treatment). It was concluded that the study failed to show any advantage in adding thiacetazone as the third drug to INH & Streptomycin in the initial stages of treatment in patients with bacilli initially sensitive to all three drugs); Initial and acquired isoniazid and rifampicin resistance to *M. tuberculosis* and its implications for treatment[7] (This study clearly indicates that if the organisms develop resistance to Rifampicin and isoniazid, it becomes very difficult to treat such patients; treatment was successful only in 7.4% of such patients as against 94.0% when the organisms were sensitive); Prevalence of HIV infection among tuberculosis patients[8] (In general HIV infection appears to be less common in Delhi population); Study of epidemiology of tuberculosis in an urban population of Delhi - report of 30 years follow up[9] (Sputum positive case rate in respect of the last survey of 1991 was 3.30 per 1000, showing no change over the entire 30 years period. The prevalence of radiologically active and probably active abacillary pulmonary tuberculosis was 5.4 per 1000, showing a decrease from 13.2 per 100 in 1962 to 5.4 per 1000 in 1991.); Radiological and bacteriological profile of pulmonary tuberculosis in diabetics[10] (Patients with uncontrolled diabetes had more extensive pulmonary tuberculosis. Patients with good control of diabetes were more likely to be sputum negative).

All the studies arrived to conclusions which made an impact on guidelines of management of TB cases under national programme. In recent years, the important studies conducted include nation wide ARTI estimation surveys[11,12] findings of which have been used by Government of India in monitoring the TB Control Programme.

When National TB Control Programme was launched in 1962, New Delhi TB Centre was one of the participating District TB Centres which covered the domiciliary area of old Delhi and provided free diagnosis and treatment facilities to the resident of the area. When Short Course Chemotherapy was introduced, many trials of treatment for evaluating duration and suitable regimens for Indian population was conducted at the Centre and the same incorporated in the programme.

The laboratory of the Centre has ever been recognized by the WHO. In July 2009, Centre's laboratory was accredited as Intermediate Reference Laboratory for State of Delhi. The Centre also conducts a TB Health Supervisors course which has the patronage of the Central TB Division of Government of India.

In recent years, TAI plays a big role in complementing the Revised National Tuberculosis Control Programme. The activities of the programme are pushed and augmented through NDTB Centre in close liaison with the Delhi State TB Control Department. NDTBC is responsible for monitoring and evaluation of

the RNTCP in the State of Delhi, analysis of quarterly programme management reports, compilation and onward transmission of feedback to Central TB Division, Government of India. Quality assurance of sputum examination, which is the vital area for success of RNTCP, is controlled by NDTBC. With the support of state affiliates, TAI also conducts sensitization programmes in Medical Colleges, state branches of Indian Medical Associations and for private practitioners.
The present major activities at Tuberculosis Association of India include:

- Providing quality diagnostic and treatment services through the NDTB Centre.

- Continuing supplementing RNTCP (Directly Observed Treatment Short Course), DOTS Services of Government of India.

- The Association is annually holding a national conference known as NATCON (National Conference on TB and Chest Diseases) in collaboration of the State TB Association. In year 2010, TAI in collaboration with NDTB Centre had the pride of holding first South East Asia Regional (SEAR) NATCON under the guidance of then Vice-Chairman Dr.V.K.Arora.

- **TB SEAL CAMPAIGN**

The annual TB seal campaign was introduced in India by the TAI in the year 1950. The campaign is inaugurated on 2nd October every year by H.E the President of India and aims at propagating TB awareness among people all over India. It also adds to raising funds to be used for promoting voluntary anti TB work in the country. The TB seal conveys the message that TB is preventable and the victim can be restored to normal life if diagnosed and treated early. The TB Seals printed by the Association have won the prize of the International Union Against Tuberculosis and Lung Diseases, Paris, for the years 2005 to 2007 and 2011.

- **Indian Journal of Tuberculosis**

TAI is uninterruptedly involved in publishing IJT, the quarterly journal for over 60 year now. This is the only renowned TB journal published at the national level. Being a highly respected journal among the medical fraternity, it is indexed in Medline of National Library of Medicine USA. The Journal incorporates original research articles on TB and respiratory diseases of international standards. Having eminent scholars and researchers on its editorial board. The journal has a good circulation among TB workers, Institutions in India and worldwide.

In addition, TAI is periodically publishing guidelines for Medical Practitioners on current issues of management of TB. Some important guidelines published include Management of Extra-pulmonary Tuberculosis[13], Management of side effects of anti TB drugs[14], Role of NGOs in TB control[15], Management of TB in special situations[16]. These are distributed during conferences and workshops.

- **Proposed Future Activities**

Much has been achieved but much more has to be done. No national programme can succeed with the government agencies alone. Community participation plays an important role in its success. TAI proposes to have a full fledged Health Education Cell. This would mainly aim at increasing public awareness about the disease, involve community leaders in the control effort and enlist cooperation of patients and their

families in seeking proper diagnosis and to complete treatment till cure. To ensure this, the cell will have Health Education expert, a publicity officer, material production equipment and office hand. Various NGOs work under the aegis of TAI in the field of TB control. Being the mother NGO, TAI proposes to publish a complete directory of these NGOs, catalogue the contribution being made by NGOs to TB control and produce a variety of hoarding, booklets, pamphlets, banners etc. with updated information on TB for use of the NGOs. There is also a proposal to set up TB-HIV cell in TAI complex for disseminating awareness about the co-infection, its prevention and management.

In conclusion, role of TAI has seen numerous changes during all these years from that of spreading awareness about TB to a partnership role for success of RNTCP.

V. K. Arora[1] and K. K. Chopra[2]

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Editorial

TUBERCULOSIS IN WOMEN - A NEGLECTED ISSUE

[*Indian J Tuberc 2014; 61:* 5-8]

8th march is observed as International Women's Day to show concern and make strong efforts to ensure equal rights and opportunities for men and women. Tuberculosis is among the top three killers of the women of reproductive age after HIV/AIDS and maternal cause. Social interaction and responsibility differ by gender in various societies. In many countries, women and men are equally participating in various public activities. But in some underdeveloped countries, life of women is very secular. Moreover, the opportunities to get infection both inside and outside home differ for men and women but the incidence rate is still high for men worldwide. This difference has again increased in developing countries like India as lot of socio-economic barriers are present along with some genetic factors.

In 2011, 8.7 million new cases of tuberculosis were estimated worldwide and 1.4 million people died of Tuberculosis.[1] TB is the third leading cause of death among women of reproductive age (15-44).[2] Three lakhs HIV negative and two lakhs HIV positive women died of tuberculosis and leaving million of women to live a miserable life with a stigma of TB.[1] The overall incidence and death from tuberculosis is more in men than women worldwide. But in some regions like Africa, mortality rate from tuberculosis is higher among women than men for both HIV negative and positive population.[1] Globally, men seem to be more affected than women with increased notification ratio of 1.9±0.6. The difference in increased ratio varies for all countries with marked increase in African and south Asia region. The notification ratio in India is 2.2 which is quite higher than other countries. The incidence rate is nearly equal below 14 years for males and females but increased after childhood in males. The decrease in notification ratio in females has been explained mainly by genetic and socio-economic factors. The contribution of both the factors has been explained by many authors and they differ in their theory.

The genetic and host factors play a very important role in the progression of disease and mortality. Resistance to TB infection is high among population as only 5-10% people develop active disease from infection.[3] Many factors like virulence of infecting strain, nutritional status, genetic makeup, gender and other sex related factors has very important role in susceptibility to infection. As the steroidal and non-steroidal hormones have their role in the immunity which vary in men and women like in pregnancy, more expression of Th2 cells may be detrimental to tuberculosis infection. On the another side in a study, estradiol has shown positive effect by enhancing macrophage activation and invariant natural killer cells by producing more interferon-gamma.[4] In an animal study, castration of male mice led to increased proliferation and recruitment of T lymphocyte showing negative effect of androgen against tuberculosis infection.[5] After the puberty, sex steroidal hormones play their role in immunity and deciding the progression of infection to active disease. This may be a reason for increased incidence of TB in men after childhood. The role of sex steroidal hormones in TB is reinforced by the fact that progression to disease and mortality rates is higher in women during their reproductive age.[6]

The genetic architecture of an individual is also a deciding factor how the host and environmental factors will interact. In some studies, sex chromosomes also contribute to different phenotypes of TB. In a genome wide linkage, analysis of TB identified a region on Xq which was linked to TB but not significant.[7] Similar results have also proved association of TB with the mutation linked to X chromosomes. So the

genetic factors are responsible for increased incidence of TB among men but the decreased notification rate and increased mortality among women are still unanswered. A lot of socio-economic factors like poverty, nutrition and diet, social stigma, poor accessibility to health services, lack of knowledge are responsible for late diagnosis and increased mortality among women due to TB.

In the society, gender is divided by their different roles in the community. It is always considered that a man should earn money and women must stay at home to take care of their children and family members. From the beginning of evolution of mankind, women are always considered inferior and pathetic in the community. They had always been neglected regarding their right of equality and health status. They had to depend on men because of economic reasons and lack of work opportunities. So gender inequality is one of the most important roots of this big giant problem.

Men's health is always a priority in the family because he is the only earning member in the family and if he falls sick, then the whole family has to suffer. On the other hand, women's health is least concerned in the family. Their job is to stay in the house and look after children and family members. Women usually need permission from their husbands to seek medical services and sometimes actively interfered by their husbands. Women always neglect their own health and priorities because they are more concerned towards their family. Men usually don't want to spend money on women's health. Like, a woman can come to visit clinics regularly for her husband while it's not true *vice versa*. It has been observed that women come to community health programme not for themselves but for their children and husbands. They hardly care about their health status and disease progression.

Poverty is directly associated with the incidence of tuberculosis and 70% of world's poor are women.[8] Poverty leads to multiple factors like improper nutrition, cramped living conditions and unavailing medical services that make them more vulnerable to TB infection. In India and other developing countries, more than 50% reproductive women are undernourished and anaemic. Incidence and mortality from TB is directly related to the nutritional status of population. Women reported that they sacrifice their nutrition and health for their family. Good part of the diet is always served to children and husband. Women even use the food packages provided by the tuberculosis programme, which are intended for patients' nourishment, to feed their families. They always give their family members a better care and nutrition to fight against the pathogens. On the other hand, pregnant and lactating women need high protein rich diet and by compromising nutrition, she makes herself more prone to infection and mortality from TB. Women who use biomass as a fuel are also more prone to TB as smoke weakens the respiratory and immune system.[9] Furthermore, poverty has pushed the woman into the sex trade and at an increased risk of contracting HIV and TB. Over one million girls from India are forced into commercial sex work each year.[10] These women are at increased risk of contracting HIV and TB from clients. The dual infection of HIV and TB has a very high mortality rate.

In the developing countries, women are not able to seek proper medical attention and facilities. Women usually need permission from their spouses and family members to visit a health care facility. Sometimes, they need a higher referral centre for better care and management of disease but not able to avail as men don't want to spend money or they neglect their problem. A study in Vietnam has found that women waited nearly twice as long to visit a hospital from the onset of a cough when compared to men.[11] Women are less likely to be screened than males due to gender bias in TB. TB is always considered a male disease and this myth leads to under-diagnosis of TB in women. The sputum positivity rate is low in women as 70% of total sputum positive cases were of males in 2011 report.[1] The immunity and host factor may be an important reason for this but still sputum sample produced by women is not from proper technique, instead they give saliva as a sample. A study in Pakistan has reported that women feel uncomfortable producing the mucus, resulting in under-diagnosis.[12]

Many activities are going on to educate people regarding RNTCP programme but only a few people attend meetings. Usually, women are not allowed to participate in these meetings due to social barriers and remain unaware of the disease and programme. Still a lot of people don't know that services related to TB are free. In an interview a woman said "she does not want to go to a health centre as still many hidden charges are present and she does not have the money". In low socio-economic countries, women are more illiterate than men as families are more reluctant for their education. Education has a big influence on the community or one's health. Many persons don't know about TB, how it occurs, how it can be prevented, what precautions are to be taken and where to go for medical services. People who are illiterate still have too many misconceptions about the disease and convey the same message to the community.

Tuberculosis continues to be a social stigma in the community. This stigma is more for women as they are always considered inferior and weak in the society. Society and family members usually avoid or neglect the TB patients. But this is the time when they need more social and emotional support from their family members and community. Women always have a fear of divorce or neglect as many men leave their wives just because of TB. In an interview, a woman said that her husband had left her because he thought that the food cooked by her could infect him also. More and more cases of divorce have been seen in the community due to tuberculosis. The girls who are unmarried always have a fear of revealing the disease to others as it may affect her future. This stigma is further augmented by new strategy of TB treatment i.e. DOTS (Directly Observed Therapy, Short Course). The DOTS strategy has done tremendous improvement in decreasing the incidence of therapy failure and mortality. But still people, especially women, think that they can't go to a health centre for the medication on alternative day as it will affect their daily work and privacy. Some women said that they felt very bad as people observed them when they went for medication. They want more privacy in receiving therapy. A randomised controlled study in South Africa has shown a greater success in self-supervised treatment than DOTS.[13] A few women are scared to come to health centres as they have to carry their children with them and it may affect their children's health. So fears of social stigma always delay diagnosis, treatment and increase the mortality in women.

In India, nearly 20000-40000 women suffer from active tuberculosis during pregnancy.[14] Tuberculosis is lately diagnosed in pregnancy due to restricted use of investigations like X-ray and coinciding signs and symptoms with other infections associated with pregnancy. Limited use of invasive procedures like pathological biopsy for extra-pulmonary TB makes the diagnosis more difficult in pregnancy. TB poses a considerable risk for mother and child. Although use of anti-TB treatment decreases the burden of tuberculosis but TB may complicate pregnancy and lead to preterm labour, premature birth, low birth weight, growth retardation and increased perinatal death.[15] In pregnancy, women need more nutritional and emotional support from their family. But incomplete and irregular treatment increases the morbidity and mortality. Some women do not take treatment during pregnancy and lactation as they think that drugs will cause bad effects to the child. A pregnant HIV positive mother has 20-30 times more susceptibility for TB infection than an HIV negative. The dual infection is a very lethal combination as more than two lakh deaths in 2011 were due to HIV-TB infection.[1] HIV works as a fuel for the epidemics of TB. A lot of HIV positive women in developing countries are living without knowing their HIV and TB infection status and die without seeking any medical care and treatment. So the high burden HIV areas must be screened and monitored for TB infection and the treatment. The poverty, socio-economic factors and misbeliefs augment the mortality in women due to tuberculosis.

So to reduce the burden of TB among women and for better care, the barriers like social stigma, poor financing and lack of political will should be removed. Though little has been done to address gender disparity but a strong and immediate action in this direction is required to control this disease among women to save the lives of millions of women so that they can look after their families. All pregnant

women should be routinely screened for TB, especially in the endemic areas. TB screening should be a part of maternal and child health programme and an integrated approach from TB specialists and mother and child health specialists is highly required. TB control programme needs to focus on greater access and reduce delay in diagnosis and treatment.

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The Editors-in-Chief and the members of the Editorial Board of the ***Indian Journal of Tuberculosis*** wish all its readers a Very Happy and Prosperous New Year 2014.

Dr. (Prof.) V.K. Arora
EXECUTIVE EDITOR

Indian J Tuberc 2014; 61: 9 - 11

MULTI-DRUG RESISTANT TUBERCULOSIS IN INDIA

Rupak Singla[1] and V.K. Arora[2]

There was a panel discussion on the management of MDR/XDR tuberculosis in NAPCON, held in Chennai from 27th to 30th November 2013. It was chaired by Dr. V.K. Arora. The other panelists were Drs. Rupak Singla, N.K. Jain, Balakrishnan Menon, Anshuman Mukhopadhyay and Rajesh Solanki.

Dr. Arora introduced the panel to the audience. He briefly explained the definitions of MDR-TB and XDR-TB. MDR-TB is defined as resistance to INH and rifampicin with or without other drugs. XDR-TB is defined as resistance to INH, rifampicin, one of the three injectable second-line drugs, namely kanamycin, amikacin or capreomycin, and one of the fluoroquinolones.

The moderator mentioned that among the notified cases of TB in 2010, there were about 6.3 lakh cases of MDR-TB globally and about 66 thousand MDR-TB patients in India. In India, among new cases, MDR-TB accounts for 2.1% and among retreatment cases, it accounts for 15%, varying from 13-17%. Among retreatment cases, around 9% of MDR-TB cases have XDR-TB globally and around 3.5% of MDR TB cases have XDR-TB in India. Overall among retreatment cases, 0.5% of patients are XDR-TB cases.

The moderator mentioned that total drug resistance (TDR) was in the news across the world and in WHO ever since it was reported from India. Dr. Arora asked Dr. Rupak Singla, who is a technical member of the Central TB Division (CTD) committee on diagnosis and treatment of TB, to express his view about TDR. Dr. Singla said that the DST against most of the second-line drugs and the newer so-called third-line drugs are not easily available and not reliable. Since many new third-line drugs are available in India and are effective as well, it is not technically correct to use the words 'total drug resistance' when these drugs have not been used. Even on humanitarian grounds, it is not correct to inform the poor suffering patients that he/she is suffering from TDR TB when many of the anti-TB drugs that can be used are still available. Dr. Singla also mentioned that even WHO has reported that due to the above reasons, the TDR terminology should not be used. WHO has also mentioned that any term beyond XDR-TB as of now is not justified. Dr. Arora concluded that it appears, at present, we should not use the term 'TDR' for our patients.

The moderator Dr. Arora asked Dr. Anshuman Mukhopadhyay how a case of suspected MDR-TB could be diagnosed using the current rapid diagnostic tests. Dr. Mukhopadhyay explained that currently using the genotypic methods, namely Line probe assays (LPA) and Gene Xpert, the diagnosis of MDR-TB or rifampicin non-resistant TB is possible within two days. These methods are available within the national programme network and they are rapidly being scaled up. He said that the Gene Xpert method can give diagnosis within two hours although it has limitation in that it only detects rifampicin resistance. Dr. Arora added that mono-resistance to rifampicin represents MDR-TB in most of the situations. Dr. Rupak Singla further emphasized that for new cases of TB, a single report of Gene Xpert positive for rifampicin resistance should be further

* Excerpts from the panel discussion on "Multi-drug Resistant Tuberculosis in India" held in Chennai during National Pulmonary Conference (NAPCON), 2013 from 27th to 30th November, 2013

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confirmed by another method, which could be LPA or a liquid culture, such as MGIT, before a patient is put on MDR-TB treatment.

It was asked what should be done in a patient who is resistant to rifampicin but sensitive to INH. Dr. Arora replied that as per programme guidelines, even such patients need to be given standardised MDR-TB treatment that does not contain INH. However, in an individual case management, the treating physician may consider adding INH in such cases.

The moderator asked Dr. Balakrishnan Menon about the role of radiology in the diagnosis of TB and MDR-TB. He said that in MDR-TB, X-ray, along with sputum AFB culture reports, helps in the follow-up of patients. Chest X-ray is recommended at 6-12 months of treatment and at the end of treatment. Other radiological tests, such as CT scan and MRI, help in extra-pulmonary TB cases, such as neurological TB, bone and joint TB, and abdominal TB. However, CT scan may not be done routinely for pulmonary TB unless surgery is warranted.

The moderator asked Dr. Jain to explain how a regimen for MDR-TB should be designed. Dr. Jain said that as per WHO 2010 guidelines, we should follow some basic principles. First, we must use at least four new drugs to which a patient is likely to be sensitive and which have not been used earlier. These drugs are likely to be effective for these patients. The first choice should be first-line drugs if they are available. The next choice should be one of the injectable second-line drugs. The third choice should be one of the quinolones. The fourth drug should comprise second-line oral anti-TB drugs, which include ethionamide, cycloserine, or PAS. For XDR-TB patients, one has to use drugs from group V, which contains drugs that are relatively new and still under experiment. These include linezolid, amoxycylin-clauvulanic acid, clofazamine, imipinem, high-dose INH, clarithromycin, etc. Also, we should not use drugs that have cross-resistance. We should also be careful not to use drugs that have side effects and may cause harm in a patient. For example, cycloserine should be used carefully in patients who already have severe depression. Similarly, injectable amino glycosides should be used carefully in patients with underlying renal impairment.

The moderator also invited the audience to ask questions, which were answered by the panellists. Dr. Arora highlighted that there have been challenges in the expansion of the country's PMDT programme. The biggest challenge is the rapid expansion of laboratory services. Also, the establishment of various DRTB centres for the management of MDR-TB patients is also a big challenge. He said that however the PMDT programme (PMDT) has shown a rapid expansion in the last two years despite these challenges and now there is a complete geographical coverage of the entire country so that all districts have access to diagnosis and treatment for MDR-TB patients.

The moderator asked Dr. Rajesh Solanki about supportive measures that can be used for MDR-TB patients. He said that although the anti-TB drugs have a major role in the cure of patients, good diet may supplement to boost the immunity of the patients. Also, incentives and the enablers to the patients may also help in improving the outcome of the treatment.

Dr. Arora asked Dr. Singla about new drugs and vaccines. Dr. Singla said that among the 11 new compounds currently in the pipeline, four drugs are in phase-III trials and seven are in phase-II trials. The drugs in phase-III trials include moxifloxacin, gatifloxacin, rifapentine and delamanid. Dr. Singla explained that Linezolid appears to be a cheap and effective drug and the experience of using this drug has also been published from India. Dr. Arora mentioned that a new drug, Bedaquiline, has been approved by the FDA for use in difficult cases of MDR-TB for patients who have not responded to the commonly available drugs or where, due to some other reasons such as drug intolerance, these drugs cannot be used. However, this drug may cause cardiac toxicity and it needs to be monitored. Dr. Singla also mentioned that currently an oral regimen of three drugs, namely PA 824, moxifloxacin and Pyrazinamide, is also being tried. It could be effective in drug-sensitive as well as drug-resistant cases.

Dr. Arora also highlighted the global experience on the outcome about the MDR and XDR-TB patients. He mentioned that as per a recent individual patient data systematic review and meta-analysis, among MDR-TB patients, around 48% had successful outcome, while 28% defaulted. Among XDR-TB patients, only one-third of them had successful outcome and 26% of them died. He also explained that in India, as per early Programmatic Management of Drug resistant TB (PMDT) experience, a high rate of deaths and defaults are being observed. Dr. Arora emphasized that the management of M/XDR-TB needs expensive treatment with a poor outcome.

In reply to a question from the audience, Dr. Arora asked Dr. Singla about the scope of infection control measures at healthcare facilities. Dr. Singla said that basic simple measures, such as a distance of at least 6 feet between two beds, good cross-ventilation to provide at least 12 air exchanges per hour, covering the TB patients' mouths, and the proper disposal of their sputum, can prevent the spread of infection at healthcare facilities. Dr. Arora emphasized the need for implementing such measures by all administrators. Dr. Singla also stressed that the provision of negative pressure rooms is not required in most healthcare facilities as it is very expensive. He also discussed that in high-risk settings, such as operation theatres, laboratories dealing with liquid culture inoculations, bronchoscopy rooms, healthcare providers should wear N-95 masks.

Dr. Arora summed up that MDR and XDR-TB is a man-made problem and it is always better to prevent it rather than try to manage it since the management of MDR and XDR-TB is difficult, expensive, and is very resource-intensive. He emphasized that all doctors involved in the management of TB should avoid the misuse of first-line and second-line drugs, especially quinolones, that will help in the prevention of MDR and XDR-TB. He thanked all the panelists and the audience for the successful discussion on this important subject.

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Reveiw Article

IMPROVING QUALITY OF TUBERCULOSIS CARE IN INDIA*

Madhukar Pai[1], Srinath Satyanarayana[1] and Phil Hopewell[2]

Summary: In India, the quality of care that tuberculosis (TB) patients receive varies considerably and is often not in accordance with the national and international standards. In this article, we provide an overview of the third (latest) edition of the International Standards of Tuberculosis Care (ISTC). These standards are supported by the existing World Health Organization guidelines and policy statements pertaining to TB care and have been endorsed by a number of international organizations. We call upon all health care providers in the country to practice TB care that is consistent with these standards, as well as the upcoming Standards for TB Care in India (STCI). **[*Indian J Tuberc 2014; 61:* 12-18]**

INTRODUCTION

Although progress has been made with global tuberculosis (TB) control, an estimated 8.6 million people developed TB in 2012, and 1.3 million died of the disease.[1] Of the estimated 8.6 million cases, 2.2 million cases (25%) occurred in India, making India the world's highest TB burden country.

The WHO Global TB Report 2013 emphasized two major challenges for controlling the TB epidemic. First, of the estimated 8.6 million cases, nearly three million cases were 'missing' either because they were not diagnosed or not notified to health systems. Second, the growing crisis of multidrug-resistant TB (MDR-TB), where three out of four cases with MDR-TB are still not being diagnosed. The report also underlined the worrisome gap between MDR cases diagnosed and treatment services for such patients.[1]

India accounts for 30% of the so called 'missing 3 million' cases and India is also doing poorly on diagnosing and treating MDR-TB.[1] Of the estimated 64,000 cases of MDR-TB among notified cases in 2012, only 17,373 cases were diagnosed under the Revised National TB Control Programme (RNTCP). While some of the missing cases in India may be totally undiagnosed, it is likely that a large number sought care in the informal and private sectors, but never got notified, despite the 2012 Governmental Order that made TB notification mandatory.

Studies have repeatedly shown the importance of private sector in India, and suggest that patients often begin seeking care in the informal private sector (chemists and unqualified practitioners), then seek care from qualified practitioners, and eventually end up in the RNTCP for free treatment.[2-4] A systematic review of 23 studies has shown that, on an average, TB is diagnosed in India after a delay of about two months, and three providers are seen before they are finally diagnosed and put on TB treatment.[5] Prescription studies have shown in the past[6] and continue to show[7,8] widespread use of irrational drug regimens. Diagnostic practices in the private sector remain suboptimal and heavily reliant on unreliable blood tests for TB.[9,10] In the public sector, large numbers of TB patients do not get drug-susceptibility testing.

Thus, quality of TB care in India is variable and often not aligned with international standards.[11,12] This matters a lot because poorly

* Editor's Note: RNTCP of Government of India has formulated standards of TB care in India which are broadly based on recommendations of International Standards of TB care. Standards of TB care in India have been formulated keeping in view local culture, patients load, available health infrastructure, diagnostic and treatment modalities agreed upon by experts working in Indian scenario. These will be shortly available on website www.tbcindia.nic.in.

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managed TB is a major driver of the epidemic, and a critical risk factor for mortality and drug-resistance. One of the first steps in improving quality of TB care is to set standards and expectations.

International Standards of TB Care

All patients with TB should receive the same quality of care, based on the best evidence available. Indeed, best practices for TB are enshrined in the International Standards of TB Care (ISTC), which was first published in 2006.[13] ISTC was envisioned to be a living document, to be updated to keep up with new advances and policies. Accordingly, the second Edition of ISTC was published in 2009, and the third Edition will be released on World TB Day 2014 (all ISTC documents are available at www.istcweb.org).

The standards in the ISTC are all supported by existing WHO guidelines and policy statements, many of which had recently been developed using rigorous methodology, including systematic reviews. The draft standards were reviewed by an expert committee of 27 members from 13 countries. The final version was endorsed by organizations that include the WHO, American Thoracic Society (ATS), US Centres for Disease Control and Prevention (CDC), the Japan Anti-tuberculosis Association (JATA), the Royal Dutch Tuberculosis Foundation (KNCV), and the International Union against Tuberculosis and Lung Disease. ISTC has inspired several country-specific adaptations, including the European Union Standards of TB Care[14] and the upcoming Standards for TB Care in India (STCI).[15]

Why are standards necessary? Standards aim to describe a widely accepted level of care that all practitioners, public and private, should seek to achieve in managing patients who have, are suspected of having, or are at increased risk of developing TB. The basic principles of care for persons with, or suspected of having, TB are the same worldwide: a diagnosis should be established promptly and accurately; standardized treatment regimens of proven efficacy should be used, together with appropriate treatment support and supervision; the response to treatment should be monitored; and the essential public health responsibilities must be carried out.

Below, we present the 21 Standards included in the third Edition of ISTC. A complete document with evidence summaries will be published in March 2014.

Standards for Diagnosis

Standard 1. To ensure early diagnosis, providers must be aware of individual and group risk factors for tuberculosis and perform prompt clinical evaluations and appropriate diagnostic testing for persons with symptoms and findings consistent with tuberculosis.

Standard 2.All patients (including children) with unexplained cough lasting two or more weeks or with unexplained findings suggestive of tuberculosis on chest radiographs should be evaluated for tuberculosis.

Standard 3. All patients (including children) who are suspected of having pulmonary tuberculosis and are capable of producing sputum should have at least two sputum specimens submitted for smear microscopy or a single sputum specimen for Xpert MTB/RIF®testing in a quality-assured laboratory. Patients at risk for drug resistance, who have HIV risks, or who are seriously ill, should have Xpert MTB/RIF® performed as the initial diagnostic test. Blood-based serologic tests and interferon gamma release assays should not be used for diagnosis of active tuberculosis.

Standard 4. For all patients (including children) suspected of having extra-pulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microbiological, and histopathological examination. An Xpert MTB/RIF® test is recommended as the preferred initial microbiological test for suspected tuberculous meningitis because of the need for a rapid diagnosis.

Standard 5. In patients suspected of having pulmonary tuberculosis whose sputum smears are negative, Xpert MTB/RIF® and/or sputum cultures

should be performed. Among smear and Xpert MTB/RIF® negative persons with clinical evidence strongly suggestive of tuberculosis, antituberculosis treatment should be initiated after collection of specimens for culture examination.

Standard 6. In all children suspected of having intrathoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis, bacteriological confirmation should be sought through examination of respiratory secretions (expectorated sputum, induced sputum, gastric lavage) for smear microscopy, an Xpert MTB/RIF® test and/or culture.

Standards for Treatment

Standard 7. To fulfill her/his public health responsibility, as well as responsibility to the individual patient, the provider must prescribe an appropriate treatment regimen, monitor adherence to the regimen and, when necessary, address factors leading to interruption or discontinuation of treatment. Fulfilling these responsibilities will likely require coordination with local public health services and/or other local services.

*Standard 8.*All patients who have not been treated previously and do not have other risk factors for drug resistance should receive a WHO-approved first-line treatment regimen using quality assured drugs. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide and ethambutol.* The continuation phase should consist of isoniazid and rifampicin given for four months. The doses of antituberculosis drugs used should conform to WHO recommendations. (*Ethambutol may be omitted in children who are HIV negative and who have non-cavitary disease.)

*Standard 9.*A patient-centred approach to treatment should be developed for all patients in order to promote adherence, improve quality of life, and relieve suffering. This approach should be based on the patient's needs and mutual respect between the patient and the provider.

Standard 10. Response to treatment in patients with pulmonary tuberculosis (including those with tuberculosis diagnosed by a rapid molecular test)should be monitored by follow-up sputum smear microscopy at the time of completion of the initial phase of treatment (two months). If the sputum smear is positive at completion of the initial phase, sputum microscopy should be performed again at three months and, if positive, rapid molecular drug sensitivity testing (Line probe assays or Xpert MTB/RIF®) or culture with drug susceptibility testing should be performed. In patients with extra-pulmonary tuberculosis and in children, the response to treatment is best assessed clinically.

Standard 11. An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance (if known), should be obtained for all patients. Drug susceptibility testing should be performed at the start of therapy for all previously treated patients. Patients who remain sputum smear-positive at completion of three months of treatment and patients in whom treatment has failed, have been lost to follow-up, or relapsed following one or more courses of treatment should always be assessed for drug resistance. For patients in whom drug resistance is considered to be likely (see Table 8), an Xpert MTB/RIF® test should be the initial diagnostic test. Line-probe assay or culture and testing for susceptibility to at least isoniazid and rifampicin should be performed promptly if rifamycin resistance is detected. Patient counselling and education, as well as an empiric second-line treatment regimen, should begin immediately to minimize the potential for transmission. Infection control measures appropriate to the setting should be applied.

Standard 12. Patients with or highly likely to have tuberculosis caused by drug-resistant (especially MDR/XDR) organisms should be treated with specialized regimens containing quality-assured second-line antituberculosis drugs. The doses of antituberculosis drugs should conform to WHO recommendations. The regimen chosen may be standardized or based on suspected or confirmed drug susceptibility patterns. At least pyrazinamide and four drugs to which the organisms are known

or presumed to be susceptible, including an injectable agent, should be used in an 8-month intensive phase and at least three drugs to which the organisms are known or presumed to be susceptible, should be used in the continuation phase. Treatment should be given for at least 18-24 months beyond culture conversion. Patient-centred measures, including observation of treatment, are required to ensure adherence. Consultation with a specialist experienced in treatment of patients with MDR/XDR tuberculosis should be obtained.

Standard 13. An accessible, systematically maintained record of all medications given, bacteriologic response, outcomes, and adverse reactions should be maintained for all patients.

Standards for Addressing HIV Infection and other Co-morbid Conditions

Standard 14. HIV testing and counselling should be conducted for all patients with, or suspected of having, tuberculosis unless there is a confirmed negative test within the previous two months. Because of the close relationship of tuberculosis and HIV infection, integrated approaches to prevention, diagnosis and treatment of both tuberculosis and HIV infection are recommended in areas with high HIV prevalence. HIV testing is of special importance as part of routine management of all patients in areas with a high prevalence of HIV infection in the general population, in patients with symptoms and/or signs of HIV-related conditions, and in patients having a history suggestive of high risk of HIV exposure.

Standard 15. In persons with HIV infection and tuberculosis who have profound immuno-suppression (CD4 counts less than 50cells/mm3), antiretroviral therapy (ART) should be initiated within two weeks of beginning treatment for tuberculosis unless tuberculous meningitis is present. For all other patients with HIV and tuberculosis, regardless of CD4 counts, ART should be initiated within eight weeks of beginning treatment for tuberculosis. Patients with tuberculosis and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.

Standard 16. Persons with HIV infection who, after careful evaluation, do not have active tuberculosis should be treated for presumed latent tuberculosis infection with isoniazid for at least six months.

Standard 17. All providers should conduct a thorough assessment for co-morbid conditions and other factors that could affect tuberculosis treatment response or outcome and identify additional services that would support an optimal outcome for each patient. These services should be incorporated into an individualized plan of care that includes assessment of and referrals for treatment of other illnesses. Particular attention should be paid to diseases or conditions known to affect treatment outcome, for example, diabetes mellitus, drug and alcohol abuse, undernutrition, and tobacco smoking. Referrals to other psychosocial support services, or to such services as antenatal or well-baby care should also be provided.

Standards for Public Health and Prevention

Standard 18. All providers should ensure that persons who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. The highest priority contacts for evaluation are:

- Persons with symptoms suggestive of tuberculosis
- Children aged <5 years
- Contacts with known or suspected immuno-compromised states, particularly HIV infection
- Contacts of patients with MDR/XDR tuberculosis

Standard 19. Children <5 years of age and persons of any age with HIV infection who are close contacts of a person with infectious tuberculosis, and who, after careful evaluation, do not have active tuberculosis, should be treated for presumed latent tuberculosis infection with isoniazid for at least six months.

Standard 20. Each healthcare facility caring for patients who have, or are suspected of having,

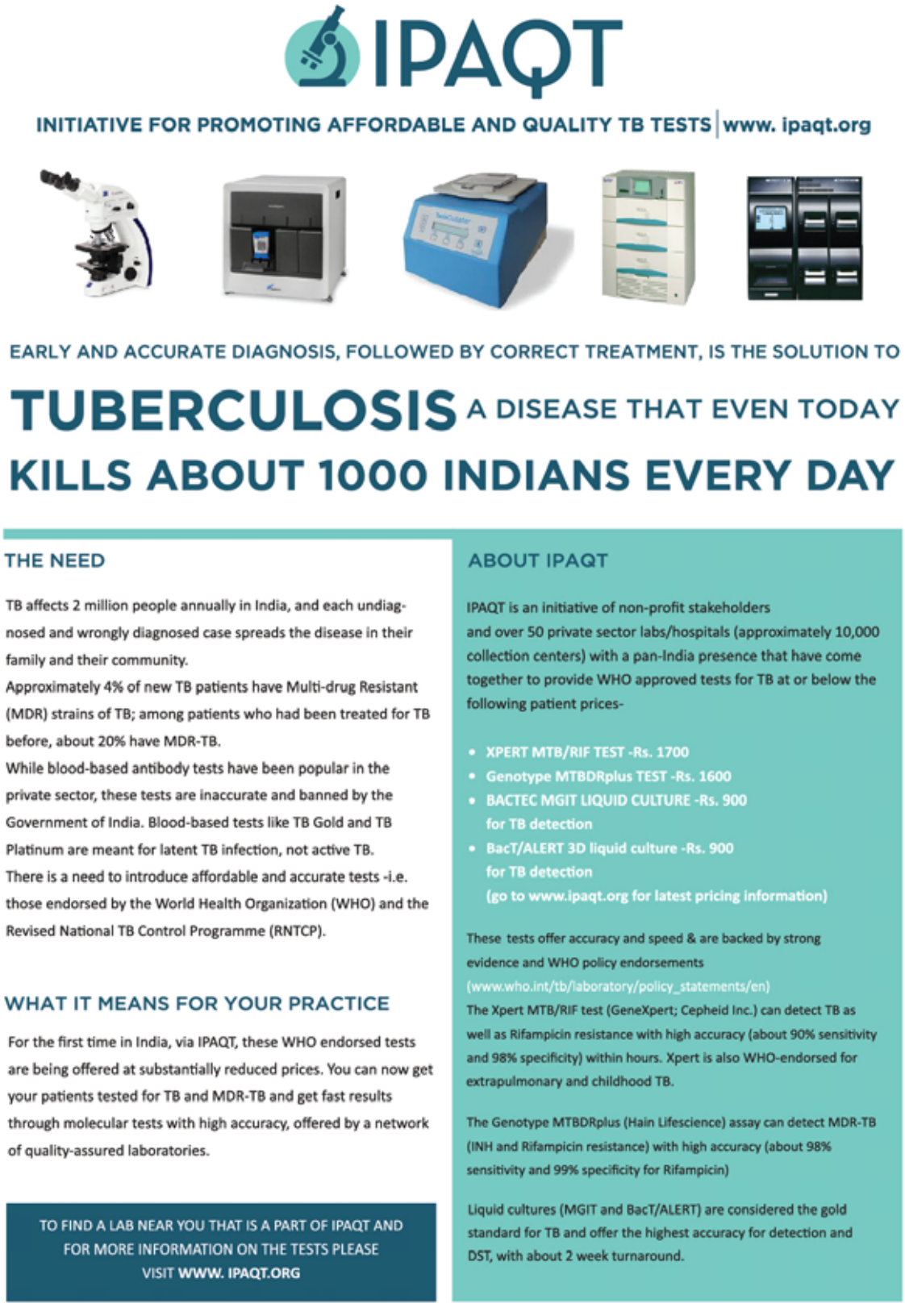

Figure 1: Initiative for Promoting Affordable, Quality TB tests (IPAQTwww.ipaqt.org)[20]

infectious tuberculosis should develop and implement an appropriate tuberculosis infection control plan to minimize possible transmission of *M. tuberculosis* to patients and health care workers.

Standard 21. All providers must report both new and re-treatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformity with applicable legal requirements and policies.

Translation of Standards into Improved TB Care in India

Establishing standards is a necessary and important step, but it is equally important to engage healthcare providers (at scale), educate them on the use of ISTC and STCI, establish a quality surveillance system to monitor their adherence with standards, and provide ongoing training and support. It is also critical to understand the microeconomics of private healthcare and ensure that public-private mix (PPM) schemes and projects are better aligned with the incentive structures that exist in the private market.[16]

This is where the situation becomes challenging in India, where a large proportion of private and informal providers are not currently engaged in TB control, and the RNTCP is unable to reach or engage these large numbers of providers, or make available PPM schemes attractive enough for private providers to participate in. Only a small fraction of the RNTCP case finding is *via* PPM schemes, and most providers in the private sector are not currently notifying cases to the RNTCP.

In a recent study of private practitioners in Andhra Pradesh, only 14% complied with a combination of three core ISTC standards (cough for tuberculosis suspects, sputum smear examination and use of standardized treatment regimens).[17] Another study among private qualified physicians in Meerut showed that only a third were even aware of ISTC.[18]

So, while the development of STCI is a welcome development, it is important to develop a plan for its dissemination, implementation, and evaluation. The RNTCP has announced *"universal access to quality TB diagnosis and treatment for all TB patients in the community"* as its new goal in the new National Strategic Plan [NSP] (2012 – 2017).[19] The NSP will seek to engage the private sector using the "Public Private Interface Agency" (PPIA) model. PPIAs will aggregate healthcare providers, educate them on STCI, incentivize them to diagnose and treat TB as per established standards, monitor adherence to the standards, and use information and communication technologies (ICT) to notify cases, improve treatment adherence, and make performance-based payments. Two PPIA urban pilot projects are now underway (in Mumbai and Patna), and the results of these pilot projects may enable evidence-based new policies on PPM.

Apart from the PPIA intervention, IPAQT is another initiative that aims to improve the quality of TB diagnostic practices in the Indian private sector.[10]Initiative for Promoting Affordable, Quality TB tests (IPAQTwww.ipaqt.org), a coalition of private laboratories in India, supported by industry and non-profit groups, that has made several WHO-endorsed TB tests (e.g. Xpert MTB/RIF, Hain Genotype MTBDR plus, and liquid cultures)available at more affordable prices to patients in the private sector (Figure 1).[20]This initiative is transitioning the Indian private market from a premium pricing model to a high-volume, low-margin model for WHO-endorsed tests.

Since its launch in March of 2013, the IPAQT initiative has already achieved a pan-India presence – with 50 accredited labs which encompasses over 3500 franchisee labs and greater than 10,000 collection centres committed to providing these tests at affordable prices.All cases diagnosed by IPAQT labs will be notified to the RNTCP.

Initiatives like PPIA and IPAQT emphasize the need to try out newer models for private sector engagement.[16] Such experiment scan provide insights on which innovative business models may succeed in the private market. For example, such models have worked to make high quality eye care[21] and heart care[22] affordable in India, and it remains to be seen whether they can work to make high

quality TB care affordable and accessible to large numbers of Indians.

DISCLOSURE

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Review Article

THE DYNAMICS OF TUBERCULOSIS EPIDEMIOLOGY

Hans L Rieder[1]

***Summary*:** A conceptual framework to study the epidemiologic basis of tuberculosis control is provided. The basic model to discuss the epidemiology of tuberculosis is based on a classification of tuberculosis based on its pathogenesis with exposure, latent infection, tuberculosis, and death from tuberculosis, showing the conditional probabilities leading from one to the next step in the chain of events. Historical data are utilized to demonstrate how the dynamics of tuberculosis over multiple decades have contributed to shape the present. It is shown that the key concept to understand the dynamics is related to current and past incidence and prevalence of latent infection with *M. tuberculosis*. The dynamics of the epidemic are shaped both by the behaviour of the causative organism of tuberculosis as well as the population structure and changes that take place in parallel in which *M. tuberculosis* thrives. Both the present and the future shape of the epidemic, as well as the principles applied to its control lie very much in the past of a society. While new risk factors such as HIV or diabetes have been or are emerging more strongly, it is noted that the majority of all new cases emerging cannot be pinned to one or the other such factor. It is the historical experience of a population that offers the most valuable key to understanding the present and the future. **[*Indian J Tuberc 2014; 61:* 19-29]**

Key words: TB, Epidemiology, Dynamics

Introduction

Both the tuberculosis epidemic and the population on which it thrives undergo continuous changes mutually affecting each other. Snap shots from prevalence surveys or notifications of incident cases in a given year provide useful but incomplete information. Bacteria replicate in less than one hour, but the generation time of *Mycobacterium tuberculosis* is half a day to a day.[1] As a result, a tuberculosis outbreak in a community lingers for a much longer time than what might be expected from other pathogens.[2,3] Accordingly, an epidemiologic analysis also preferably takes the slow pace of the epidemic into consideration.

This review attempts to provide some guidance into the epidemiologic study of tuberculosis. It should assist to obtain deeper insight into the gradual transition from the past leading up to the present and into what might rationally be expected from our endeavours to lessen the impact of tuberculosis on humanity.

A simple epidemiologic model

The pathogenesis of tuberculosis can be compartmentalized into sequential steps. The classification system of the American Thoracic Society[4] provides a model not only for diagnosis and treatment of tuberculosis but also for a better appreciation of its epidemiologic basis (fig. 1).[5] Transitions from one to the next stage are perhaps not as rigidly boxed as the graph suggests, but the principle of distinguishing between exposure, latent infection, manifest tuberculosis, and death from tuberculosis proves invaluable to our understanding of the dynamics of tuberculosis.

It is further useful todistinguish between "etiologic" and "administrative" epidemiology. [6]Etiologic epidemiology examines risk factors that promote progression from one stage to the next, while administrative epidemiology describes the magnitude of the problem in terms of incidence and prevalence where applicable.

Exposure to *M. tuberculosis*

Demonstration and proof for the air borne mode of transmission of *M. tuberculosis* through

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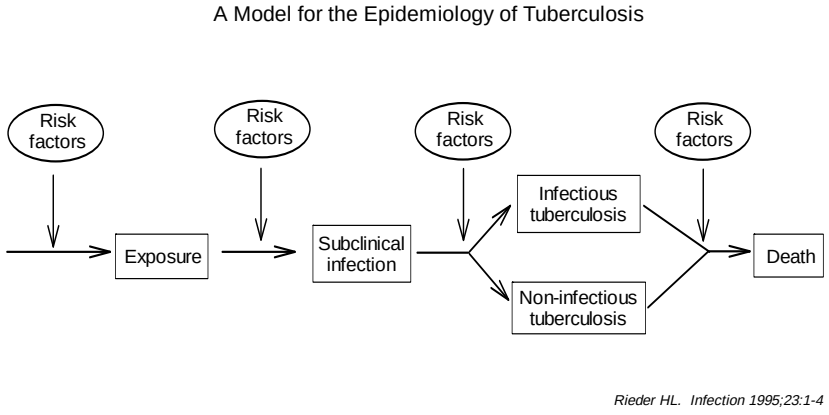

Fig. 1: The classification scheme of tuberculosis by the American Thoracic Society[4] is used as an appropriate model to examine the epidemiologic basis of tuberculosis control.[5]

droplet nuclei resulting from evaporation of liquid droplets expelled into the air during respiratory maneuvers (notably cough) took half a century following Robert Koch's seminal discovery.[7] The commonly encountered terms "close" and "other" contacts in the context of discussing exposure are somewhat inappropriate, because proximity is likely rather irrelevant indoors but highly relevant outdoors.

We define an exposure as "relevant" if it results in a reasonably measurable risk of actually becoming infected, pragmatic perhaps but certainly imprecise: a risk of 1 in 1,000 might not be "reasonably measurable", while 1 in 10 is.

Outdoors, the fate of droplets is to fall ineffectively to the ground if large enough or to be dispersed rapidly in a virtually infinite amount of air where they tend to be killed rapidly by ultraviolet radiation even if there is just skyshine rather than full sunshine.[8] As the tidal inhalation volume of air per breath is only about half a liter, the probability that the minimum dose of one bacillus is inhaled during one hour outdoors is not reasonably measurable unless one is in talking distance and thus exposed to the direct exhalation stream of a small droplets-producing tuberculosis patient. Outdoors, proximity matters.

Indoors,the amount of available air is "closer" to finite,affecting the resulting concentration of bacilli in the ambient air. The product of bacillary combination and the amount of time a susceptible individual breathes that air determines the probability of inhaling bacilli. Indoors the determinant is not proximity as bacilli float with the prevailing air currents. Indeed, a source who has expelled bacilli-containing droplets may leave a room and a person entering the room subsequently may inhale droplet nuclei containing live bacilli. What can be manipulated indoors is ventilation to reduce the concentration of bacilli in the inhalable air. Hospitals in Thailand with air-conditioning had overall poorer ventilation than older hospitals relying on opening the windows.[9] In cold climates, a large amount of time is spent indoors and windows may be opened infrequently to economize on fuel consumption. The majority of transmissions are likely to take place indoors.

Opportunity of getting exposed depends both on the epidemiologic situation and population characteristics. Exposure risk is related to person-time of infectiousness in the community. In addition, the opportunity for a relevant exposure is modified by population density: the number of encounters between persons is higher in e.g. urban than rural settings. Behavioural factors by both source and the potentially exposed will further modify the probability of an encounter between them. It is noteworthy that the largest magnitude of the tuberculosis epidemic

ever recorded has been in one of the coldest human habitats.[10] Tuberculosis increased during urbanization in the wake of industrialization.[11] Virtually always it has been substantially higher in urban than rural settings.[12,13]

While there is no tool to actually measure exposure risk, it is essential to reflect on it as it is the first and thus decisive step in the chain of events. Effective tuberculosis control based on case-finding and chemotherapy results in a reduction of person-time of infectiousness in the community and thus a reduction in the risk of exposure in the community (figure 2).[5] Epidemiologically, tuberculosis control is all about reducing the incidence of infection with *M. tuberculosis* by reducing person-time of

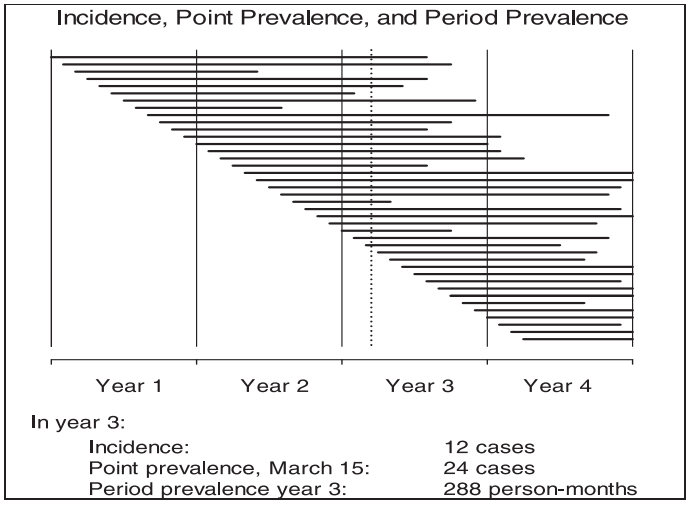

Fig. 2a: Incidence and prevalence of infectious tuberculosis, and duration of infectiousness are displayed in a community without intervention.[5]

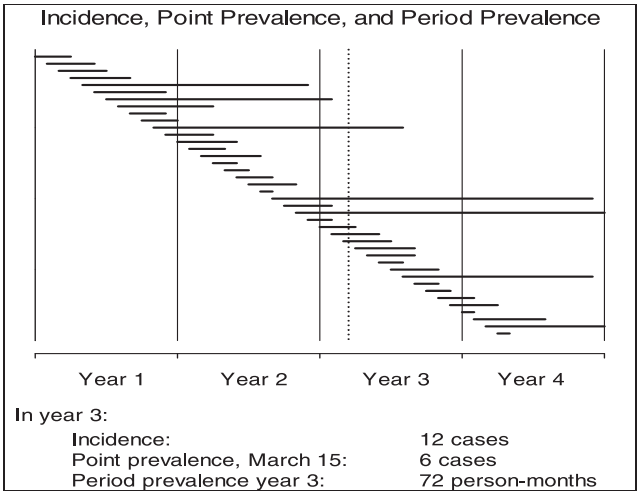

Fig. 2b: Incidence and prevalence of infectious tuberculosis, and duration of infectiousness are displayed in a community with an effective case finding and treatment program. The immediate impact is not on incidence, but on the prevalence and on person-time of infectiousness in the community, thereby reducing the risk of exposure among community members.[5]

infectiousness and thus exposure risk in the community. As fewer people become infected, future incidence of tuberculosis will decline.

Latent infection with *M. tuberculosis*

The risk of becoming infected with *M. tuberculosis* given exposure is generally assumed to be largely exogenous in nature, i.e. the risk of becoming infected is determined by the concentration of bacilli in the ambient air and the duration of breathing exposure to that air. Experiments in small mammals have shown the number of lesions following air borne infection to equal approximately the number of bacilli calculated to have been inhaled.[14] Therefore, any non-specific killing of tubercle bacilli by alveolar macrophages was ineffective. To what extent this also holds for humans is unknown. It is, however, generally accepted that *M. tuberculosis* is fairly robust in subverting the primary non-specific killing ability of macrophages.[15]

The proportion of the population becoming infected during a specified period of time (incidence of infection) and the proportion of the population that remains infected after acquisition of infection (prevalence of infection) are the primary determinants both of current and future tuberculosis incidence. This is notably so because the incubation period of tuberculosis is ill-defined. While the purposefully exaggerated dictum "Once infected, always infected"[16] has been convincingly disproved a long time ago,[17] it is still essential to re-emphasize that the immunologic responses obtainable with available test systems for "latent infection" do no equate the presence of life bacilli. They reflect an immunologic memory about an infection with *M. tuberculosis* acquired in the past.[18] Nevertheless, even if only a small fraction of persons remain incapable of entirely eliminating *M. tuberculosis*, they can substantially contribute to overall incident tuberculosis through re-activation disease if this fraction comes from a large number of people. It is thus of importance to know about the risk of becoming infected, the secular changes in that risk and the resulting prevalence of persons ever infected. As changes are gradual and relatively slow, long time series are necessary to describe them properly and to notice their impact. Importantly, not only the risk of infection in a population may change, the population structure may also change in parallel.In many countries life expectancy has been increasing, fertility decreasing, and child survival improving, all leading to population structure changes. Fig. 3a and 3b juxtapose an initial

Fig. 3a: The population structure in Switzerland in the year 1900 and the subset of persons who have ever been infected with *M. tuberculosis* (cross-hatched area). Data on infection risk from[19], data on population figures from http://www.bfs.admin.ch/bfs/portal/en/index/themen/01.html

Fig. 3b: The population structure in Switzerland in the year 2009 and the subset of persons who have ever been infected with *M. tuberculosis* (cross-hatched area). Data on infection risk from[19], data on population figures from http://www.bfs.admin.ch/bfs/portal/en/index/themen/01.html

snapshot from Switzerland in the year 1900 and a final one in the year 2009. In 1900, the risk of becoming infected with *M. tuberculosis* was about 13%, declined by about 3.9% annually until 1945. Subsequently, the decline accelerated to almost 12% annually.[19] By 2009, the annual risk of infection is estimated to have declined to about 1 per 100,000 population. In 1900, 2.5% of the population were below one year of age. With a 13% risk of becoming infected during the first year of life, 0.33% of the total population had become infected by the time of the first birth day. Ten years later, the under-one-year-old made up less than 2.3% and their probability of having become infected by the first birth date had declined to 9%. As a result, only 0.20% of the total population was infected by the first birthday in 1910.In 1900, the under-5-year-old constituted 11.6% of the total population, by 2009 this proportion had shrunk to 4.9% and the risk of infection had massively declined. As a composite result, virtually everybody was infected by age 20 in 1900, while by 2009, the residual pool of persons who ever got infected with *M. tuberculosis* remained almost exclusively among those aged 60 years and older. This transition over more than 100 years has important repercussions on future incidence of tuberculosis morbidity as tuberculosis can by necessity only emerge from within the pool of those who have ever become infected.

Age and cohort effects in incidence and prevalence of infection with *M. tuberculosis* are of primordial importance. Observable differences in morbidity by sex can be attributable to differences in the risk of becoming and being infected, differences in morbidity risk given infection, and finally the gender issue of differences in accessibility to diagnosis.Among children, no important differences in the prevalence of infection have been observed between boys and girls even where accessibility to schooling has substantially disfavoured girls. [20] The risk of becoming infected in the school itself – barring the exceptional teacher with transmissible tuberculosis – is negligibly small as the most frequent social interaction and thus exposure risk is with age peers and children rarely have transmissible forms of tuberculosis. Differences start to emerge when adolescents

assume gender-specific behaviour and transmissible forms of tuberculosis become the norm rather than the exception. Among young adults, age-specific sex ratios in infection prevalence differ substantially across cultures, as exemplified in the selective comparison from Denmark and India, but almost anywhere males are the higher infection prevalence group (figure 4).[21,22]

Exposure risk differences by population density have been mentioned. One example of its impact on resulting age-specific prevalence of infection is shown for Norway (fig. 5).[12,13] By age 20 years, the prevalence of infection among the urban working class was almost thrice as large as among rural farmers.

In summary, secular changes and structural population changes prominently affect the risk of becoming and being infected. Age cumulatively adds to prevalence of infection. It also affects the incidence of infection which varies by age- and

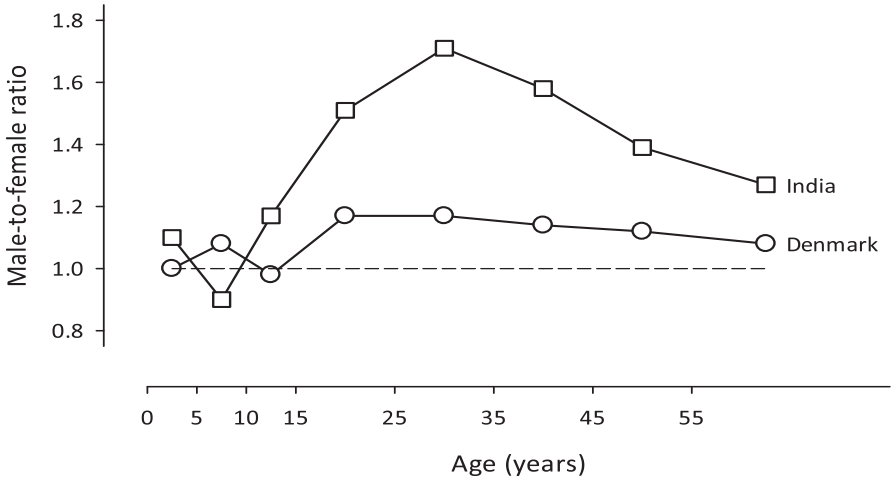

Fig. 4: Age-specific female-to-male ratio of the prevalence of infection with *M. tuberculosis*, comparatively shown from surveys in Denmark and India.[21, 22]

Fig. 5: Age-specific prevalence of infection with *M. tuberculosis* in Norway 1927-1928, among farmers and workers.[12, 13]

gender-related behavioural changes that occur with growing up and are observably different across societies.

Tuberculosis

Trivial as the statement may be, but the most important risk factor for tuberculosis is harbouring live tubercle bacilli.Incidence of tuberculosis is a result of the underlying incidence and prevalence of infection with *M. tuberculosis* in the community. Numerous factors are known to increase an individual's risk of progressing from latent infection to overt and manifest tuberculosis.[5] However, the majority of incident cases in the world cannot be pinned to a known risk factor: they are not due to infection with human immunodeficiency virus (HIV), diabetes, smoking, other immuno-suppressive disorders or treatments, or other less frequent factors, etc.[5]

A prominent shaping feature of individual disease risk is time elapsed since infection was acquired (figure 6).[23,24] Two interlinked or perhaps even a single mechanism might be operating. The effectiveness of the cellular immune system acts as a filter favouring or disfavouring rapid progression to tuberculosis. Persons with an effective cellular immune response may contain bacillary multiplication and variably also progressively eliminate surviving bacilli over time. After the initial high-risk period, the incidence drops to about 1 in 1000 person-years. Over a remaining life span of 50 years, this could accumulate to about 5%. Adding the early and late components yields approximately the often quoted 10% life time risk.[25]

The risk of tuberculosis given infection varies importantly by age.[25] It is the highest in infancy, drops to a nadir during primary school years, then starts rising again with adolescence, and peaks in young adulthood. There is no evidence for a risk increase with older age: the increased incidence among the elderly is better explained by accumulated infection prevalence and cohort effects.

Several studies have shown (or allow calculation to show) that among young adults,

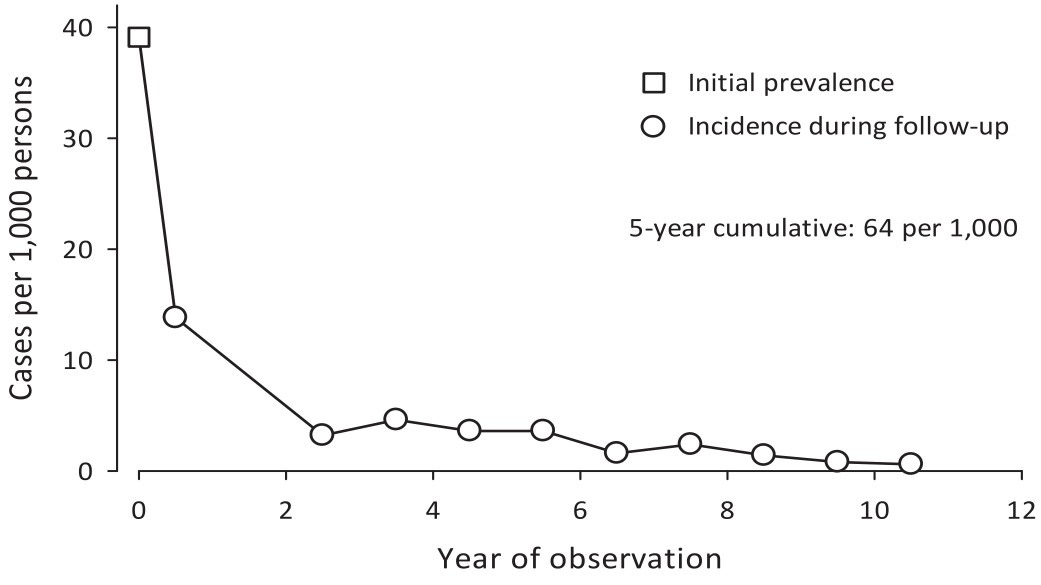

Fig. 6: Tuberculosis prevalence among contacts of recently identified index cases and incidence of tuberculosis in the same cohort of contacts during follow-up in a controlled clinical trial of preventive therapy in the placebo group.[23,24]

women infected with *M. tuberculosis* have a higher risk of progression to tuberculosis than their age-peer males.[25-27] This is thus in the opposite direction than infection prevalence. The excess female-to-male risk ratio lessens with increasing age and gradually reverts to the disadvantage of males.[28] It is therefore not unexpected that the crude incidence of tuberculosis was higher among women than men when tuberculosis was highly incident and occurred predominantly among young adults.[21]

In 1930, Andvord[29] proposed that a cross-sectional view of tuberculosis mortality failed to tell the whole story and more insight could be gained by looking at events within birth cohorts.[30] Cross-sectional, age-specific data show an increase in the notification rate of incident cases with increasing age, increasingly pronounced over sequential birth cohorts (figure 7).[31] Males aged 70 to 74 years (average 72.5 years) in 1984 were born in 1922. In 1974, this cohort was 62.5 and in 1954 32.5 years old. Earlier birth cohorts can be followed to an even into younger age. The high rates observed cross-sectionally among the currently oldest are only a residual of even higher rates each birth cohort experienced when it was younger.[32] This perhaps baffling phenomenon is explained by the secular decline in the incidence of infection with *M tuberculosis*.It resulted in a gradual shift of the infection prevalence from the young to the elderly over time, accelerated in an aging population. Societies that have experienced a substantial decline in infection incidence over the past century see now tuberculosis case rates peak among population segments born at a time when the risk of becoming infected was large and who accumulated infection prevalence over a long life. Some of these elderly still harbour persisting live bacilli and it is these from whom cases of tuberculosis continue to emerge at a low rate, which might nevertheless be a substantial number at the population level. However, nothing changes the earlier presented fact that given infection, the risk is the highest among young adults and those with recent infection. Therefore, the currently oldest birth cohorts experienced substantially higher disease rates when they were younger. Their tuberculosis risk has actually decreased with aging, likely due to the progressive elimination of persisting *M tuberculosis* from the host with the passage of time. With the secular decline in the risk of getting infected, the risk of getting re-infected also declined.

Numerous risk factors that increase the risk of tuberculosis have been identified, but none has

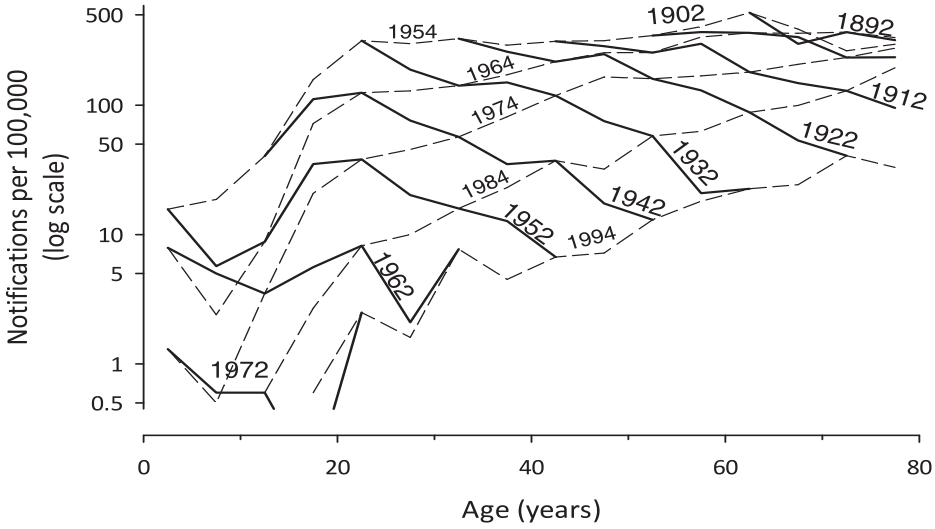

Fig. 7: Age-specific notification rates of incident tuberculosis cases, cross-sectionally in decades 1954 to 1994 (dashed lines). Same data shown by birth cohorts (solid lines) born from 1892 to 1972, Finland.[31]

had a larger impact thanHIV infection, devastatingly so in sub-Saharan Africa.[33,34] Only now are tuberculosis programmes starting to harness the power of proven intervention strategies to revert the epidemic.[35]

Other risk factors have been recognized for a long time. Changing life styles permit them now to increasingly make their imprint, such as diabetes in India.[36,37]

Death from tuberculosis

In the pre-chemotherapy era, sputum smear-positive pulmonary tuberculosis had a cumulative case fatality of 70% (figure 8).[38-41]

Mortality figures are available for a much longer time than morbidity data, allowing insight into the deep past, at least in the industrialized world. Three time factors are of interest in epidemiologic analysis: the age at diagnosis, the birth year, and the event year.[42] The first two factors, age and birth cohort effect, have been introduced. The period effect could be an event like war or the smoking epidemic affecting all or a large proportion of members of a society, irrespective of their age or when they were born. If the lines of the age cohorts are drawn with a logarithmic scale on the ordinate, a deviation from parallelism between sequential lines points to the presence of a period effect as illustrated in figures 9a and 9b.[43] The vertical arrow among males aged 45 years between the 1906 and 1916

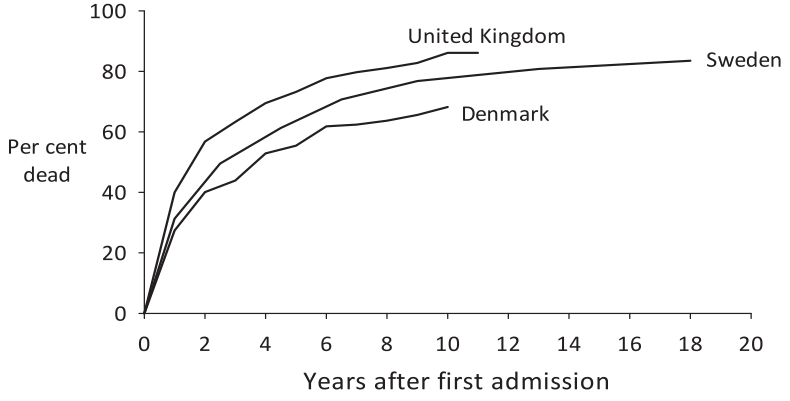

Fig. 8: Cumulative case fatality from sputum smear-positive pulmonary tuberculosis in three selected studies from Sweden,[38] the United Kingdom,[39] and Denmark.[40]

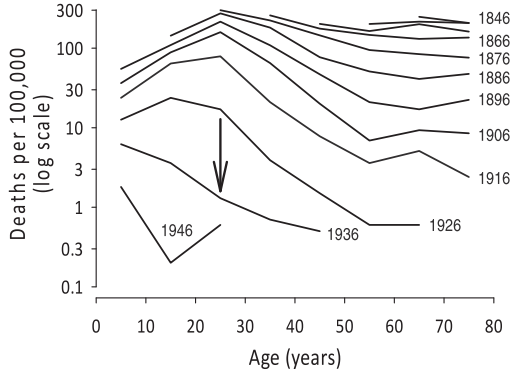

Fig. 9a: Tuberculosis mortality from respiratory tuberculosis in birth cohorts, semi-logarithmic scale, among females,

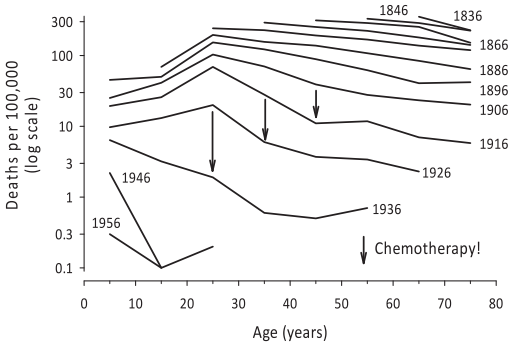

Fig. 9b: Tuberculosis mortality from respiratory tuberculosis in birth cohorts, semi-logarithmic scale, among males,

birth cohort points to such a departure from the previously observed parallelism. Born in 1916 and 45 years old locates the calendar time at 1961. Effective triple chemotherapy came about in the late fifties.[44] By the early sixties this regimen had likely become both affordable and an accepted standard in Switzerland. The powerful effect of chemotherapy on fatality is most impressive among the 20- to 29-year-old who had been at highest risk of death. In the 1936 birth cohort the earlier observed mortality peak was simply shaved off. While impressive among men, it is even more so among females who had fared a disproportionately high mortality at that age. The 1876 cohort had a mortality of 300 per 100,000 women among the 20-to 29-year-old. In the cohort born 70 years later, mortality in that age group had dropped more than 100-fold. Chemotherapy had commuted a death sentence.

Final remarks

Concepts largely using historical data collected by our forefathers have been presented here. We best honour them by upholding principles of quality surveillance. Our colleagues at the World Health Organization diligently compile data provided by numerous dedicated health care workers around the world. Desirable as it is to arrive at sensible conclusions from often imperfect data [45] it remains a challenging task. Best estimates are that in 2012, 8.6 million people developed tuberculosis and 1.3 million died of it.[46] These are sobering figures and there is a long way ahead to conquer tuberculosis. It is hoped that this framework contributes to a basis for a better understanding of what the past teaches us about the present and the future and how to rationally continue our fight against tuberculosis.

Afterword: A series of flash files with spoken and written narrative on the dynamics of the tuberculosis epidemic is available to watch or download from http://www.tbrieder.org.

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UPDATE ON REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAMME*

R. S. Gupta**

1. Introduction:

a. The Revised National TB Control Programme (RNTCP), based on the internationally recommended Directly Observed Treatment Short-course (DOTS) strategy, was launched in 1997 expanded across the country in a phased manner with support from World Bank and other development partners.

b. Full nation-wide coverage was achieved, then covering over a billion population (1114 million) in March 2006, expanding to 1247 million people in first quarter of 2013. In terms of treatment of patients, RNTCP has been recognized as the largest and the fastest expanding TB control programme in the world. RNTCP is presently being implemented throughout the country.

2. Estimated TB Burden in India

- Incidence: 2.2 million new TB cases annually – 176 cases per 100,000 population
- Prevalence: 2.8 million cases - 230 cases per 100,000 population
- Deaths: About 270,000 deaths each year - 22 deaths per 100,000 population
- Approximately 5% of TB patients estimated to be HIV +ve
- DR-TB (Drug resistant-TB)
    - 2.2% in New cases and
    - 15% in previously treated cases

India is the highest TB burden country in the world, accounting for about 23.3% of the global prevalence and in 2012. Out of the estimated global annual incidence of 8.6 million TB cases, 2 - 2.4 million were estimated to have occurred in India, with the best case estimate of 2.2 Million cases. India has contributed to approximately 25.5% of the total global new cases detection during the year 2012 as per the WHO Global Report 2013.

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* This is an update on Revised National TB Control Programme in India. In subsequent issues, we will be publishing quarterly data/record of the activities of the programme carried out by Central TB Division.

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3. Goal of the programme:

The goal of TB control Programme is to decrease mortality and morbidity due to TB and cut transmission of infection until TB ceases to be a major public health problem in India.

4. Objectives of the programme:

- To reduce the incidence of and mortality due to TB
- To prevent further emergence of drug resistance and effectively manage drug-resistant TB cases
- To improve outcomes among HIV-infected TB patients
- To involve private sector on a scale commensurate with their dominant presence in health care services
- To further decentralize and align basic RNTCP management units with NRHM block level units within general health system for effective supervision and monitoring

5. RNTCP Achievements:

a. In 2005, 1.29 million, in 2006, 1.39 million; in 2007, 1.48 million patients; in 2008, 1.51 million; in 2009, 1.53 million TB patients; in 2010, 1.52 million TB patients, in 2011 1.51 million, and in 2012, 1.46 million TB patients have been registered for treatment. Till the end of 2nd quarter 2013, 7,25,332 patients have been registered.

b. Treatment success rates have tripled from 25% in pre-RNTCP era to 88% presently (2012) and TB death rates have been reduced from 29% to 4% during the same period.

c. Since 2007, RNTCP has also achieved the NSP case detection rate of more than 70% in line with the global targets for TB control while maintaining the treatment success rate of >85%. In 2010, the NSP Case detection rate was 72% and treatment success rate 87%. In 2011, the NSP case detection rate was 71% and treatment success rate 88%. In 2012, the NSP case detection rate was 68.4% and treatment success rate 88%.

d. Quality-assured diagnostic facilities are available through more than 13,209 Designated Microscopy Centres (DMCs) across the country.

e. To ensure quality of sputum microscopy, external quality assurance is being routinely conducted throughout the country as per a standardized protocol based on international guidelines with all components for ensuring quality – on site evaluation, panel testing and blinded cross-checking.

f. All states are implementing the 'Supervision and Monitoring strategy' – detailing guidelines, tools and indicators for monitoring the performance from the PHI level to the national level.

g. The programme is focusing on the reduction in the default rates amongst all new and re-treatment cases and is undertaking steps for the same.

h. To improve access to tribal and other marginalized groups, the programme has developed a tribal action plan which is being implemented with the provision of additional TB Units and DMCs in tribal/difficult areas, additional staff, compensation for transportation of patient & attendant and higher rate of salary to contractual staff.

i. The programme has introduced pediatric patient-wise boxes, in 2006, with formulations and doses specifically designed for convenient usage in children.

j. 2708 NGOs collaborations and 13,311 private practitioners are involved in the programme in different signed schemes under NGO/PP schemes. 319 medical colleges (including private ones) have been involved in RNTCP by the end of Quarter 2 of 2013.

k. Health facilities in government sectors outside Health Ministry have been involved, *viz*. ESI, Railways, Ports and the Ministries of Mines, Steel, Coal, etc.

l. Intensified Public Private Mix project is being undertaken with Indian Medical Association (IMA) in 16 states and with Catholic Bishop Conference of India (CBCI), a faith-based organization (FBO), in 19 States under the Global Fund supported Single Stream Funding Project.

m. Under the Global Fund Round 9 project civil society organizations are undertaking activities in 374 districts across 23 states to enhance the visibility and reach of the programme and engage with communities and community-based care providers to improve TB care and control.

6. <u>TB HIV Coordination</u>:

a. The TB-HIV collaborative activities which were being undertaken in 14 states in 2006 were scaled up to all the states in 2007.

b. NACP (National AIDS Control Programme) & RNTCP have developed "National framework of Joint TB/HIV Collaborative activities" in 2007 and revised it in 2009. The framework articulates the policy of TB/HIV collaborative activities in the country.

c. The 2009 revision establishes uniform activities at ART (Anti-retroviral treatment) centres and ICTCs (Integrated Counselling and Testing Centres) nationwide for intensified TB case finding and reporting, and set the ground for better monitoring and evaluation jointly by the two programmes. The Intensified TB-HIV package was scaled up in the entire country in June 2012.

d. In 2012, out of total registered cases, HIV status of 8,21,807 (56%) TB patients was known. Of them, about 44,063 were HIV positive. 92 % of these patients were put on CPT while 74% of them received ART.

e. In 2013, out of total registered cases (7,25,332) in first two quarters, HIV status of 4,57,572 TB patients was known. Of them, about 22,355 were HIV positive.

7. <u>Impact of the programme</u>:

Prevalence of all forms of TB has been brought down from 465/ lakh population (1990) to 230/ lakh population in 2012 and TB mortality in the country has reduced from over 38/lakh population in 1990 to 22/lakh population in 2012 as per the WHO global report 2013.

8. PMDT services:

The PMDT services have been initiated in all 35 States/UTs of India with in some districts. All the districts in the country have achieved complete geographical coverage by March 2013 and we are now moving towards universal access to quality diagnosis and treatment of MDR TB patients by gradually extending the opportunity to diagnose early during the treatment of TB. Till June 2013, 31,350 MDR-TB patients and 284 XDR TB patients were reported to be initiated on treatment.

9. Use of Newer Rapid Diagnostics under RNTCP

a. Other newer rapid diagnostic tests, such as Automated Nucleic acid amplification test (NAAT) are also under consideration. The programme has undertaken a feasibility studies for implementation NAAT under the Programme setting in terms of Infrastructure, HR requirements and skills & EQA procedures involved.

b. These technologies will reduce the turnaround time (TAT) from four-six weeks in case of solid culture to two-three weeks in liquid culture, eight hours in LPA and as less as 2 hours in automated NAAT for diagnosing TB and resistance to Rifampicin. This is vital for increasing the laboratory capacity to meet vision of programme to provide MDR-TB laboratory services to all sputum smear positive retreatment cases.

10. Advocacy, Communication and Social Mobilization (ACSM)

ACSM is a priority activity in the programme. The ACSM activities are inbuilt into the programme and are implemented intensively from the National level to the most peripheral level, the community. RNTCP has a well-conceived ACSM strategy in place. There is a dedicated IEC Resource Centre in the programme website with relevant communication material in various languages for local use. RNTCP has established its own branding of DOTS with a logo which has been widely recognized. Further provision of dedicated human resources at State and district levels for ACSM activities has been made in the programme. In addition, a large number of partners are also associated with the Programme for implementation of ACSM activities.

11. Ban on Commercial serology tests for TB diagnosis

The Gazette of India, Ministry of Health and Family Welfare (Department of Health and Family Welfare) has notified G.S.R. 432 (E) for prohibiting the import of the commercial sero-diagnostic test kits for tuberculosis and G.S.R. 433 (E) for prohibiting the manufacture, sale, distribution and use of the sero-diagnostic test kits for tuberculosis on 7th June 2012. The serological tests are based on antibody response, which is highly variable in TB and may reflect remote infection rather than active disease. The WHO experts Group and STAG-TB which reviewed the data and concluded that currently available commercial serological tests provide inconsistent and imprecise estimates of sensitivity and specificity and strongly recommended that these tests should not be used for the diagnosis of pulmonary and extra-pulmonary TB.

12. TB Notification:

TB continues to be a major public health problem accounting for substantial morbidity and mortality in the country. Early diagnosis and complete treatment of TB is the corner-stone of TB prevention and control strategy. Inappropriate diagnosis and irregular/incomplete treatment with anti-TB drugs may contribute to complications, disease spread and emergence of Drug Resistant TB. In order to ensure proper TB diagnosis and case management, reduce TB transmission and address the problems of emergence and spread of Drug Resistant-TB, it is essential to have complete information of all TB cases. Towards the same, a Government Order No Z-28015/2/2012-TB dated 7th May 2012 has been issued by the Government of India mandating all the healthcare providers to notify every TB case diagnosed and/

or treated to local authorities i.e. District Health Officer/Chief Medical Officer of a district and Municipal health Officer of a Municipal Corporation/Municipality or to the Nodal Public Health Authority (for this purpose) or officials designated by the States/UTs for this purpose every month in a given format. For the purpose of this notification, healthcare providers will include clinical establishments run or managed by the Government (including local authorities), private or NGO sectors and/or individual practitioners.

13. Case-based web-based Reporting System: Nikshay

The database of Revised National Tuberculosis Control Programme (RNTCP) was conventionally on Epi-info-based software for reporting with electronic data transmission from district level upwards. The digitization of information being an ongoing process, the generation of data in aggregated form and report submission is currently being done on quarterly basis. This causes a delay of more than three months and loss of case-based data.

To address this gap, Central TB Division in collaboration with National Informatics Centre developed a case-based web-based platform - 'Nikshay', which has been now scaled up nationally.

Since implementation in last one year, till recently (October 2013) over 1.9 million patients including MDR cases have been registered in Nikshay. 56,000 private health facilities have been registered and more than 34,000 TB patients notified by these private health facilities have been registered in Nikshay. Details of more than 5,800 contractual staff have also been entered in Nikshay.

Further developments on the platform are ongoing, and it is hoped that soon, the programme will be able to generate a real time, aggregated case-based information and latest data trends without significant information losses.

14. Twelfth Five Year Plan – Key Activities Proposed

In addition to the continuation of existing activities as per 11th Five Year Plan the following key activities are proposed during the 12th Five Year Plan for achieving the objectives of RNTCP including universal access:

- Ensuring early and improved diagnosis of all TB patients, through improving outreach, vigorously expanding case-finding efforts among vulnerable populations, deploying better diagnostics, and by extending services to patients diagnosed and treated in the private sector.

- Improving patient-friendly access to high-quality treatment for all diagnosed cases of TB, including scaling-up treatment for MDR-TB nationwide.

- Re-engineering programme systems for optimal alignment with NRHM at block level and human resource development for all health staff.

- Enhancing supervision, monitoring, surveillance, and programme operations for continuous quality improvement and accountability for each TB case, with programme-based research for development and incorporation of innovations into effective programme practice.

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Original Article

PERCEPTION OF STIGMA TOWARDS TB AMONG PATIENTS ON DOTS & PATIENTS ATTENDING GENERAL OPD IN DELHI*

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Summary

Background: In India, Tuberculosis (TB) continues to be a public health problem. One of the key reasons for it is the stigma associated with the disease which affects the treatment seeking behaviour and hence the outcome.

Objectives: To assess the perceived and enacted stigma among TB patients and perceptions of other patients related to TB in Central Delhi.

Methods: A cross-sectional study conducted in urban field practice area of a medical college of Delhi, using a pre-designed questionnaire containing items for assessment of stigma being faced by a TB patient in family, social life and workplace. It also contained questions pertaining to reaction of patients from general OPD to a family member who develops TB.

Results: A total of 100 patients on DOTS and 200 patients from general OPD were interviewed. There were 21 patients who reported to have delayed treatment seeking due to stigma. Nearly one third patients (n=34; 34%) noted negative changes in the behaviour of their family members towards them while 40% were isolated on being diagnosed with the disease. Out of the 36 employed TB patients, 65.5% (n=23) experienced negative change in the behaviour of their colleagues. In general OPD patients, significantly higher proportion of female patients said that they would not disclose the disease status of a family member suffering from TB to their neighbours ($p<0.001$).

Conclusions: Perception of stigmatizing effect of Tuberculosis was high both amongst TB and other patients. Behaviour Change Communication (BCC) strategies are needed to address the effects of stigma like delayed treatment seeking. **[*Indian J Tuberc 2014; 61:* 35-42]**

Key words: Social Stigma, Tuberculosis, Workplace, Behaviour change communication

INTRODUCTION

Tuberculosis (TB) continues to be a major cause of disability and death globally.[1] TB is not only recognized as an individual health problem but also psychological, social suffering wherein the basic rights of a patient may also be negated.[2] Furthermore, once identified, sufferers experience considerable stigma on account of their disease, leading to delay in diagnosis and treatment and causing a major impact on TB control.[3]

Stigma may be defined as an undesirable or discrediting attribute that an individual possesses, thus reducing that individual's status in the eyes of the society.[4] It is a process already worsening the existing inequalities and exclusions.[5] TB is already a highly stigmatized disease.[6] It is known that stigma in TB is perpetrated and reinforced by health staff, family, neighbours, and other groups.[7]

Beliefs due to misinformation have led people with TB to be physically isolated and terminated from work.[8] The study by Gemeda Abebe *et al*, reported that a large proportion of the TB suspects (51.3%) perceived that other people would think less of them if they knew they had TB, 30.3% thought that other people would avoid them if they had TB and 15.1% wanted to keep a possible diagnosis of TB concealed from a confidant.[9] For women, the results have been particularly severe: divorce, desertion, and separation from their children.[8] Stigma related to TB is very rampant in India. In a multi-country study by Somma *et al* in 2008, the overall stigma index was found to be the highest for India.[10] Another clinic-based study from Chennai reported that TB patients aged < 45 years felt

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* This study was presented at the Indian Public Health Association National Conference held at Belguam (Karnataka) from 28th to 30th January, 2011 and Zonal task Force Workshop on the involvement of Medical Colleges in RNTCP held on 14th and 15th September, 2011 at Maulana Azad Medical College, New Delhi.

inhibited discussing their treatment with their relatives and friends.[11] Thus it is evident that stigma related to TB, needs further exploration as without knowledge regarding the perception of stigma associated with TB among DOTS patients, it is difficult to formulate strategies for reducing it.

It has been suggested that non-sufferers of the disease provide a better idea of the social contacts and stigma that patients must live with.[12] Therefore, the present study was undertaken to characterize TB stigma (both perceived and enacted) among TB patients and assess the people's perception towards the TB patients if they would encounter in life in Delhi. The information gathered by such an endeavour would help in designing and targeting interventions that specifically address the impact of TB stigma on a given group and geographic region.[13,14] This is pertinent in TB control, as stigma influences illness health seeking behaviour.

MATERIAL AND METHODS

Setting and sampling: This was a cross-sectional study conducted at DOTS Centre attached to Chest Clinic in a teaching Hospital and general Out Patient Department (OPD) of Urban Health Centre (UHC) in Central Delhi from October to December 2011. There were 206 patients on treatment under DOTS for TB at the Chest Clinic during the study period while 2000 patients visited the OPD of UHC. The sample size was calculated based on the magnitude of perceived stigma (51.3%) as found in a previous study[9] with 95% confidence interval and allowable error of 15%. The sample thus calculated was 167. But, overall 300 patients were studied. First 100 patients more than 15 years of age visiting the DOTS for treatment and 200 patients from general OPD and consenting to participate were included in the study. Patients less than 15 years or not in state to participate (e.g. under the influence of alcohol, mentally ill etc.) were excluded from the study.

Study Tool: Data from patients on DOTS was collected through a pre-tested pre-designed semi-structured patient interview schedule based on Explanatory Model Interview catalogue (EMIC).[15] The EMIC is framework for flexible interviews and an instrument for studying illness related experience.[16] The Cronbach's alpha of the schedule was 0.75. The schedule included items for identification of the patients and socio-demographic variables, various questions pertaining to the response of their family and friends on being diagnosed with the disease, their experience at work and changes in their social relations after contracting the disease. The schedule for general OPD patients included knowledge about tuberculosis and whether they would like to socialize with the patients of tuberculosis or their response in case their relative develops TB.

Key definitions: Perceived stigma[17]: a fear of the patient about other's behaviour to him and a sense of inferiority due to development of tuberculosis.
Enacted stigma[17]: due to actual discrimination or being actually avoided by the people since the patient has now tuberculosis.

Acceptable treatment delay[18]: 2 days

Statistical Analysis: The collected data was fed and analysed in SPSS 16.0 and EPI INFO 2005 software of World Health Organization. Descriptive statistics including mean, standard deviation and range for quantitative data and proportions for qualitative variables were used to characterize the study population. For quantitative data, difference between the means of the two groups was compared by t-test. The difference between two groups was taken significant only when error was less than 5%.

Ethical Considerations: The study subjects were explained the purpose of study and assured privacy and confidentiality of the information provided by them and their written informed consent was taken before taking detailed information. The approval was taken from Institutional Ethical Committee of the research institution.

RESULTS

Socio-Demographic characteristics of the study population: A total of 300 patients consented to participate. The socio-demographic profile of general OPD patients was comparable to TB patients except that the former group was older ($p<0.001$) and

had more number of participants who were married (p=0.007). (Table 1)

Perceived Stigma among TB patients: A total of 21 patients (21%) reported delay in seeking treatment for the disease due to stigma. 'Being afraid of social stigma' was reported as the third common cause (3%), with 'lack of awareness about free treatment' (16%) and 'lack of time' (10%), being the first two reasons. While more than half of the patients felt 'inferior' (n=52; 52%), and 'stressed' (n=51; 51%), nearly one third (n=31; 31%), reported to have felt 'ashamed' of themselves after being diagnosed with the disease. One fifth of the respondents (n=19; 19%) also felt that people may feel inferior of their family (Fig. 1)

Enacted stigma was assessed by analysis of items pertaining to stigma actually being faced at family, society and workplace level.

Stigma faced in family life by TB patients: There were only five patients who reported hesitation in disclosing their disease status to their family members. While, there were only 23% patients who disclosed that their family

Table 1: Socio-demographic features of TB patients and general population

S.No	Socio demographic variables	TB Patients (n=100)	General OPD patients (n=200)	p value
1.	Age in years (mean±s.d.)	30.51±11.3	39.77±14.9	<0.001**
2.	Sex Male Female	 50 (50) 50 (50)	 109 (54.5) 91 (45.5)	 0.461
3.	Education Illiterate Primary Higher sec. Graduate-Above	 26 (26) 20 (20) 44 (44) 10 (10)	 63 (31.5) 40 (20) 84 (42) 13 (6.5)	 0.613
4.	Occupation Clerk, shop -owner Skilled worker Semi-skilled Unskilled Unemployed	 6 (6) 6 (6) 14 (14) 10 (10) 64 (64)	 5 (2.5) 7 (3.5) 32 (16) 24 (12) 132 (66)	 0.139
5.	Marital status Married Unmarried	 72 (72) 28 (28)	 170 (85) 30 (15)	 0.007*
6.	Income [Employed percentage (Range)]	45 (45) (Rs. 1000-21000)	68 (34) (Rs. 1000-35000)	0.063

*P<0.05 , **P<0.001 - significant level.
(Note: p value for education & occupation has been calculated as literate *vs* illiterate & Employed *vs* unemployed)

Note: Illiterates are those without the ability of reading and writing with understanding in any language[27]. Unemployment refers to the share of the labour force that is without work but available for and seeking employment[28]. Those who were unemployed at the time of study and for a minimum of past one year were considered.

members could not accept at first their diseased status, 'Isolation' (40%) and 'Change in behaviour of the family' (34%) were perceived by higher proportion of TB patients. (Fig. 2).

Type of isolation of the TB patients by the family: Among TB patients, 40% (n=40) experienced isolation by their family. Regarding the various ways of isolation by the family members, all were given separate utensils (n=40; 100%). Out of the total 40 patients who faced isolation, 30 (75%) reported to have been given separate room and 28 (70%) were asked to wash their clothes separately. Nearly one third patients reported being neglected by the family (n=12; 30%)

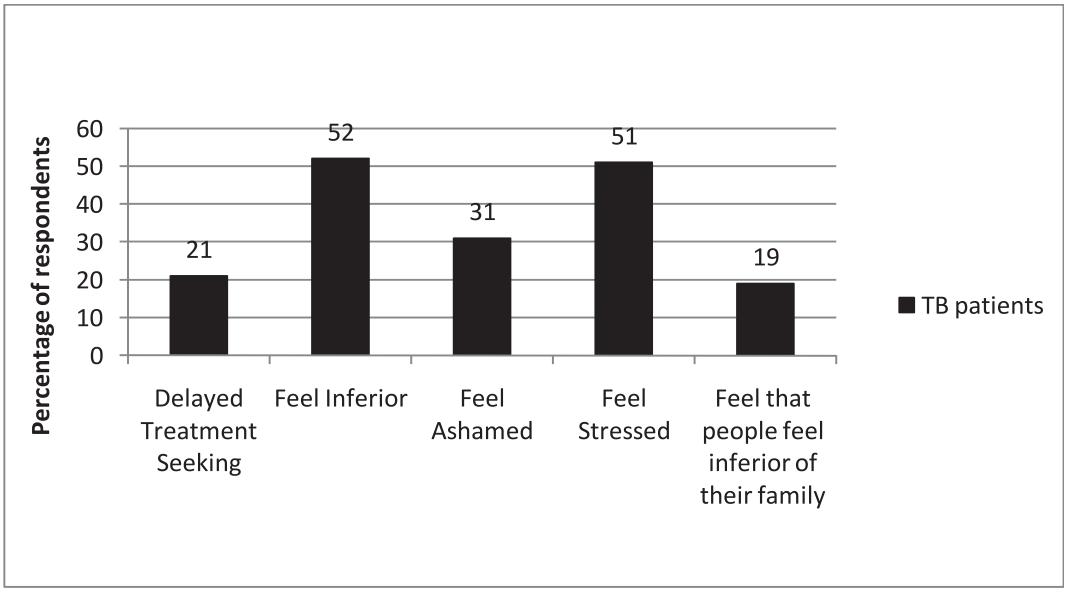

Fig. 1: Percieved Stigma of TB patients

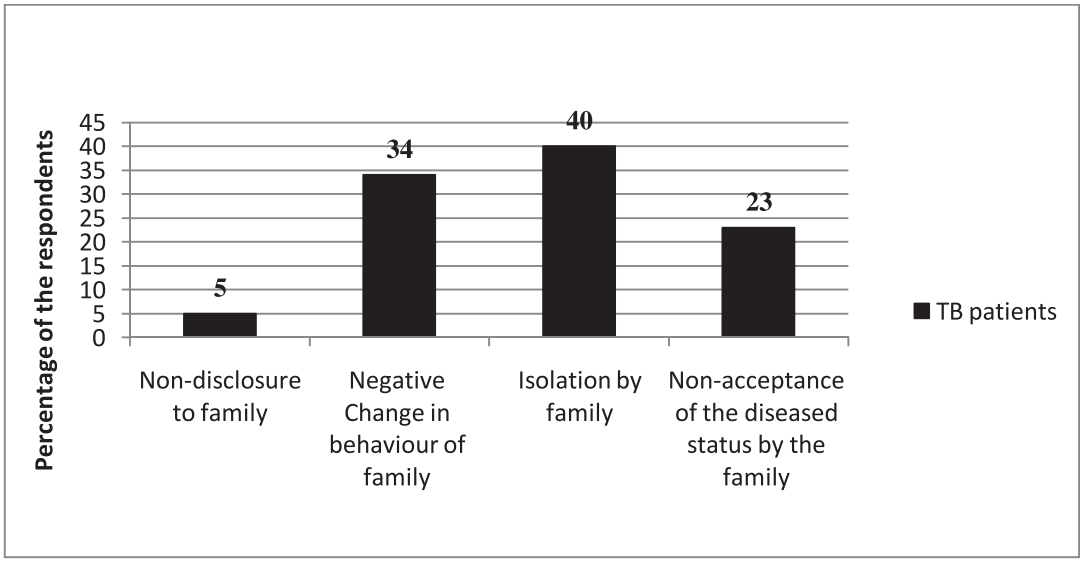

Fig. 2: Stigma faced in family life by TB patients

while 15% (n=6/40) said that they were not permitted to attend family functions.

Stigma faced in social life by TB patients: Non-disclosure of the disease status to friends and colleagues was reported by 41% of the TB patients and this was more among female patients (n=24; 48%). Significantly higher proportion of male patients reported change in the behaviour of the neighbours when they came to know their disease status. They also felt that they were being avoided by people ($p<0.001$) and they were not invited for social functions as before ($p<0.01$). (Table 2)

Stigma at the level of workplace by TB patients: Out of the total 100 patients, there were 36 who were employed and all were men. More than half of them experienced negative change in the behaviour of their colleagues and employer (n=23; 65.5%). Only a few were allowed to continue their job (n=13; 34.5%) or attend DOTS centre (n=8; 24%). Nearly 79.3% (n=28) men were isolated in their workplace. Isolation was in the form of giving separate cabin, avoidance in meetings and abandonment by colleagues.

Knowledge of general OPD patients about TB: Out of the 200 respondents, 61% (n=122) knew that TB is an airborne infection. There were 91% (n=182) patients who believed that TB is curable.

Perception of general OPD patients towards TB patients in family and community: Items on perception of stigma by other patients (not having TB) revealed that 18% (n=36) could not accept the fact that their family members could suffer from TB. Nearly one third of the participants said that they would isolate the patient in their family if he/she was suffering from TB. However, significant gender-wise difference was noted in disclosure of disease status to neighbours with 63.6% (n=70) males reporting that they would disclose the disease status of their patients to them. Nearly one fourth participants (27%) revealed

Table 2: Stigma encountered by patients in social life by area and sex

S.No	Reactions at community level	Male (N =50), n (%)	Female (N =50), n (%)	Total N=100 (%), p value
1.	Non-disclosure of disease status to friends	17 (34)	24 (48)	41 (41) 0.154
2.	Reaction of neighbours on disclosure Change No change	 36 (72) 14 (28)	 16 (32) 34 (68)	 52 (52) 48 (48) 0.000**
3.	People's reaction on meeting you Avoid Speak normally	 30 (60) 20 (40)	 14 (28) 36 (72)	 44 (44) 56 (56) 0.004*
4.	Not invited for social functions as before	25 (50)	11 (22)	36 (36) 0.004*
5.	Not going out to social functions as before	25 (50)	11 (22)	36 (36) 0.004*

*P<0.005, **P<0.001- significant level.

Table 3: Reaction of general OPD patients towards TB patients in the family and community

S.No.	Reaction towards TB patients	Male (N=110) n (%)	Female (N=90) n (%)	Total N=200 (%), p value
1.	**In family**			
a.	Supportive	89 (80.9)	75 (83.3)	164 (82)
b.	Shocked	21 (19.1)	15 (16.7)	36 (18)
				0.288
c.	Isolate them	36 (32.7)	30 (33.3)	66 (33)
				0.454
d.	Disclose to neighbours about TB patients in family	70 (63.6)	40 (44.4)	110 (55)
				0.000**
2.	**In community**			
a.	Speak normal	81 (73.6)	65 (72.2)	146 (73)
b.	Avoid	29 (26.4)	25 (27.8)	54 (27)
				0.823
c.	Afraid of socializing	45 (40.9)	37 (41.1)	82 (41)
				0.250

Note: Shocked- Non-acceptance of the facts or reality. Supportive- Furnishing support or assistance of any kind- physical, mental, emotional, economic, etc. Isolation- Enforced isolation of patients suffering from a contagious disease in order to prevent the spread of diseases.

that they would avoid TB patients in the community in which they live. However, 41% were afraid of socializing with such patients. (Table 3)

DISCUSSION

The present study revealed that perception about stigmatizing effect of tuberculosis was high both among the patients on DOTS and general OPD patients. Stigma is a social determinant of health. When diseases are stigmatized, the fear of the social and economic consequences following diagnosis can make individuals reluctant to seek and complete medical care. The current study showed that nearly one-fifth of the patients had sought the treatment late. The health seeking behaviour of the patients in our study was probably better than study done by Abebe *et al*[9] in which 46.2% (n=220) of the study participants did not seek help for their illness at all. This could be due to the successful functioning of the IEC component of Revised National Tuberculosis Control Programme (RNTCP) in Delhi.

There was evidence of both perceived stigma and enacted stigma in context of personal, family, marital and workplace interactions. About 52% patients on DOTS reported negative change in the behavior upon disclosure of the disease status. A study by Jaggarajama *et al*[16] reported 10-25% of the patients experiencing the same. High finding in our study suggests that there is scope to motivate patient's family to provide family support and involvement of community DOTS providers in order to reduce negative reactions. Interestingly, more than half of the male patients reported a negative change in the behaviour of the family members. More number of male patients reported isolation by the family. The possible explanation for this could be the fact that higher number of males in the study disclosed their disease status to their families and friends. Further, females generally have small circles of socialisation, and their awareness about the disease prevention, treatment and cure is also very minimal. This leads to more stigmatising effect over the affected males. Apart from the social constraints,

economic constraints due to loss of income further contribute to higher stigmatising effect over the male population.

TB patients experience psychological and social sufferings. The present study supports this further as 52% patients 'feel inferior'; 31% reported that they 'feel ashamed'; and 51% 'feel stressed'.

In India, it is a customary belief that the food/utensil gets contaminated on being used by a person who eats from it, if he or she belongs to a lower socio-economic class or is having some disease. TB patients are often subjected to such unnecessary sanctions at home. Fears about getting infected with TB, often lead to isolating experiences such as forcing a TB patient to use a separate utensil. In the current study too, all the 40 patients who reported that they were isolated by their family members, had been given separate utensils. Other forms of isolation included washing clothes separately, giving separate room, neglect by the families and not being permitted to attend the social functions with more male patients reporting this.

Higher number of TB patients also reported stigma in their social life. The findings are in line with a CDC study where the majority of respondents felt that having TB would change the way others treat a person.[19] The presence of stigma could be attributed to traditional beliefs about TB which still exist, mainly among older people, but also resorted to by other people once ill. These traditional beliefs may contribute to long delays in TB diagnosis and increased social stigma and isolation of patients and their families due to erroneous beliefs in transmission routes.[20] Social stigma might persist despite effective treatment.

Research from high-burden areas has shown that TB patients face various levels of isolation and rejection including fear of or actual job loss.[10,21] In the present study, more than 50% male patients reported to have encountered isolation and stigma at work place. The findings are in contrast to that found in a study by Dhingra *et al* in 2010.[22] The possible reasons for such contrast findings cannot be ascertained in the present context and hence need to be explored further. We need to study a larger sample to have some conclusive evidence with respect to workplace interactions of TB patients.

Assessment of reaction towards a TB patient in family revealed that, only 36 general OPD patients said that they would 'not accept the diseased status of their patient' as against majority displaying supportive behaviour ($p < 0.001$) while 33% (n=66) replied that they would isolate the TB patient in their family ($p=0.016$). This finding is in contrast to a study by Deribew *et al* in 2010[23] in Ethiopia on 750 randomly selected adults, in which 56% reported high prejudice towards a TB patient. Studies in China[24] and Thailand[25] also reported higher prejudice by general population towards a TB patient. The possible reason for this could be the fact that the population of our study was more knowledgeable with respect to TB as compared to studies elsewhere.

A large number of the female respondents in general OPD (n=50; 55.6%) revealed that they would not disclose the information about TB patients in their families to the neighbour, as compared to 36.4% males (n=40) ($p < 0.001$). This finding is consistent with studies elsewhere.[10,21,25,26]. Feeling of insecurity, lack of support at family, less autonomy and power could explain the reason for this finding.

CONCLUSIONS

Thus, to conclude, the study contributed considerably in understanding the many ways in which stigmatizing behaviour manifests in relation to Tuberculosis. Though RNTCP focuses on reducing incidence of Tuberculosis by increasing case detection and cure rate, lack of understanding of the community perspectives towards TB may be the possible reason for TB remaining as a major public health problem. TB is rightly called "a social malady with a medical facet". Thus, to effectively manage the disease, we need to address the misconceptions. Behaviour Change Communication strategies need to be formulated with a focus to change the community's knowledge and attitude about the cause, transmission and treatment of TB by also highlighting the counterproductive effects of stigma like delayed diagnosis which would lead to spread.

Limitations of the study

The study was undertaken to examine the site specific social and gender-related factors at designated TB treatment sites and General OPDs. However, it may not represent the profile of patients or general population of the entire country. Limitations notwithstanding, the study provides a deep insight into peril of stigma that is so much prevalent among the patients of one of the best developed cities with successful implementation of RNTCP, in the country.

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Original Article

HIV-INFECTED PATIENTS RETREATED FOR TUBERCULOSIS WITH INTERMITTENT CATEGORY II REGIMEN - TREATMENT OUTCOME AT 24-MONTH FOLLOW-UP

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Summary

***Background*:** The management of tuberculosis re-treatment in HIV-infected individuals is complex. The clinical and radiological manifestations in this group and response to Category II treatment is not well described.

***Methods*:** We performed a prospective cohort study of HIV-infected patients retreated for TB due to failure, relapse or default after treatment, at Tuberculosis Research Centre, Chennai, between February 2001 to September 2005. The Category II regimen followed in the TB programme in India (RNTCP) was administered (2 months of Streptomycin (S), Ethambutol (E), INH (H), Rifampicin (R), Pyrazinamide (Z)/1 month of EHRZ/5 months of HRE all given thrice weekly). Antiretroviral treatment was not routinely available at that time.

***Results*:** Of the 42 patients enrolled, 35 (83%) were males. The mean age was 33.2 (SD-6.3) years. Cough was the commonest (67%) presenting symptom and opacities were the commonest (48%) radiographic occurrence. 31 patients were culture-positive at baseline, drug susceptibility results showed that 21 (68%) were fully susceptible to all first line drugs, four patients (13%) had MDR TB and four had resistance to INH alone. Among the 31 culture-positive patients, 15 patients (48.4%) completed treatment and were declared cured, of whom two subsequently relapsed. All four MDR patients died. Six patients who received ART, survived.

***Conclusion*:** Only 50% of HIV-infected, ART-naive patients who were retreated for tuberculosis using an intermittent Category II regimen had a favourable response to treatment. Early detection of MDRTB and concurrent antiretroviral therapy could contribute to improved outcomes. **[*Indian J Tuberc 2014; 61:* 43-50]**

Key words: Re-treatment for TB, HIV infection, Intermittent regimen, Drug susceptibility, Treatment response

INTRODUCTION

In 2011, there were an estimated 8.7 million incident cases of TB (range, 8.3 million–9.0 million) globally, among which 1.0 million–1.2 million (12–14%) were among people living with HIV, with the best estimate of 1.1 million (13%).[1] In 2011, 6.2 million people with TB were notified to NTPs and reported to WHO. Of these, 5.8 million had a new episode of TB, among which 5.5 million had TB for the first time and 0.3 million were people who had a recurrent episode of TB after being previously cured of the disease. Among people who were diagnosed with TB for the first time (new cases), 2.6 million had sputum smear-positive pulmonary TB, 1.9 million had sputum smear-negative pulmonary TB, 0.2 million did not have a sputum smear done and 0.8 million had extrapulmonary TB.[1] Because of the fact that recurrences are much more common in HIV-infected than uninfected patients, it is likely that the contribution of patients who are HIV-infected could be disproportionately higher among retreatment cases. Retreatment group itself is a mixed group of patients consisting of relapse, treatment after default (TAD) and failure of treatment. In 2012, RNTCP notified 1,467,585 total cases, of which 629,589 were new sputum smear-positive cases, 317,616 were smear-negative cases, 234,029 were new extra-pulmonary cases and 284,212 were previously treated cases, of which 106463 were relapses, 16,400 failures, 64782 were TAD and 96,567 were retreatment others.[2] Among smear-positive re-treatment cases, the treatment success rate has been >68% since implementation Category II in RNTCP.[3]

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The treatment success rate has been relatively less favourable among re-treatment TAD cases and failure cases when compared to the treatment success rate among other smear positive TB cases.[3] The death rate has shown increase from 7% to 8%, failure rate about 6% and the death rates among failure cases has been consistently higher by about 1-2% when compared to the death rates among other types of re-treatment cases. High default rates >15% has been an area of concern among the re-treatment cases.[3] There is very little published information on the outcome of HIV-infected TB patients treated with a standard fully-intermittent re-treatment regimen (Category II). We report the long-term outcomes of a prospectively followed cohort of HIV-infected patients with a second episode of TB, who were treated with the standard regimen used in the Revised National TB Control Programme.

METHODS

This was a prospective cohort study under trial-like conditions. HIV-infected patients with symptoms and signs suggestive of TB, with previous history of anti-tuberculosis therapy >1 month, aged 15-years or above, not moribund and not pregnant were considered for enrolment. The study was done in National Institute for Research in Tuberculosis (NIRT), [formerly Tuberculosis Research Centre] clinics at Chennai and Madurai. The study period was from February 2001 to September 2005. Patients had a complete history and clinical examination performed. Baseline investigations included a chest X-ray (postero-anterior view), three sputum specimens (two overnight and one spot collection) for acid-fast bacilli (AFB) smear and mycobacterial culture. Sputum smears were stained with auramine–rhodamine and examined by fluorescence microscopy, processed by modified Petroff's method, and cultured on Lowenstein-Jensen medium. Positive cultures of *Mycobacterium tuberculosis* were graded as 1–20 colonies, 1+ (21–100 colonies), 2+ (>100 discrete colonies), or 3+ (>100 colonies forming a confluent mass). Species identification was done by high-performance liquid chromatography and drug susceptibility tested by the minimal inhibitory concentration method for isoniazid (H), rifampicin (R), and ethambutol (E) and by the resistance ratio method for streptomycin (S). Chest X-rays were read by a panel of three doctors and a consensus reading was determined. HIV testing was offered after pre-test counselling by a trained social worker and after obtaining written informed consent. National guidelines concerning HIV testing (positive on three different tests) and related issues with respect to informed consent and confidentiality issues were followed. Other blood investigations including CD4 cell count and viral load were also done. The diagnosis of pulmonary TB was based on clinical and/or, radiological and/or bacteriological criteria. The study was approved by the institutional ethics committee and written informed consent was obtained from each patient.

Treatment and follow up

All patients were treated with RNTCP Category II regimen consisting of intramuscular Injection of streptomycin (0.75gm), along with isoniazid (600mg), rifampicin (450/600 mg for body weight = or >60kg), pyrazinamide (1,500mg), and ethambutol (1,200mg) given orally for the first two months, followed by one month of these drugs without streptomycin (three months of intensive phase), following which patients received five months of isoniazid, rifampicin and ethambutol (same doses) in the continuation phase. Drugs were administered thrice-weekly throughout. Patients were reviewed clinically every month and three sputum specimens (two overnight and one spot) were collected for smear and culture during treatment and two sputa (one overnight and one spot) during follow up after treatment. Co-trimoxazole prophylaxis was given to all patients with CD4+ cell count less than 250 cells/mm^3. Patients were antiretroviral therapy naive at study entry and a few were started on ART during TB treatment and follow up.

Monitoring during treatment and follow up

All doses in the intensive phase (three months) were directly observed by study staff. During the continuation phase, patients attended the clinic once a week, when they took drugs under supervision. Two doses were then handed over for self-administration and patients were counselled and motivated to take them regularly. Treatment cards

were maintained by study nurses who signed when the patient took drugs under their supervision. If a patient complained of any symptoms, he/she was asked to see the study physician, who completed an adverse event form if indicated. Management, especially change of treatment as well as retreatment for TB, was decided by a panel of doctors, statisticians, and bacteriologists who reviewed the case history and results of all the relevant investigations. All patients were followed up for a period of 36 months from study entry. Patients who fulfilled the NACO (Stage III/IV disease or CD4 count <200 cells/mm^3) criteria at that period for starting ART were referred to government ART centres for evaluation and management (from April 2004 onwards when free ART became available). Of the 42 patients started on Category-II regimen, one patient developed Immune Restoration Inflammatory Syndrome(IRIS) in the form of tuberculous lymphadenitis, the lymph node size increased in size, and one patient developed hepato-biliary toxicity and warranted a change of treatment.

Outcome measures

A patient was considered to have had

1. A favourable response, if all the six cultures were negative during the last two months of treatment.

2. An unfavourable response, if one or more cultures were positive in the last two months of treatment, death, or a change of treatment for clinical/ radiographic deterioration occurred.

3. A recurrence of TB, if one or more cultures became positive or there was clinical/ radiographic deterioration during follow up among patients who had a favourable response at the end of treatment.

Statistical analysis

Data was entered and analysis was performed using SPSS version 14.0. Data was expressed as percentage, mean values with standard deviation, median values with Inter quartile Range, as appropriate. Comparison between two groups (Favourable and Unfavourable responders) was performed using Mann Whitney U test for medians, independent sample t test for means and Chi square test for proportions. Results were defined as statistically significant when the p value was <0.05.

RESULTS

Of the 42 patients enrolled, 35 (83%) were males and the mean age was 33.2 (SD 6.3) years. All had pulmonary TB while six patients had extra-pulmonary tuberculosis in addition. Cough was the commonest presenting symptom, in 67% of patients, followed by anorexia (55%), fever (52%), dyspnoea (50%), weight loss (50%), chest pain (41%) and haemoptysis (24%). Mean CD4 (for n=40) was 187 cells/mm^3 (SD 190) and median viral load (for n=24) was 184500 copies/ml, IQR (11225 to 963500).

Table 1 lists the radiographic abnormalities observed among these patients - parenchymal opacities were seen most commonly followed by cavitation, fibrosis and pneumothorax. Five patients

Table 1: Radiographic features and drug susceptibility pattern at baseline (n=42)

Radiographic features	**Number**	**%**
Opacities	20	**47.6**
Miliary TB	1	**2.4**
Cavities	9	**21.4**
Pneumothorax	4	**9.5**
Pleural effusion	3	**7.1**
Hilar LNs	4	**9.5**
Normal	5	**11.9**
Drug Susceptibility Test Results (n=31)		
Susceptible to all drugs	21	67.7
Resistant to isoniazid alone	4	12.9
Resistant to HR±S	4	12.9
Resistant to S alone	1	3.2
Resistance to R alone	1	3.2

* Some patients *(n=14)* had > 1 radiographic abnormality

had normal chest x-rays. Fourteen patients had multiple radiographic abnormalities.

Thirty three patients were smear positive, while 31 had cultures positive for *M. tuberculosis* at baseline. Drug susceptibility results showed that 21 (68%) were fully susceptible to all first line drugs. Four patients (13%) had MDR TB (two H+R resistance and two H+R+S resistance) while four had resistance to INH alone, one R alone and one S alone. Fifty eight per cent had culture negative at first month of treatment and 83% negative at 2nd month. Only six (14%) patients received anti retroviral therapy from the government ART centres and except for one (for whom ART was started before completion of three months of ATT), ART was started after completion of ATT in all others.

During treatment phase (Table 2 and Figure 1)

Analysis of outcomes was performed for all 42 patients and the 31 culture-positive patients separately. Among the 31 culture positive patients, 24 patients (77%) had culture conversion. At the end of treatment, among the 31 culture positive patients, 15 patients (48.4%) completed treatment and were declared cured (favourable). Among the remaining 16 cases, five patients had failure (one clinical and four bacteriological failure), and four were identified as MDR TB, all of whom died subsequently (three TB death and one non-TB death), six patients defaulted to treatment, one patient died during treatment (non-TB cause). Among those 24 patients, who had culture converted at two months, 13 completed treatment and declared cured.

Among the 11 culture negative patients, six patients completed treatment and among the remaining five patients, two had failure, one died during treatment (non TB), one had a change of ATT due to toxicity, one diagnosed atypical mycobacteria warranting change of treatment.

During follow up

Among the 15 patients who had a favourable response, two patients had a recurrence (one at 18th month and one at 42nd month) and the remaining 13

Table 2: Comparison of baseline characteristics among patients with a favourable and unfavourable response to treatment

Variable	Culture Positive Patients (n=31)		P value	Culture negative Patients (n=11)		P value
	Favourable response at end of ATT n=15	Unfavourable response (death, failure), n = 16		Favourable n = 6	Unfavourable n = 5	
Age	33.7 ± 7.3	33.5 ± 6.4	0.946	29.7 ± 4.5	35.2 ± 4.1	0.065
Sex	M-14, F-1	M-12, F-4	0.333	M-6, F-0	M-3, F-2	0.182
Baseline CD4 Count (median cells/mm³)	169 IQR 81 - 360	58 IQR 30-182	0.052	Median 90 (52 - 261)	Median 160 (116-235)	0.464
Baseline viral load (Copies/ml)	Median 28500 IQR 3220-257500	Median 602000 IQR 9650 -1240000	0.151	NA	NA	
Isoniazid resistance	3	1		-	-	
MDRTB/R res	-	4		-	-	

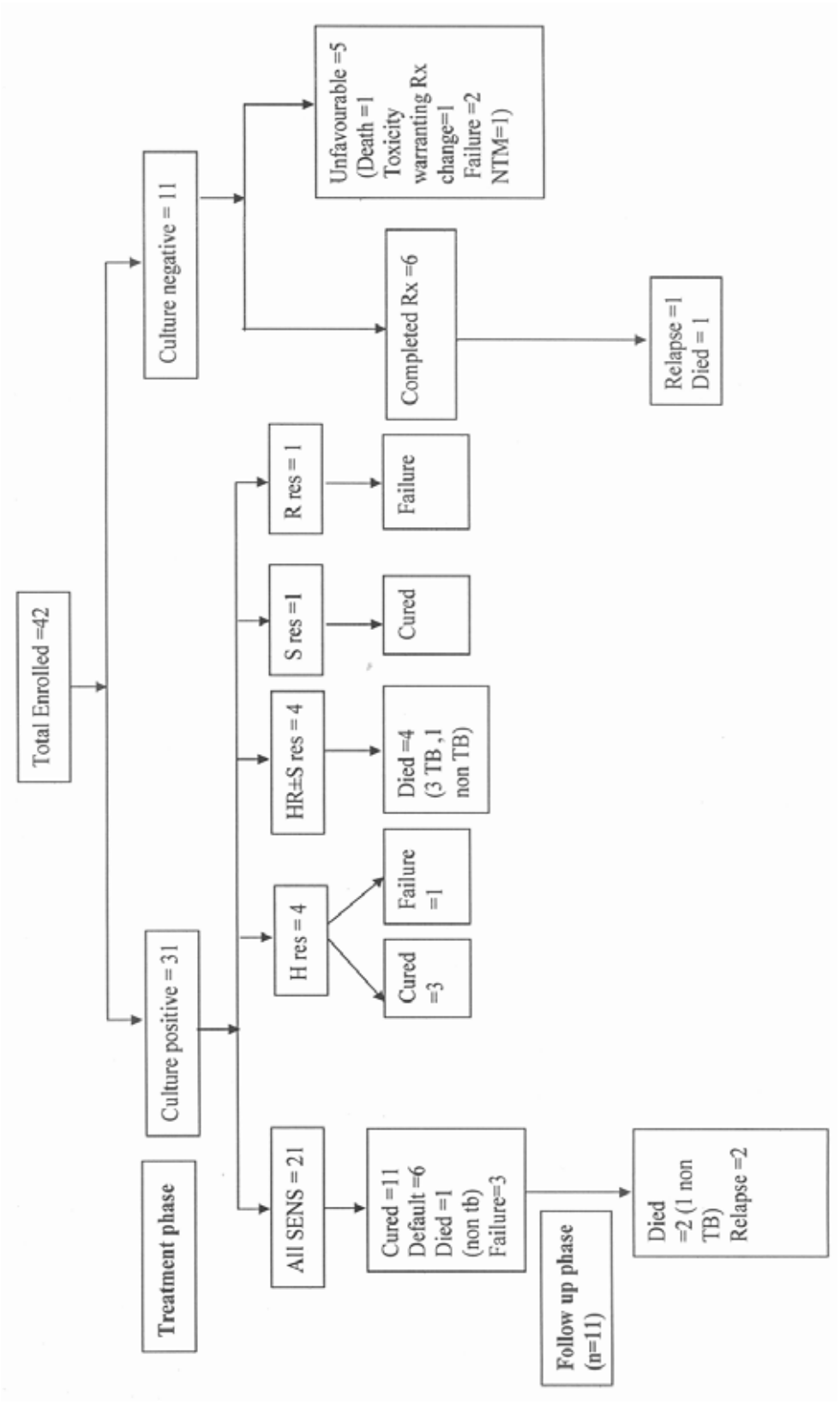

Figure 1: Profile of Patients Enrolled and Followed up

patients survived (including the three with INH mono resistance, and one with S resistance). Among the failure cases, with all drugs susceptible at enrolment, one patient survived with retreatment and one died of TB and the third case died of a non-TB cause. Among the four INH mono-resistance cases, three cases which were declared cured at treatment, completed follow up and survived and one who was declared failure and started retreatment again completed it and survived. Streptomycin mono-resistance patient who was declared cured during treatment, completed follow up and remained alive. Rifampicin mono-resistance patient who was declared failure and subsequently put on re-treatment, died of TB. Among the four MDR cases, three patients died of TB during MDR management and the other one died of a non-TB cause. Among the 11 culture negative patients, out of the six cases who completed treatment, one had relapse at 12th month and one died at 14th month (non-TB) and others survived. One of the failure cases died of non-TB at 9th month and the other failure case survived. The patient who had change of treatment due to toxicity, died of a non-TB cause. Patient with the atypical mycobacteria survived with treatment.

All the six patients who had got ART, survived at 24-month follow up. Among those six patients started on ART, pre and post-treatment CD4 count results were available for four patients, which were 78 and 527; 154 and 597; 141 and 532; and 600 and 1020 cells/mm^3 respectively. Among the remaining who did not get access to ART, 12 (33%) died and 24 survived.

DISCUSSION

In this prospective study, we have shown that among HIV-infected individuals retreated for TB with a fully intermittent Category II regimen, the cure/completion rate was 50%. This is less than the cure rate shown by the TB programme in India (which is more than 68% for all cases treated with Cat II) irrespective of HIV status.[3] Our extensive literature search could not identify any clinical trial that has studied the efficacy of Cat II regimen in HIV infected patients. An observational study[4] to assess treatment outcome and mortality (at one and half year follow-up) of HIV-infected TB patients under TB Control Programme in Bangalore district of South India, reported a 50% favourable outcome. The authors concluded that 'retreatment cases' had a significantly higher probability of having 'unfavourable' treatment outcome as compared to 'New Cases' [OR-4.04, CI (1.96–8.35)].

A prospective cohort study on the effectiveness of the Standard WHO recommended retreatment regimen (Category II) given daily in Kampala, Uganda,[5] described the treatment outcome of both HIV infected and HIV uninfected TB patients. The study showed that 26% of HIV-infected patients retreated for TB had an unsuccessful treatment outcome compared with 20% in HIV uninfected and concluded that HIV-infected patients retreated for TB had a poor long term outcome. HIV infected patients also had a higher death rate (mortality rate 21.4 per 100 PYO) compared to HIV uninfected (5.9 per 100 PYO). A cohort study in Haiti,[6] to measure the effectiveness of the standard TB retreatment regimen for PT in HIV infected adults showed that 73% achieved treatment success (cure, treatment completed), but all patients had access to ART and ATT was given daily.

A systematic review[7] of treatment outcomes in patients with a history of previous treatment shows that there is little published evidence to support the continued use of the currently recommended retreatment regimen, without knowing their resistance status. From our observations, all five patients with pre-treatment R resistance had an unfavourable outcome, whereas three of four with INH resistance did well. Further studies are needed to explore optimal treatment regimens for INH mono or poly-resistant TB patients. Currently, many high burden countries are expanding their capacity to perform initial drug susceptibility tests at least for re-treatment patients and tailor the regimen accordingly[8].

In our study, as a usual presentation of TB, cough was the commonest presenting symptom (67%) followed by anorexia and fever. Opacities were the commonest radiographic features, and the next commonest was cavity (21.4%); it is well

known that risk factors for relapse include residual cavitation on chest radiograph[9].

There are a number of factors that could influence the outcome of HIV infected retreated TB patients like TB treatment adherence, pre-treatment drug susceptibility, baseline CD4+ cell count, concomitant ART use and Karnofsky score. Among HIV-positive patients, the rate of recurrence has been reported to be higher in those patients with lower CD4 counts in some studies,[10-12] but not in other studies.[13,14] In our study at baseline, median CD4 count for all patients enrolled was 116 while the median baseline CD4 for the culture-positive TB patients with unfavourable response was 58 compared to 169 for favourable responders. In the Uganda study[5] discussed earlier, the median CD4+ cell count in HIV-infected patients was 120 cells/mm^3 (interquartile range [IQR] 34–287 cells/mm^3) and one of the risk factors for death during follow-up among HIV infected patients were CD4 less than 50 cells/mm^3. In an earlier trial comparing 6 *versus* 9-month-thrice-weekly treatment, we showed that the risk factors for recurrence were baseline INH resistance, low baseline CD4 count and adherence, of these only INH resistance was significant in multivariable analysis.[15]

Concomitant ART would be expected to improve overall health and thereby influence the TB treatment outcome.[16-18] Free ART was initiated in India in April 2004, whereas most of the patients were recruited to our study prior to that period; this could partially explain the high mortality observed. Further, the cut-off for eligibility was a CD4 count of <200 cells/mm^3 and patients had to complete the intensive phase of ATT before initiating ART. In our study, out of the 42 patients, only six patients received ART and all six patients survived. Many of the defaulters could have died but information on the exact cause of death was not available in most cases.

Multidrug-resistant TB at enrolment is a risk factor for death and this has been observed by us also. In the Ugandan study, the adjusted hazard ratio for death was 17.9; 6.0–53.4 p<0.001 for patients with MDRTB, but the authors could not ascertain if death was a consequence of advanced HIV disease, TB, or both. In our study we had four MDR TB cases and all of them died, three were due to active TB.

Default rate in our study was 14%. The RNTCP (Indian TB Programme) reports a default rate of 15%[19] for Cat II patients. One of the factors associated with an unsuccessful treatment outcome is poor adherence both among HIV-infected and uninfected patients.[4] In our study, among those who were regular for treatment, about 43% had taken 100% of the doses of the study treatment, and overall adherence was more than 85% of the scheduled doses.

Limitations of our study

Our study was observational in nature, had a relatively smaller sample size and therefore may not be generalizable. DNA fingerprints were not available, so we could not classify TB recurrences as relapse or re-infection. Access to ART was limited at the time of this study; treatment outcomes with the provision of ART are likely to be better.

In summary, we have shown that less than half of the HIV-infected patients who receive TB re-treatment with a thrice-weekly Category II regimen have a favourable long-term outcome. With access to rapid anti-TB drug susceptibility testing (and subsequent treatment for MDR TB if diagnosed) and early initiation of ART, TB treatment outcomes could be improved substantially. Another question that needs to be answered is whether the current Category II regimen is adequate for patients with isoniazid resistant TB alone.

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Original Article

LONG-TERM FOLLOW-UP AFTER THORACOSCOPIC RESECTION OF SOLITARY PULMONARY TUBERCULOMA

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Summary

Background: Pulmonary tuberculosis continues to be a significant health problem, especially due to increasing incidence of multi-resistant mycobacteria and patients with immunodeficiency. Pulmonary tuberculoma, like other solitary lung nodules, can often be a diagnostic challenge; moreover no consensus exists on the management strategy.

Aim: To analyze the results of tuberculoma treatment with thoracoscopic lung resection, followed by anti-tuberculosis treatment (ATT).

Methods: All patients who underwent thoracoscopic resection of tuberculoma between 1996 and 2008 were retrospectively analyzed. The diagnosis was confirmed morphologically and/or microbiologically. Data were collected from case reports, outpatient medical records, Estonian Tuberculosis Registry and National Population Registry.

Results: Forty-three patients (25 men, 18 women) with mean age of 43.3 (range 15-68) years were included. Thoracoscopic approach was converted to thoracotomy in three cases. Median postoperative stay in surgical department was four days. No intra-hospital mortality occurred. Eleven patients received pre-operative ATT for 8 to 288 (median 115) days and 42 patients were treated post-operatively for 40 to 672 (median 185) days. One patient defaulted in ATT. First-line drugs were prescribed in 37 and second-line in five patients. During the median follow-up of 9.0 (range 3.2 to 16.1) years, none of the patients developed relapse.

Conclusions: Thoracoscopic pulmonary resection provides a minimally invasive opportunity for morphological and microbiological diagnosis of tuberculoma; and results in an excellent cure rate in combination with ATT. **[*Indian J Tuberc 2014; 61:* 51-56]**

Key words: Thoracoscopy, Tuberculosis, Pulmonary nodule

INTRODUCTION

Incidence of pulmonary tuberculosis (TB) including tuberculoma is now-a-days relatively low in most developed countries. However, it continues to be a significant health problem in many areas due to considerable number of patients infected with multi-drug-resistant mycobacteria and growing patient population with immunodeficiency. In several cases, the localized form of TB - pulmonary tuberculoma, can be a diagnostic challenge among other causes of solitary pulmonary nodule. Even with computed tomography (CT) and positron-emission tomography computed tomography (PET-CT), it is not always possible to distinguish tuberculoma from a malignant pulmonary nodule[1,2]. Moreover, when the definite diagnosis has been established, there is no clear consensus on tuberculoma management strategy. Surgical treatment has been suggested by several authors[3,4].

In one of the largest surgical series analyzing the distribution of solitary pulmonary nodules (during the seventies of last century), tuberculomas accounted for 23.6%[5]. Over the years, the incidence of tuberculoma has significantly decreased. Still, in studies published during the last decade, tuberculomas accounted for 1.8-13.6% of all surgically removed nodules and 5.2-33.3% of those, which were benign[6-10]. Thus, tuberculoma has remained an important clinical problem, with limited data on pre- and post-resection management strategy and treatment results.

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Several recent publications evaluating surgical treatment of TB have included different tuberculous lesions, various approaches to thoracic cavity and volumes of lung resection from wedge resection to pneumonectomy[11]. In one recent paper, focusing only on the thoracoscopic approach for TB treatment, even patients with tuberculous pleurisy were included[12], thus making the patient population very heterogeneous. Hsu and colleagues have reported video-assisted thoracoscopic (VATS) resection of tuberculoma, but without follow-up[13].

The current study was designed to analyse long-term treatment results of a homogeneous patient population - we included only patients who underwent VATS resection of solitary pulmonary tuberculoma. Indication for surgical treatment was intention to remove a residual tuberculous nodule to avoid disease relapse or suspicion of malignancy, especially in older patients without clear previous TB history. Main objectives of the study were to analyse early and late post-operative complications and long-term freedom of TB relapse.

MATERIAL AND METHODS

Institutional Ethics Committee approved the study protocol. All patients who underwent VATS wedge lung resection for pulmonary tuberculoma in Tartu University Hospital, Estonia from year 1996 (first VATS in our hospital) to 2008 were included into this retrospective study. Tuberculoma was defined as tumour-like localized tuberculous infection in the lung without any other evidence of pulmonary tuberculosis. Pre-operative chest CT to evaluate and localize the pulmonary nodule was routinely performed. FDG-PET was not available at the study period in our institution. Pre-operative sputum smear was negative in all patients.

Indication for surgical treatment of tuberculoma was intention to remove a residual tuberculous nodule to avoid disease relapse. In cases of unknown diagnosis pre-operatively, the indication for nodule removal was suspicion of malignancy (Figure). In all cases, the operation was done in general anaesthesia using single lung ventilation. Two or three five to ten millimeter trocars were inserted into the pleural cavity for the camera and instruments. Wedge resection of the lung with a stapling device was performed and the specimen removed from thoracic cavity with a retrieval bag. In case macroscopic finding was not obvious to tuberculoma, intraoperative frozen section of the specimen was performed to rule out malignancy. In all patients, the final diagnosis of tuberculoma was confirmed by post-operative morphological and/or microbiological investigations.

Information about patient demographics, exact surgical and medical management and long-term follow-up was collected retrospectively from hospital case reports, out-patient medical records, Estonian Tuberculosis Registry and National Population Registry.

RESULTS

Altogether 43 patients were operated on by VATS for tuberculoma within the study period. Twenty-five patients were males and 18 females with mean age of 43.3 (range 15-68) years. During the same time-period, 226 patients were operated on by VATS due to a solitary pulmonary nodule, including 94 malignant and 132 benign nodules. Tuberculoma accounted for 19.0% of all nodules and 32.6% of those, which were benign.

Initial thoracoscopic approach was converted to thoracotomy in three cases (7%). The reasons for conversion were either dense pleural adhesions or inability to find a deeply located pulmonary nodule without manual palpation of the lung.

The tuberculoma was located in the right lung in 28 and in the left lung in 15 of the cases. Twenty-six tuberculomas were removed from the upper, one from the middle and 16 from the lower lobe.

During the whole study period, median post-operative stay in the surgical ward was 4 (range 1-52) days. The duration of hospital stay decreased over the study years to median three (range 1-5) days during 2006-2008. Twenty patients were

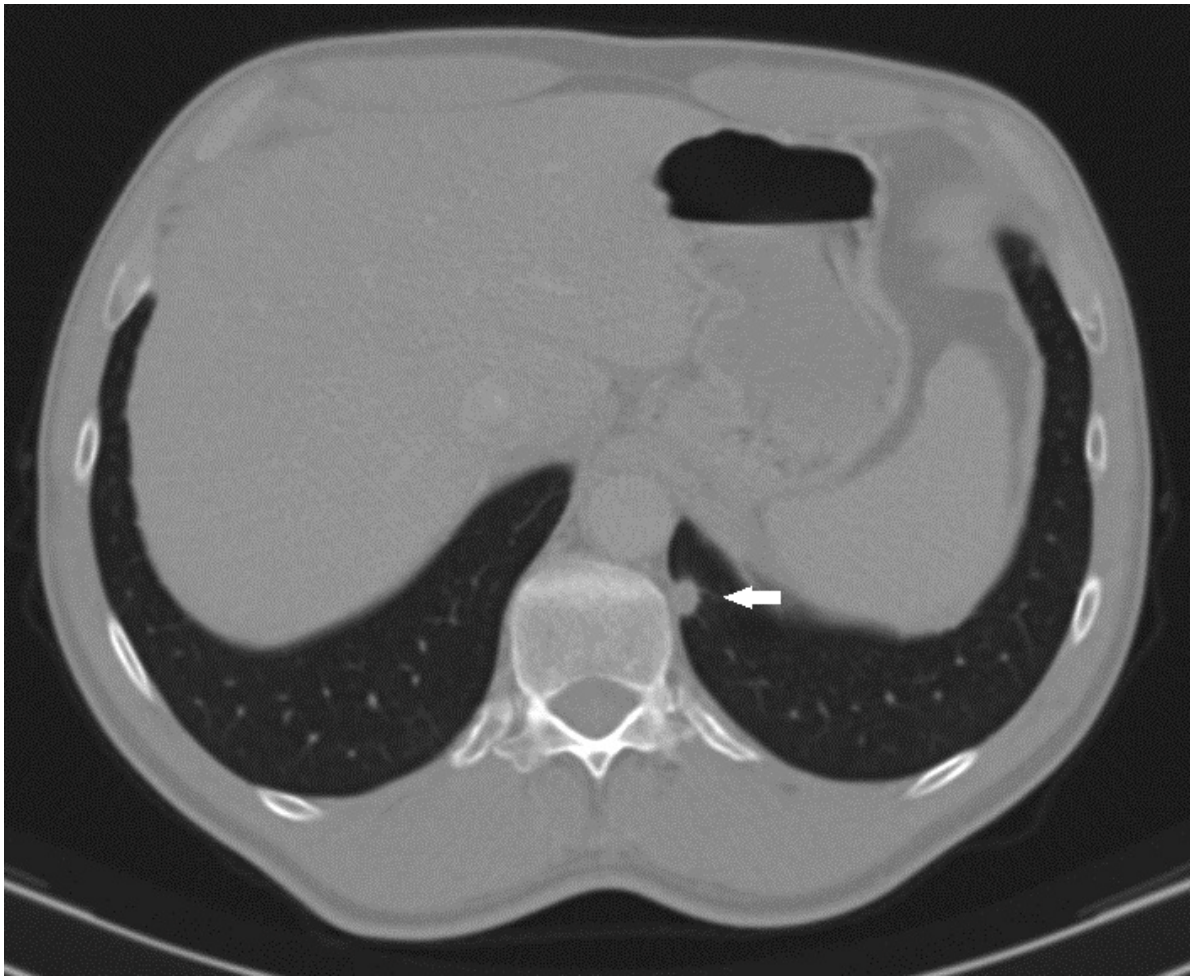

Figure: Chest CT of a 58-year-old male patient (smoker) with left lower lobe tuberculoma. The incidentally found spiculated pulmonary nodule (arrow) was suspected to be a primary lung cancer.

transferred to other hospital departments for TB treatment continuation. None of the patients required re-operation and no hospital mortality occurred.

Eleven patients received pre-operative TB treatment for median 115 (range 8-288) days. Post-operative treatment with anti-TB drugs was prescribed in 42 cases for median duration of 185 (range 40-672) days. First-line drugs (*Rifampicin, Isoniazid, Ethambutol and Pyrazinamide*) were prescribed for 37 patients. Second-line drugs (*Ofloxacin, Amikacin, Protionamide, Para-aminosalicylic acid, Streptomycin or Cycloserin*) were used due to drug resistance in five patients. One patient defaulted in TB treatment, others completed their therapy as prescribed.

The median duration of follow-up was 9.0 years (range 3.2 to 16.1 years). No relapse of TB was recorded during the follow-up period. Seven patients died during follow-up due to unrelated causes, without evidence of TB.

DISCUSSION

Pulmonary tuberculoma continues to be diagnosed occasionally in patients with a solitary pulmonary nodule. Similarly in one recent study, we found that even now-a-days tuberculoma

accounts for up to 1/3 of benign surgically removed nodules[10]. According to our study, tuberculoma can occur in any lobe of the lung. Although, as commonly expected, the upper lobes were predominantly affected; still in 37% of cases it was removed from the lower lobes.

In majority of cases, especially in older patients, indication for solitary pulmonary nodule removal was suspicion of malignancy. Despite remarkable advances in radiological diagnostics, thoracoscopic lung wedge resection has often remained the final step to establish the definite diagnosis for a pulmonary nodule. Although chest CT and FDG-PET have become widely used to differentiate benign and malignant nodules, tuberculoma is not similar to other benign nodules. In two recent studies, it has been clearly demonstrated that FDG-PET failed to distinguish malignancy and tuberculoma[1,2].

Moreover, in addition to *Mycobacterium tuberculosis*, also other non-tuberculous mycobacteria can cause formation of tuberculoma, which cannot be radiologically differentiated. Therefore, surgical removal of tuberculoma gives us, in addition to the definite morphological diagnosis, also valuable microbiological data influencing further treatment strategy[14].

The other indication for surgical treatment in our study population was intention to remove a residual tuberculous nodule to avoid disease relapse. All such patients had pre-operatively established TB diagnosis and some of them had been treated with anti-TB drugs before surgery. Although no clear guidelines exist to support such treatment, ten of our patients received anti-TB drugs for various time periods. The aim of pre-operative TB treatment is to reduce the probability of TB dissemination in post-operative period[11]. Generally, 3-month treatment is prescribed. Paradoxically, it has also been found that patients with pre-operative ATT had more post-operative complications, compared to patients without such treatment[11]. However, the study was not randomized and included all forms of TB, not only tuberculoma. In another series of tuberculoma surgical treatment, it was found that pre-operative ATT did not influence post-operative outcome regarding TB relapse during one-year follow-up[15]. Thus, it is not unanimously clear whether pre-operative ATT, especially in case of tuberculoma, is indicated at all. Most of our patients did not receive any pre-operative treatment, as they had no prior pathologically or microbiologically confirmed diagnosis of tuberculoma. Despite that none of our patients got TB relapse after operation.

Surgical treatment of tuberculoma has been supported by a few studies perfomed in this field[3,4]. To avoid TB relapse, TB focus cleaning through mini-thoracotomy[4] or VATS wedge resection has been suggested[3]. However, similarly in our study group, tuberculoma is usually an incidental finding after surgical removal of a solitary pulmonary nodule. Our strategy was to treat all such patients with anti-TB drugs post-operatively. Treatment was initiated with first line drugs and changed to second-line drugs in case of drug resistance. Treatment had to be switched in five cases only. Currently, with increasing incidence of multidrug-resistant tuberculosis (MDR-TB, resistant to isoniazid and rifampicin) and extensively drug-resistant tuberculosis (XDR-TB, resistant to isoniazid and rifampicin, to any fluoroquinolone and to at least one second-line injectable agent: amikacin, kanamycin and/or capreomycin) in some countries, treatment of those patients will be more challenging, as data on drug susceptibility would not be immediately available. In addition, there is no consensus on the duration of post-operative ATT. In our study population, the median duration of treatment was approximately six months.

Considering the importance of information about susceptibility to anti-TB drugs in the era of MDR-TB and XDR-TB, it is mandatory to send part of the surgical specimen, in addition to pathology laboratory, also to microbiology laboratory for mycobacteriological tests. When exact pre-operative diagnosis of a pulmonary nodule has not been established, the operating surgeon should always keep in mind the possibility of tuberculosis.

Very few data is published on long-term follow-up after thoracoscopic treatment of TB.

During the fifties and sixties, major lung resections due to TB were common and the results well described. In those days, the surgical access was always thoracotomy. Now-a-days, lung resections due to TB are rare and most operations performed due to MDR-TB or XDR-TB[16-18]. Usually, thoracotomy is still used for surgical access and lobectomy or pneumonectomy is performed. Results of surgical resection in combination with anti-TB chemotherapy remain good. The overall treatment success rate is as high as 90-98%[16-18]. The results are better if lobectomy is performed (compared to pneumonectomy) and after resection of tuberculoma (compared to cavitary lesions or lung destruction)[19].

More and more thoracic operations, including resection of tuberculous lesions, can be performed thoracoscopically, however it is not always technically possible[17,20]. CT findings of multiple cavities, multiple aspergillomas, multilobar tuberculoma, extensive pleural thickening, and peribronchial lymph node calcification preclude use of VATS[20]. Removal of tuberculoma is usually both a diagnostic and a therapeutic operation. Whether this is also a curative operation with no need for further treatment, remains unclear. In most cases, when the operation is performed because of TB, post-operative anti-TB treatment has been recommended[13,15-17,20] and we also followed this strategy. However, it has been described that in some cases ATT has not been applied when a histologically "old tuberculoma" has been diagnosed[12].

Based on the results of our study, we might conclude that thoracoscopic resection, followed by ATT, provides excellent cure for patients with solitary pulmonary tuberculoma, as no relapses were detected and no major complications occurred. Therefore, thoracoscopic removal of solitary pulmonary tuberculoma as a low risk operation that prevents TB reactivation can be recommended.

Operating on patients in a minimally invasive way results in reduced inflammatory response and less impaired cellular immunity, compared to open operations[21] and thus in each case anti-TB drugs might not be indicated in the post-operative period.

Further studies to establish the need for and duration of post-operative anti-TB treatment are required.

Limitation of the study is its retrospective nature and inability to compare the VATS wedge resection to other treatment modalities, however due to limited number of patients and the need for long follow-up period, it is probably impossible to perform randomized prospective study in this particular patient population.

CONCLUSION

VATS pulmonary resection enables exact morphological and microbiological diagnosis of pulmonary tuberculoma in a minimally invasive way. VATS resection, followed by ATT gives an excellent cure rate for tuberculoma.

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Original Article

INITIATION OF MDR TB TREATMENT: IS HOSPITALIZATION WORTH?

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Summary

Background: The treatment for MDR TB is quite prolonged and associated with adverse effects and hence costly.

Aim: The aim of study was to study the side-effects of reserve line drugs developing in initial seven days of starting therapy, so as to weigh the need for admission for initiation of treatment against heavy economic burden by admission of huge number of MDR TB patients, and to identify the factors which may have an effect on the number of patients developing side-effects

Methods: All MDR TB patients (930) admitted during study period, who were initiated on Cat IV treatment for MDR TB under RNTCP were questioned daily for any side-effects throughout the day, during initial seven days of treatment.

Results: On day one, 342 (36.8%) patients developed side-effects, on 2nd day 456 (49%), on day 3 356 (38.3 %), on fourth day 257 (27.6%), then on fifth day only 172 (18.5 %) patients respectively had reported side-effects. Further decline of side-effects was reported on sixth day 94(10.1%) and seventh day 39(4.2%). Number of events also decreased from 669 on day1 and 965 on day 2, to only 61 on day 7 of treatment. Most of the patients had nausea, vomiting, pain abdomen, restlessness, dizziness, insomnia and headache. Patients with low Hemoglobin had more side-effects from day 2 onwards ($p<0.05$).Age, BMI, gender and co-morbidities had no significant effect on side-effects in these patients.

Conclusion: Many patients report side-effects initially on treatment, which gradually decrease from day 4 onwards , so hospitalization for atleast seven days during initiation of Cat IV may not be required in all the patients. **[*Indian J Tuberc 2014; 61:* 57-64]**

Key words: MDR TB, Reserve Drug Regimen, Hospitalization, Cost of Treatment

INTRODUCTION

TB is the greatest killer of people in recorded history. Dr. Robert Koch, the German scientist who identified the TB bacterium, wrote "one-seventh of all human beings die of tuberculosis, and if one considers only the productive middle-age groups, tuberculosis carries away one-third and often more of these"[1]. The emergence and spread of multi-drug resistant tuberculosis (MDR-TB) is threatening to destabilize global tuberculosis control. The prevalence of MDR-TB is increasing throughout the world both among new tuberculosis cases as well as among previously-treated ones[2]. MDR TB is now thought to afflict between 1 and 2 million patients annually[3]. Indian national guidelines of programmatic management of drug resistant Tuberculosis, recommend admission of MDR TB patients in designated Drug Resistant-TB Centre (DR-TB centre) for at least seven days for initiation of reserve drugs regimen for these patients. This period of admission is for necessary investigations, initiation of the regimen for MDR TB, monitoring of tolerance of the regimen, motivation, counselling and providing health education[4]. Since the drugs used for the treatment of MDR-TB are known to produce adverse effects, this period gives an opportunity for monitoring side-effects developing soon after initiation of therapy. In this study, we aim to study the side-effects of reserve line drugs developing in initial seven days of starting therapy, so as to weigh the need for admission for initiation of treatment

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against heavy economic burden by admission of a huge number of MDRTB patients.

MATERIAL AND METHODS

Study design

This study was a prospective type of cohort study. We included all MDR TB patients who were admitted in our institute for initiation of Category IV treatment for MDR TB under the Revised National Tuberculosis Control Programme (RNTCP) from January 2012 to October 2012.

Study Site

This study was done at tertiary care institute for tuberculosis and pulmonary diseases, which is also a designated centre for programmatic management of drug resistant tuberculosis (PMDT) under RNTCP. This centre caters to three DR-TB centres' site for providing indoor facilities for management of drug resistant TB patients in Delhi.

METHOD

The patients from three DR-TB centres in Delhi were referred at this institute for admission and initiation of treatment of MDR TB and these patients were enrolled for the study after informed written consent. The study was approved by the institutional Ethics Committee.

Age, sex, height, weight, hemoglobin, any known co-morbidity, DOTS plus number and date of start of treatment were recorded for every patient. The patients were enquired for initial seven days daily for any side-effect they experienced since the initiation of standardized Category IV regimen which was given under direct supervision of ward nurse. These symptoms and the management given for these symptoms were recorded. The patients were divided according to four age groups consisting of group 1: below 15 years, group 2: 15 to 45 years, group 3 :46 to 60 years and group 4:above 60 years. They were also grouped according to WHO BMI classification[5]. The Hemoglobin was divided in three groups 1: Below 8 gm%, group 2: 8 to 10 gm% group 3: More than 10 gm% ,for the purpose of analysis. The data collected was tabulated using Microsoft excel and analyzed for descriptive analysis, comparison of groups using Chi square test using statistical software SPSS version 13 on a personal computer.

RESULTS

We could register 930 patients, of which 557 were males and 373 patients were females. Eight males and 22 females were below age 15 years, 425 males were of age group 15 to 45 years and 324 females belonged to this age group, 99 males and 22 females were of age group 46 to 60 years. 25 males and 5 females were above 60 years' old.

Majority of patients were in low BMI group i.e.714 (76.8%), 210(22.6%) were in normal BMI group and only 6(0.6%) patients were overweight. Hemoglobin of 664 (71.4%) patients was less than 8 gm%, of 228(24.5%) patients was between 8 to 10 gm per cent. Only 38(4.1%) patients had hemoglobin more than 10 gm%

Diabetes Mellitus was found in 31 patients, three patients were HIV positive, two patients had associated COPD

On the first day of treatment, 342(36.8%) patients developed symptoms, of which 201(21.6%) developed nausea, 104(11.2%) had vomiting, 24(2.6%) patients developed pain in abdomen, restlessness was found in 91(9.1%). Dizziness was found in 94(10.1%), while 41(4.45%) developed insomnia, 31(3.3%) patients developed headache, 14(1.5%) patients developed anorexia. Diarrhoea was found in 17(1.8%) patients. Four patients developed metallic taste, epigastric discomfort was found in 10(1.1%). Excessive salivation was there in 7(.8%), while 10(1.1%) developed belching and bloating was found in 15(1.6%). One patient (0.1%) developed gastro colic reflex and one developed somnolence. Visual disturbance was reported in one patient,

two patients (0.2%) developed fever. The number of patients reporting each side-effect on each day of treatment has been tabulated in Table no 1.

There was significant decrease in number of patients who developed symptoms, as 36.8% and 49% patients had symptoms on day one and day two respectively, which had dropped to only 5% on day seven. Symptoms decreased gradually from day 4 onwards (Figure 1). Majority of patients had gastrointestinal symptoms such as nausea, vomiting, pain in abdomen, anorexia, diarrhoea, epigastric pain,

Table 1: Side effects reported on each day by the patients after taking MDR TB treatment

Symptoms	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Nausea	200(21.6)	322(34.6)	279(30)	193(20.8)	125(13.4)	77(8.3)	31(3.3)
Vomiting	104(11.2)	174(18.7)	118(12.7)	72(7.7)	38(4.1)	13(1.4)	11(1.2)
Pain abdomen	24(2.6)	24(2.6)	18(1.90	5(0.5)	11(1.2)	3(0.3)	3(0.3)
Restlessness	91(9.8)	116(12.5)	88(9.5)	57(6.1)	31(3.3)	4(0.4)	4(0.4)
Dizziness	94(10.1)	104(11.2)	63(6.8)	28(3)	18(1.9)	4(0.4)	1(0.1)
Insomnia	41(4.4)	25(2.7)	4(0.4)	0	0	0	0
Headache	31(3.3)	24(2.6)	19(2)	7(0.8)	4(0.4)	1(0.1)	0
Anorexia	14(1.5)	66(7.1)	63(6.8)	56(6)	24(2.6)	13(1.4)	11(1.2)
Diarrhea	17(1.8)	18(1.9)	10(1.1)	5(0.5)	1(0.1)	0	0
Metallic taste	4(0.4)	2(0.2)	0	2(0.2)	4(0.4)	0	0
Epigastic discomfort	10(1.1)	43(4.6)	42(4.5)	19(2)	15(1.6)	1(0.1)	0
Excess salivation	7(0.8)	16(1.7)	10(1.1)	4(0.4)	0	0	0
Belching	10(1.1)	8(0.9)	6(0.6)	3(0.3)	0	0	0
Bloating	15(1.6)	10(1.1)	8(0.9)	3(0.3)	3(0.3)	0	0
Gastrocolic reflex	1(0.1)	2(0.2)	0	0	4(0.4)	0	0
Visual disturbances	1(0.1)	0	0	0	0	0	0
Fever	2(0.2)	6(0.6)	0	0	0	0	0
Pruritis	1(0.1)	4(0.4)	4(0.4)	0	0	0	0
Acne	1(0.1)	0	0	0	0	0	0
Disorientation	0	1(0.1)	0	0	0	0	0
Convulsion	0	0	1(0.1)	0	0	0	0
Tremor	0	0	0	0	1(0.1)	1(0.1)	0
Somnolence	1(0.1)	0	0	0	7(0.8)	0	0
Total events	669	965	773	454	286	117	61

Values shown as n (% age)

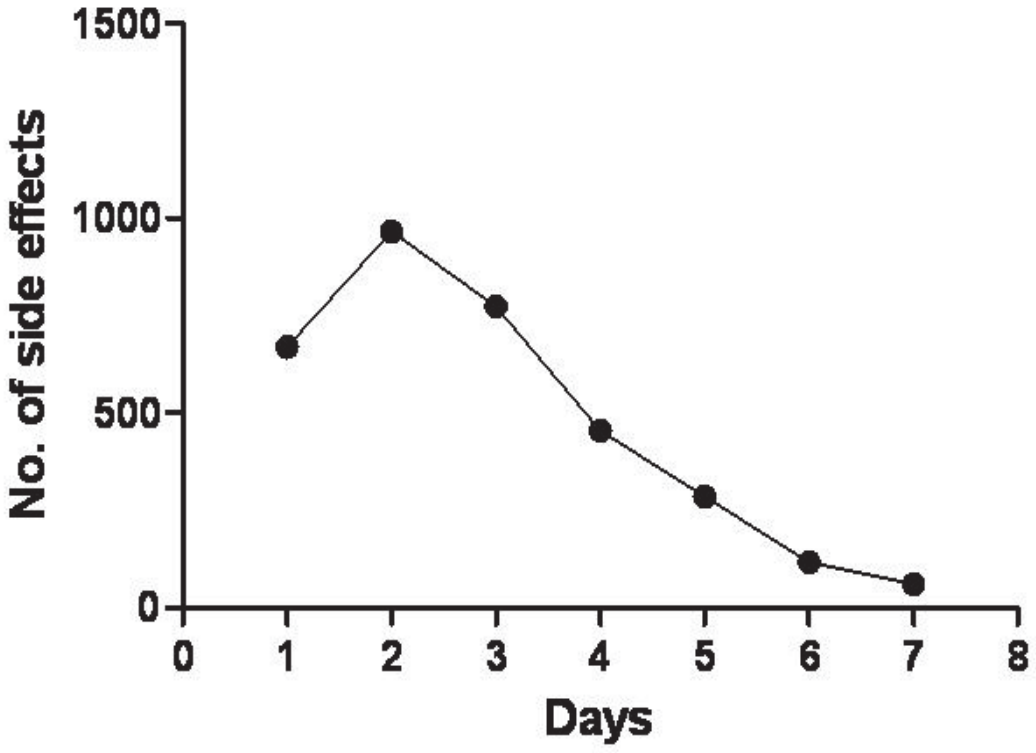

Figure: Graph showing number of side effects reported increased on day 2 of treatment and from day 3 onwards started decreasing

Table 2: Side effects in relation to hemoglobin

Days	Hemoglobin			P value
	Group 1(< 8 gm %)	Group 2(8 to 10 gm %)	Group 3(> 10 gm %)	
Day 1	250(26.9)	82(8.8)	10(1.1)	0.335
Day 2	305(32.8)	133(14.3)	18(1.9)	**0.005**
Day 3	232(24.9)	106(11.4)	18(1.9)	**0.004**
Day 4	167(18)	78(8.4)	12(1.3)	**0.026**
Day 5	101(10.9)	62(6.2)	9(1)	**0.000**
Day 6	42(4.2)	43(4.3)	9(1)	**0.000**
Day 7	22(2.4)	13(1.4)	4(0.4)	**0.041**

Values shown as n (% age)

Table 3: Side effects in relation to body mass Index

Days	BMI Groups			P value
	Underweight	Normal	Overweight	
Day 1	275(29.6)	64(6.9)	3(0.3)	0.084
Day 2	344(37)	108(11.6)	4(0.4)	0.487
Day 3	258(27.7)	97(10.4)	1(0.1)	0.17
Day 4	193(20.8)	64(6.9)	0(0.0)	0.195
Day 5	126(13.5)	46(4.9)	0(0.0)	0.190
Day 6	70(7.5)	24(2.6)	0(0.0)	0.563
Day 7	31(3.3)	8(0.9)	0(0.0)	0.827

BMI≡ Body mass Index, Values shown as n (% age)

Table 4: Side effects in relation to age

Days	Age				P value
	Group 1	Group 2	Group 3	Group 4	
Day 1	13 (1.4)	269(28.9)	51(5.9)	9(1)	0.409
Day 2	16(1.7)	365(39.2)	58(6.2)	17(1.8)	0.799
Day 3	11(1.2)	283(30.4)	45(4.8)	17(1.8)	0.215
Day 4	7(0.8)	204(21.9)	34(3.7)	12(1.3)	0.450
Day 5	6(0.6)	140(15.1)	18(1.9)	8(0.9)	0.485
Day 6	3(0.3)	72(7.7)	15(1.6)	4(0.4)	0.743
Day 7	1(0.1)	33(3.5)	4(0.4)	1(0.1)	0.934

Values shown as n (% age)

bloating, belching, excessive salivation, and other symptoms like dizziness, headache, somnolence and pruritus. Only a few had serious symptoms like convulsion and altered behaviour.

The patients with low hemoglobin (Group1) had significantly more side-effects as compared to those who had hemoglobin of more than 10gm% (group 3) from 2nd day onwards as shown in Table no. 2.

There was no statistically significant difference between various age groups and BMI groups reporting side-effects from day 1 to day 7 of treatment (Table nos. 3 and 4).

When studying the side-effects reported in patients with associated co-morbidities such as diabetes, HIV infection, COPD, etc., there was no statistically significant difference noted from otherwise healthy MDR TB patient group(p=0.95).

DISCUSSION

Treatment of MDR-TB and XDR-TB requires at least 20 months of highly toxic and costly medications[6] and the treatment success rate for MDR-TB is about 60% and that for XDR-TB about 30%[7-9].

The cost of drugs for full course of treatment for an MDR TB patient is > 50 times higher than that for a drug susceptible patient, as found in a study ,where it was about $5000 for a patient resistant only to Rifampicin and Isoniazid[10]. The estimated cost of drugs to treat MDR TB patients ranges from Rs. 200 to Rs. 400 approximately per day per patient in India. If the cost of investigations, medical consultation, infection control measures, hospitalization needs and cost of drugs are accounted together, the cost of treating drug resistant tuberculosis will be huge. The average inpatient hospital cost estimated in a study, for those with MDR-TB who survive the disease was $89,594 and this cost rose to $717,555 for those who died[11]. Although, we could not find any study in India which estimated the cost of treatment of MDR TB, it is clear that high tuberculosis burden countries can ill-afford the economic and social cost due to this disease[12]. Floyed *et al*[13], in their report while estimating the cost of treating MDR TB in Russia extrapolated that a substantial funding for TB control shall be required. India and China , which have about half the total global estimated MDR TB patients, would require enormous investments even if low costs of treatment are achieved as seen in studies in Peru[14-15].

Adverse effects of drugs used in treatment of MDR TB have been studied in various studies[16,19], but only a few studies report adverse effects on initial days of reserve line ATT intake.

Hospitalization is an extra economic burden, especially in developing countries like India, where huge number of MDR TB patients have been predicted[20]. In this study, we tried to find whether the need for hospitalization during initiation of MDR TB treatment is really required, for managing the adverse effects of reserve line ATT in initial days of starting treatment, as one of the reasons for hospitalization, so we have studied adverse effects which patients developed during initial seven days of MDR TB treatment.

In our study, we found that on initial three days the number of patients who developed adverse effects increased, but from day 4 onwards there was fall in number of adverse effects till 7th day, as on day one 342 (36.8%) patients developed symptoms, on 2nd day of treatment 456 (49%) patients developed symptoms, on day 3 of the treatment 356 (38.3 %) patients had symptoms, on fourth day 257 (27.6%) patients had symptoms, then on fifth day only 172 (18.5 %) patients had symptoms. There was further decline in number of patients who had symptoms, on sixth day 94 (10.1 %) patients had symptoms and on seventh day only 39 (4.2 %) patients had symptoms.

Most of these patients developed gastrointestinal symptoms like nausea, vomiting, anorexia, pain abdomen, diarrhoea, bloating, belching, epigastric discomfort, excessive salivation and other symptoms like headache, dizziness, fever and pruritis. Most of these symptoms had either resolved by themselves or with treatment with common medicines such as antiemetics,H2-blockers, antipyretics, etc, therefore these symptoms can be managed on out-patient department (OPD) basis also and only a few patients may require hospitalization, if these symptoms are so severe that the patients have to be managed as inpatients . Such patients can be identified in OPD and can be referred for hospitalization. Only one patient developed altered behaviour on second day and convulsions on third day. One patient developed visual disturbance on first day and one patient developed tremor. Eight patients complained of somnolence.

In a study of occurrence of serious adverse effects in patients receiving community-based therapy for multidrug resistant tuberculosis, it was

found that ,although adverse effects were common, they occurred less frequently than previously reported in the literature and were rarely life-threatening. Adverse Effects occurring most frequently in this population included: mild gastritis (100%), dermatological effects (43.3%), peripheral neuropathy (16.7%), depression (18.3%), and anxiety (11.7%). These effects never resulted in the discontinuation of anti-tuberculosis therapy, and only occasionally resulted in the suspension of an agent (11.7%), but this study recorded the occurrence of these adverse effects during the complete treatment period ,unlike in our study where we recorded adverse effects in initial seven days only[17].

In a study in Latvia among 1027 MDR TB cases, 807 (79%) experienced at least one adverse event, with a median of three events per case. The most commonly reported events were nausea (58%), vomiting (39%) and abdominal pain (24%). More serious events, such as psychiatric episodes (13%), hepatitis (9%) and renal failure (4%), were relatively infrequent. This study had concluded that elderly, female patients and those with severe TB disease should be monitored closely ,as they may have more risk of developing these adverse effects[18]. Various factors such as old age, anaemia, MDR-TB medication, overweight/obesity status, and smoking history were found to be independent risk factors associated with anti-tuberculosis adverse drug reactions in a study in Peru[21]. Another study with a large sample size of 995 MDR TB patients reported that patients with poor nutritional status(with BMI >18.5) at the time of diagnosis had greater risk of experiencing side-effects and death, as compared to patients who were normal or overweight[22]. In our study, we found that on 2nd day onwards adverse effects were significantly more in patients who had hemoglobin less than 10 gm%. But we could not find any significant relation of adverse effects with low BMI where 714 (76.8%) patients had BMI < 18.5.

It is expected that the number of patients diagnosed with DR-TB will increase in the near future, and thus the demand for beds will continue to increase, this may result in waiting lists for admission to initiate treatment that may negatively affect treatment initiation, and this delay may expose family and community members to these infectious and untreated patients. An important way to reduce the economic burden due to MDR-TB would be to reduce the time between diagnosing MDR TB through early DST and institution of effective MDR treatment to these patients. The other interventions that may be done are to reduce hospitalization and shifting clinic-based to community-based DOTS for MDR TB patients[23]. Decentralized management of MDR TB has been advocated by policy in Africa also[24], which considers the benefits from it such as; these MDR TB patients are able to better accommodate their personal needs and responsibilities while on treatment ,thereby improving the adherence to treatment as shown in studies following community-based programmes for managing MDR TB[14,15,25-27]. This also reduces the transmission of MDR TB by initiating treatment early; more beds are available for those with complications and seriously ill patients and also improve cost effectiveness by reducing hospital stays in specialized hospitals.

In this study, we limited to monitoring of adverse effects of drugs for initial seven days only and did not study the other advantage of initial hospitalization such as patient and family members counselling and contact examination, which is also an important part of MDR TB management, believing that this aspect may have to be addressed during the whole treatment period and may not be the absolute indication for which MDR TB patients may have to be hospitalized.

The treatment facilities for MDR TB patients is gradually being escalated under RNTCP so that more and more districts are being covered under PMDT programme of RNTCP, with increase in DR TB centre numbers to 92 at present[28], but still **the gap between the estimated total MDR patients and the capacity to treat them is huge, so, it may be difficult in future for poor resource countries such as ours to manage inpatient facilities for these huge number of MDR TB patients. Most of these patients can be managed on OPD basis without making hospitalization for initial seven days as a protocol to start treatment for MDR TB. If need arises later on for hospitalization of patients who develop serious**

adverse effects or complications, they can be hospitalized at DR TB centre, hence resulting in lowering cost of hospitalization per MDR patient and reducing the burden on DR TB centres by decentralization of treatment initiation at district level itself.

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Original Article

STUDY ON PREVALANCE OF DIABETES MELLITUS IN PATIENTS WITH T.B. UNDER DOTS STRATEGY

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Summary

Background: Tuberculosis is five to six times more common among diabetics than among non-diabetics and causes greater morbidity, according to reports. The effective control of each affects the control of the other. Diabetes increases the risk of developing tuberculosis, especially in developing countries with a high incidence of tuberculosis. DOTS strategy has been an effective tool on a mass basis. However, patients under DOTS are not screened for diabetes before the therapy.

Aims & Objectives: To study the prevalence of diabetes mellitus in patients with tuberculosis under DOTS strategy.

Material & Methods: A cross-sectional study was conducted in Santosh Medical College & Hospital, Ghaziabad, with the patients taken from different DOTS centres of NCR-Delhi, India. The present study was undertaken to evaluate the presence of undiagnosed diabetes under DOTS strategy. Fasting capillary blood glucose levels of patients diagnosed with tuberculosis were analyzed and were managed as per DOTS guidelines at multiple centres in the northwest region of India.

Results: We studied 700 patients. The prevalence of diabetes was 12.6% (n=88), which is quite high. When category-wise analysis of diabetic subjects was done, it was found that patients under Category-I were 11.7% (n=47), patients under Cat-II were 15.5% (n=39) and those under Cat-III were 3.9% (n=2). The higher percentage of patients in Cat-II indicates the poor outcome of Cat-I patients, probably due to diabetes as a co-morbid disease.

Conclusion: The higher prevalence of diabetes mellitus in DOTS patients raises immediate concerns in preventing the morbidity due to both the diseases. Therefore, it is recommended that some strategy on the lines of HIV disease should be formed under DOTS for the concomitant treatment of TB and diabetes for better outcome and care. **[*Indian J Tuberc 2014; 61:* 65-71]**

Key words: Diabetes, Tuberculosis, DOTS

INTRODUCTION

Tuberculosis in patients with diabetes is more than that of patients without diabetes[1]. The global burden of diabetes mellitus will be 300 million by 2025. In India, the number of cases of diabetes is estimated to increase from 23 million in 2003 to 57 million in 2025[2]. Reported incidence of tuberculosis in India, as per WHO, in 2008 was 168/100,000 and there are about 28 deaths/lac population in India[3]. The prevalence of diabetes and TB has ranged from 3.6% to 8.4%[4-10].

Active tuberculosis intensifies diabetes mellitus and *vice versa*; thus, the two diseases constitute a dreaded companion.[11] The dual burden of disease may make the management of both conditions more difficult. Using retrospective data, it is found that diabetes co-morbidity exceeded that of HIV/AIDS.[12] Patients with tuberculosis and diabetes were older and more likely to have hemoptysis and pulmonary cavitations, be smear-positive at diagnosis, and remain positive at the end of the first or second month of treatment. The data also suggests that baseline mycobacterium burdens might be higher in diabetic patients than in controls.[13-15] Hence tuberculosis/diabetes cases may be more contagious at diagnosis and for longer periods during treatment.[16] Directly observed treatment, short-course (DOTS) is a strategy under the Revised National Tuberculosis Control Programme (RNTCP), approved by WHO, for the treatment of tuberculosis. It has been an effective tool on a mass basis and according to global report, it is being used successfully in over 202 countries. At present, patients registered under DOTS strategy in India are not screened for diabetes before the initiation of therapy. Effective control of TB and diabetes affects

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the control of the other[15]. The treatment of pulmonary tuberculosis along with the treatment of diabetes is a challenge in the present day scenario as no specific category or guidelines have been laid down to treat the co-existing diseases under DOTS strategy. The present study was undertaken to evaluate the presence of undiagnosed diabetes under DOTS strategy.

Aims & Objectives: To study the prevalence of diabetes mellitus in patients with tuberculosis under DOTS strategy.

MATERIAL AND METHODS

Study Setting

The study was conducted at Santosh Medical College & Hospital, Ghaziabad. It was undertaken to evaluate the presence of undiagnosed diabetes under DOTS strategy. Fasting capillary blood glucose levels of patients diagnosed with tuberculosis were analyzed and were being managed as per DOTS guidelines at multiple centres in the northwest region of India.

Sample Frame

The patients were taken from various DOTS centres in different areas of Ghaziabad (4), Delhi (2) and Noida (3).

Study Unit

All patients attending DOTS centres on the respective day were included in the study. Those patients not attending the DOTS centre on that day were attended at their houses.

Sample Size

700 patients attending DOTS centres in different areas of Ghaziabad, Delhi and Noida (NCR-Delhi-India) were included in this study. The sample size was calculated as per automated method by SPSS Inc.®Chicago 17.0v. An institutional ethical clearance was obtained.

A simple fasting capillary blood glucose level blood sample was taken through a Bayer Ascensia Contour TS® glucometer, which is 97.8% sensitive.[17,18]

Procedure

For patients who came in fasting phase for taking the anti-tubercular drugs, the right/left index finger area was cleansed with antiseptic and pricked with a sharp needle or a lancet and a drop of blood was taken for the capillary blood glucose on the test strip.

Patients with a fasting capillary glucose of >7mmol/L (126mg/dL) were categorized as diabetics based on samples taken through the Bayer Ascensia Contour TS® glucometer, a gold standard test that is 97.8 % sensitive.[17,18]

All those patients who were diagnosed with diabetes were then subjected to HbA1C (glycosylated hemoglobin testing) by enzyme-based enzymatic assay to see their control. Those who were HbA1C > 6% were confirmed to be diabetics (normal range 4.5-6.0%). The same test was conducted in the Department of Biochemistry, Santosh Medical College, Ghaziabad.

Inclusion Criteria

All patients aged >15 years attending DOTS centres on the respective days (Monday , Wednesday, Friday) were included in the study. Those patients not attending the DOTS centre on that day were attended at their houses.

Exclusion Criteria

All patients aged <15 years, hypertensive patients, patients on any corticosteroid therapy as in COPD, asthma or patients in morbid state or with major systemic illnesses were excluded.

RESULTS

The multiple bar diagram (Figure 1) suggests that out of the 700 cases taken up for this study, 428 were males (61.4%) and 272 were females (38.8%), the total number of patients found

diabetic were 88 (i.e. 12.6%). Amongst males, 56 (13.08%) were found diabetic, of whom known diabetics were 15 (26.7%) (12 on OHA and three on Insulin) and females found diabetic were 32 (11.76%), of whom nine (28.125) were known diabetics (six OHA and three Insulin).The total number of diabetics when analyzed was 84 Type II and four Type I.

Of these 88 patients, 24 were already suffering from diabetes and were on irregular treatment (18 on oral hypoglycemic drugs and six on insulin). 64 patients were diagnosed during the course of the study (Figure 1 and Table 1).

Of the 700 patients, 398 (56.9%) patients were under Category I, while 251(35.9%) patients

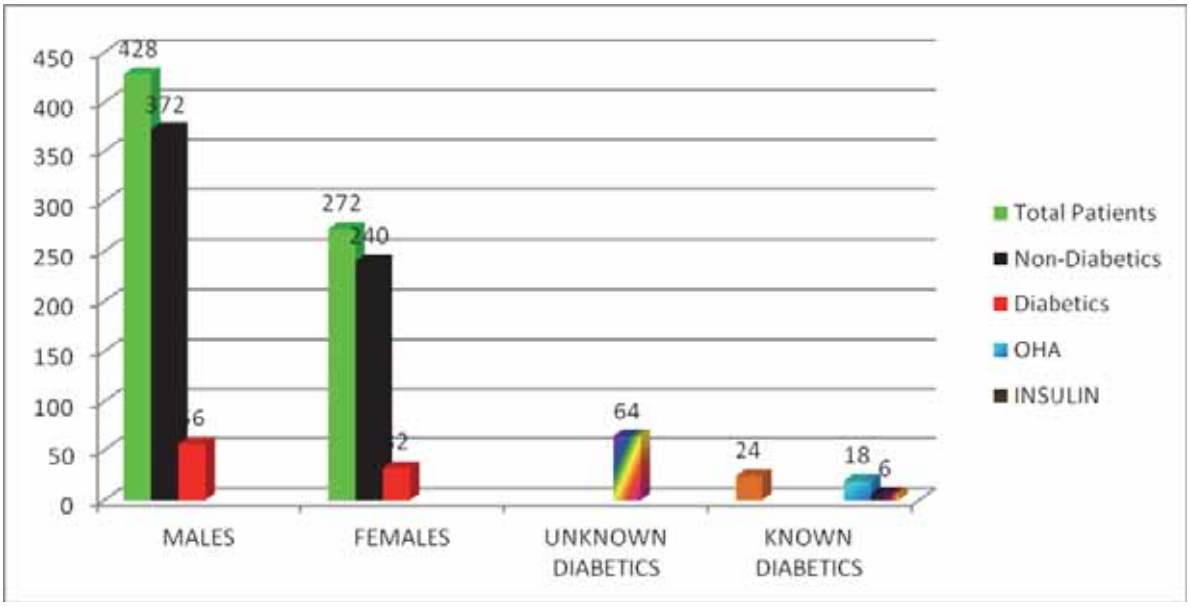

Fig. 1: Sex-wise total patients under study and their known and unknown diabetic status

Table 1: Sex-wise distribution of patients into diabetics and non-diabetics

	Males	Females	Total Patients
Total	428	272	700
Non-diabetics	372	240	612
Diabetics	56	32	88
Freshly diagnosed diabetics	41	23	64
Known diabetics	15 (12 OHA+3 INSULIN)	9 (6 OHA+3 INSULIN)	24 (18OHA+6 INSULIN)

were under Category II, and 51(7.2%) patients were under Category III. When category-wise analysis of diabetic subjects was done, it was found that patients under Category-I were 47 (11.8%), patients under Cat-II were 39 (15.5%) and those under Cat-III were two (3.9 %) (Figure 2 and Table 2).

DISCUSSION

Currently, an epidemic of diabetes is seen both in developed and developing nations. In India, the number of diabettics is estimated to increase from 23 million in 2003 to 57 million in 2025. Reported incidence of tuberculosis in India, as per WHO in 2008, is 168/100,000 and there are about 28-deaths/lac population in India. In 2001, Ramachandran *et al*[19] (in India) and Alfredo Pone de leon *et al*[20] (in Mexico) found Pulmonary Tuberculosis (PTB) to be five to six times more common among diabetics than non-diabetics and causes greater mortality.

In our cross-sectional study of DOTS subjects, out of 700 patients, the prevalence of diabetes was 12.6% (n=88).

Several previous studies on the prevalence of both diabetes and tuberculosis together were conducted before the initiation of RNTCP. A comparison of previous studies with the present study on the prevalence of diabetes and tuberculosis together is shown in Table 3.

The higher prevalence in the present study can be explained by the large number of patients in CAT II, i.e. 39 patients (15.5%) of the total, who had diabetes mellitus and could be the reason for failure under Cat I. Alisjahbana B, *et al*[21]. also suggested that there is a delay in sputum conversion of diabetics *versus* non-diabetics. This has also been supported by Banu Rekha VV, *et al*[22] and Guler M *et al*[23]. They have all suggested a 7-10-day delay in sputum conversion.

Table 2: **C**ategory-wise diabetic patients

Category I (n=398) 56.9%	47 (11.8%)
Category II (n=251) 35.9%	39 (15.5%)
Category III (n=51) 7.2%	02 (3.9%)
Total (n=700) 100%	88 (12.6%)

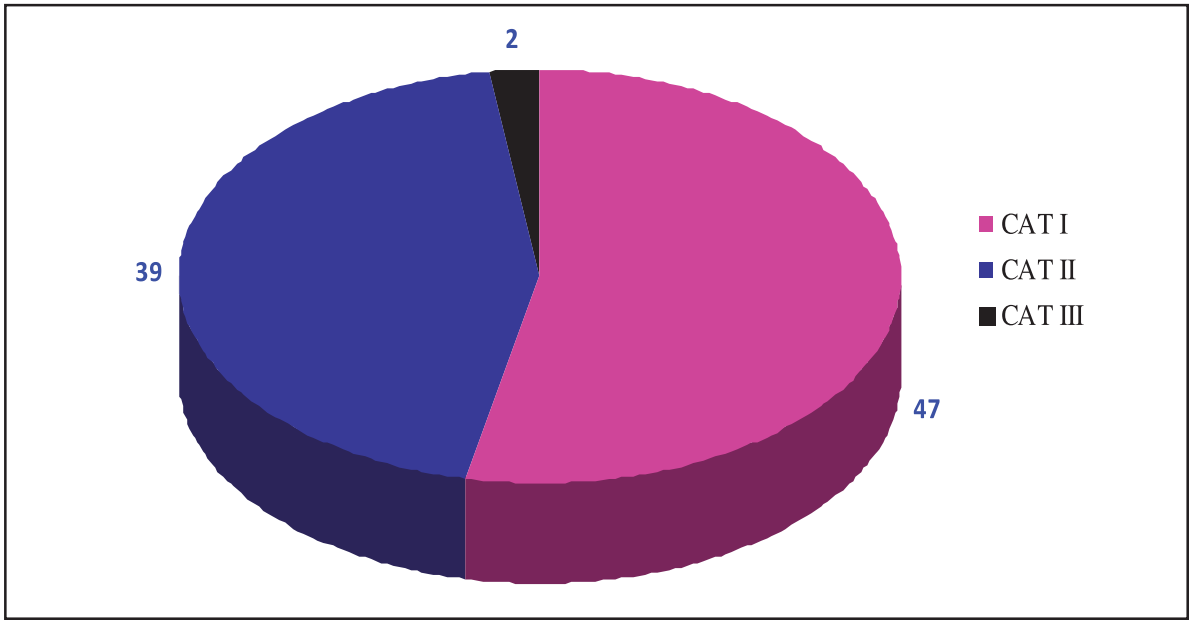

Fig. 2: Category-wise analysis of diabetics under DOTS

Table 3: Comparison of previous studies with the present study on the prevalence of diabetes and tuberculosis together

Study	Year	Prevalence of DM & TB %
Boucot *et al*[4]	1952	8.4%
Oscarsson and Silwer[5]	1958	3.6%
Davidovich *et al*[6]	1963	4.0%
Nanda and Tripathy[7]	1968	4.11%
Lahiri and Sen[8]	1974	5.2%
Bahulkar and Lokhandwala[9]	1975	5.4%
Ezung *et al*[10]	2002	6.0%
Present Study	2013	12.6%

When the study was subjected to HbA1C, it showed a poor glycemic control, more so in Category II patients. It is reported that strict glycemic equilibrium is essential for the success of anti-tubercular therapy among diabetes-tuberculosis patients [24].

Studies on the prevalence of diabetes with tuberculosis in DOTS are lacking in literature. In this present study, we observed that the prevalence of diabetes in tuberculosis was 12.6% in DOTS patients. The figure seems to be quite high compared with earlier individualized studies, which vary from 3.6% to 8.4%. Data regarding patients in India suffering from both the diseases concomitantly under DOTS is lacking. Recent systematic reviews[25] suggest that Type 2 diabetes mellitus increases individual risk of *Mycobacterium tuberculosis* (TB) disease. Country-level analysis suggests that TB prevalence is mediated both by social determinants and public health strategies[26,27]. Yet, strikingly little work has been done to assess the relationship between TB and diabetes at the individual level in countries where TB prevalence is the highest and diabetes prevalence is rising rapidly.

An increasing prevalence of diabetes may counteract the positive effects of improved curative services for TB. Globally, the incidence of tuberculosis is declining very slowly, and the non-communicable disease (NCD) burden for many countries is steadily increasing.[28] Speeding up the decline in incidence will require both scaling up of diagnostic and curative services and additional preventative action, including addressing diabetes and other risk factors that increase the individual's susceptibility to TB.[29]

Out of the 700, the total number of patients in CAT- I was 398, 251 in Category II and 51 in Categary III. When category-wise analysis of these 88 diabetic subjects in this study was done, it was found that patients under CAT-I were 47 (11.8%), under Cat-II 39 (15.5%) and under Cat-III two (3.9 %) (Fig. 2). There is paucity of data regarding the outcome of treatment among TB patients with associated diabetes. Pabloz Mendes *et al*[30] have also suggested that the adverse effects of diabetes on the treatment outcome of TB patients may result in an increased rate of failures, deaths, defaults and relapses.

Mortality rates in these patients are reported to be several times higher than in non-diabetic pulmonary TB patients and the pattern of tuberculosis in diabetics differed from non-diabetics[31]. Diabetic patients were 8.6 times as likely to have infection with a multidrug resistant strain of tuberculosis.

It was also highly noticeable that out of those 88 patients, only 24 knew that they were suffering

from diabetes and were on irregular treatment (18 on oral hypoglycemic drugs and six on insulin) all in Cat-I. The rest 64 patients (73.5%) were diagnosed during the course of our study (Fig. 1).

Type 2 DM may be the sleeping giant of TB. The sheer number of patients who have type 2 DM and exposure to TB may have significant global impact. One of the reasons for high CAT-II patients (15.5%) in the present study could be that patients were having undetected diabetes and were not screened, leading to delayed sputum conversion and failure. Diabetes also impacts TB by tripling the rate of development of active TB from latent TB infection, increasing the mortality and severity of the disease and slowing the response to effective TB treatment.[32] Oursler KK, *et al.* in their study based on clinical and molecular epidemiologic factors in patients' survival rate suggested that only diabetes and renal disease remained independent predictors of death[33]. Due to its increasing co-existence, along with lack of detection, initiating anti-tubercular therapy (ATT) in diabetics is a challenge. Those diabetics, who finally do not respond well to ATT, may have higher chances of MDR TB than non-diabetics.

Bashar M, *et al* suggested that 36% of the patients with diabetes and TB had MDR-TB, compared to only 10% in the control group.[34] Fisher-Hoch SP *et al* in their study found that Type 2 DM was significantly associated with MDR-TB in a univariate analysis (OR 1.76 95%CI 1.15–2.70)[35]. Alisjahbana B *et al* in a study carried out in the Texas border population found that multi-drug resistant TB (MDR-TB) was associated with DM with an odds ratio of 2.1[35]. Suárez-García *et al* have also suggested that diabetes is also one of the most important risk factors for multi-drug resistant tuberculosis in a tuberculosis unit in Madrid, Spain.[36]

It has been observed that the prevalence of diabetes will continue to rise rapidly in developing countries, driven by changes in diet, lifestyle and globalization[37]. India, China, Indonesia, Pakistan and Brazil alone are projected to carry nearly half the world's diabetes burden[37]. In many countries, TB epidemics continue, fuelled by drug resistance[38], HIV/AIDS[39,40] and social inequalities[41]. The impact of diabetes/TB interaction may play a substantial role in fuelling the ongoing TB epidemic in India[42].

In view of the high prevalence of diabetes mellitus, it is recommended that a Gold Standard Screening programme for diabetes should be incorporated under DOTS so that early diagnosis and treatment can be done to avoid morbidity and failure of Category-I patients under DOTS.

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Case Report

MULTI-DRUG RESISTANT NON-TUBERCULOUS MYCOBACTERIA INFECTION IN A NON-HIV INFECTED CHILD

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Summary: Non-tuberculous mycobacteria (NTM) are widely dispersed in our environment. Pulmonary disease, lymphadenitis, skin and soft tissue infections, bone and joint infections and disseminated infections are common clinical syndromes in immuno-compromised patients. NTM infections are frequently overlooked in developing countries like India with endemic TB due to non-specific clinical manifestations, unfamiliarity of clinicians with mycobacteria, and inadequacy of laboratory services. Here we report a case of multidrug resistant (MDR) pulmonary NTM infection in a non-HIV infected child and her response to therapy. **[*Indian J Tuberc 2014; 61:* 72-74]**

***Key words*:** Non-Tuberculous mycobacteria, Atypical mycobacteria, NTM, Children

INTRODUCTION

Non-tuberculous mycobacteria (NTM), also referred to as atypical mycobacteria, are members of the family of mycobacteria. These are opportunistic pathogens ubiquitously found in soil, water, milk, dust and are thus acquired from environmental sources, and rarely transmitted from humans[1]. Pulmonary disease, lymphadenitis, skin and soft tissue infections, bone and joint infections and disseminated infections are common clinical syndromes in immuno-compromised patients, with cervical lymphadenitis being the most common presentation in immuno-competent children[2]. The estimated annual incidence of NTM infection was 77 cases per 100,000 children[3]. Here we report a pulmonary infection in a non-HIV infected child.

CASE REPORT

An 11-year-old girl presented with fever, cough and chest pain for seven days and one episode of haemoptysis in December 2010. She was already on antituberculous therapy (ATT) from October 2010 in view of left lower consolidation. She had also received ATT in 2009 for six months (details of which are not available). There was no contact with a patient suffering from TB. She had no other illness in the past. On examination, she had left-sided crepitations with bronchial breathing. Her X-Ray chest in December 2010 showed left lower zone consolidation with cavity. Her sputum smear showed 3+ acid fast bacilli (AFB) on all three smear specimens. She was thus started on additional drugs of PAS, Ethionamide, Ofloxacin and Amikacin in addition to Isoniazid (H), Rifampicin (R), Ethambutol (E) and Pyrazinamide (Z) which she was already on since October 2010. In January 2011, her TB culture grew rapidly growing NTM resistant to INH, Rifampicin, TMP-SMX, Ciprofloxacin, Moxifloxacin, Doxycycline, Imipenem, Cefepime, Amoxicillin-Clavulanic acid, Ceftriaxone and Minocycline with intermediate sensitivity to Cefoxitin and sensitive to Amikacin, Clarithromycin, Linezolid and Tobramycin. She was then continued on Amikacin, Ethambutol and Linezolid and Clarithromycin were added. Other anti-TB drugs were stopped. Molecular diagnosis of species identification could not be done due to non-availability at that time. HIV ELISA was negative, sweat chlorides and echocardiography were normal. Interferon gamma and IL – 12 pathway deficiency could not be tested in the child due to non-availability. Sputum production stopped after one month of therapy and subsequent sputum testing could not be done. Amikacin was stopped after six months of therapy and she was given remaining drugs for 18 months.

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Current chest x-ray is normal. The child had no adverse effects on therapy. The child is still on follow up and is doing well.

DISCUSSION

The isolation rate of NTM from India has been reported ranging from 0.5 to 8.6 %[4]. NTM infections have been overlooked in developing countries like India with endemic TB, due to non-specific clinical manifestations, unfamiliarity of clinicians with mycobacteria and inadequacy of laboratory services[4]. The International Union against Tuberculosis and Lung Diseases (IUATLD) reviewed data from 14 HIV-TB endemic countries and found that *M. avium* complex (MAC) was the most frequently isolated species in all these countries, which included China, India, and Korea[5] though reports in children are lacking. Lymphadenitis is the most common manifestation of NTM infection in children[6]. Pulmonary infections are the most common forms of NTM infection in adults, but are rare in children[7]. The common species producing pulmonary infections include MAC, *M. kansasii, M. abscessus,* and less common species include *M. xenopi, M. malmoense, M. szulgai, M. fortuitum, and M. simiae.* Four main categories of pulmonary diseases are encountered. First, the disease occurs in middle aged or elderly persons, usually men with a history of lung disease. Second, disease occurs in otherwise healthy persons, although some may have minor or overt immune defects or predisposing pulmonary disease, notably, cystic fibrosis. Third, hypersensitivity pneumonitis (HSP) due to various species of NTM has now been well described usually in relation to aerosols of water including household water, medicinal baths, pools, hot-tubs ('hot-tub lung') and metal working fluids. Fourth, disease occurs in profoundly immuno-suppressed patients, of which HIV infection is the prevalent cause worldwide[8]. Our patient did not have cystic fibrosis or HIV infection nor a chronic lung disease suggestive of NTM infection in an immuno-competent child. A high incidence of mostly disseminated NTM disease has been observed in children with interferon gamma and IL – 12 pathway deficiency[9]. Interferon gamma and IL – 12 pathway deficiency could not be tested in the child due to non-availability.

Though, culture remains the diagnosis of choice, newer molecular methods for identification of NTM include PCR and DNA fingerprinting methods which are used to identify subtypes/ strains[10]. The presence of NTM in respiratory samples, in isolation,is insufficient to establish the diagnosis. As defined by expert consensus[11], the diagnosis of symptomatic disease due to NTM is based upon a constellation of clinical, radiographic, and bacteriologic findings. The presence of pulmonary symptoms, compatible radiographic abnormalities including nodular or cavitary opacities or bronchiectasis, appropriate exclusion of other diagnosis, and bacteriological evidence of NTM are all required to establish the diagnosis[12]. Since our patient had 3+ AFB on all three smear specimens, had a cavity on chest X-ray and responded to treatment given as per sensitivity report of NTM report , did not grow any other organism on sputum culture, the active disease was most likely due to NTM.

Though most strains of NTM respond to clarithromycin, drug sensitivity profile of NTM is quite different from mycobacterial tuberculosis (MTB). Firstly, they are sensitive at usually higher concentrations of antitubercular drugs. Secondly, rapidly growing mycobacteria are usually resistant to rifampicin and INH, whereas they are sensitive to drugs like macrolides, cephalosporins and sulphones. Newer techniques like BACTEC and E test have also been found to be quite useful for identification of rapid as well as slow growers[10]. Similarly, our patient showed resistance to multiple drugs but remained susceptible to macrolides, ethambutol and aminoglycosides.

Among the macrolides, most studies have focused on clarithromycin[13]. Azithromycin was less effective in a similar study[14]. However, the most potent combination regimen has yet to be decided. The 2007 American Thoracic Society/ Infectious Diseases Society of America guidelines have recommended i) Clarithromycin/ Azithromycin, ii) rifampin/ rifabutin and iii) ethambutol for treatment

of MAC nodular, or bronchiectatic pulmonary disease, and daily dosing of the above mentioned medications in case of fibro-cavitary disease[7]. Patients whose isolates become macrolide resistant would require parenteral amikacin or streptomycin. Sputum cultures should be obtained monthly to monitor efficacy[7]. Treatment should be continued until sputum cultures are consecutively negative for one year. Our patient was started on amikacin, clarithromycin, ethambutol and linezolid in view of multidrug resistance. She has responded well to therapy. **The best available regimens used in clinical trial settings, would suggest that 90% clinical response rates for *M. kansasii* treatment, 70% for MAC, 90% for *M. malmoense* and 45% for *m. xenopi* pulmonary infections can be achieved by adhering to evidence regimens[15].**

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Case Report

VENTRAL HERNIATION DUE TO TUBERCULOSIS AT SPACE OF RETZIUS: A RARE PRESENTATION

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Summary: Tuberculosis may involve any organ in the body[1] and extra-pulmonary tuberculosis is commonly seen in immuno-compromised patients[2-4] mostly in developing countries. Here we report an unusual case of tuberculosis of space of retzius (pre-peritoneal space) forming a lump, this lump caused weakness of anterior abdominal wall which later developed ventral hernia, corrected by surgery in a 62-year immuno-competent person. This type of presentation of extra-pulmonary tuberculosis at space of Retzius has been rarely reported[2,5]. **[*Indian J Tuberc 2014; 61:* 75-78]**

Key words: Extra-pulmonary, Tuberculosis, Ventral hernia, Pre-peritoneal space.

INTRODUCTION

Tuberculosis may involve any organ in the body but involvement of abdominal muscle/skeletal muscle is very uncommon[1]. Autopsy studies have shown abdominal wall involvement in less than 1% of patients who died of tuberculosis[2]. Extra-pulmonary tuberculosis is commonly seen in immuno-compromised (HIV seropositive) patients[3,4] mostly seen in developing countries. Here we present an unusual case of tuberculosis of space of retzius (pre-peritoneal space) and this leading to anterior abdominal wall weakness which later on developed hernia which needed surgical correction in a 62-year immuno-competent person. This type of presentation of extra-pulmonary tuberculosis has been reported rarely in English language peer-reviewed literature[2,5].

CASE REPORT

A 62-year-old gentleman, retired postman noted an ill-defined painless swelling over hypogastric region extending up to left groin for the last four months (Figures 1A & B). This was associated with intermittent low grade fever especially at evening hours for the last five months. It was very small painless swelling to start with and then it gradually increased in size and became mildly painful. It did not increase on coughing or strenuous work. There was no history of tuberculosis in neither family members nor in the locality, no history of recent weight loss. He had a history of left-sided inguinal herniorraphy 12 years back.

On examination, average built person had got a mildly tender firm swelling of 6 X 4 cm size over hypogastrium (more on left side) with restricted mobility in both horizontal and vertical directions. Skin over the swelling was not fixed with the swelling. There was no cough impulse. On leg raising test, it mildly diminished on size but did not disappear completely. Other systemic examinations were within normal limits. On Ultrasonography, it had got no intra abdominal connection, however origin could not be delineated properly. Computed tomography had shown it to be non-enhanced multiseptate, multiloculated space occupying lesion with variegated appearance antero-inferior to the bladder reaching below symphysis pubis with erosion of right pubic bone (Figure 1C). On CT guided fine needle aspiration (FNAC), it proved to be of tubercular in origin, caseous necrosis with acute and chronic inflammatory cells and epithelioid cells (Figure 1D).

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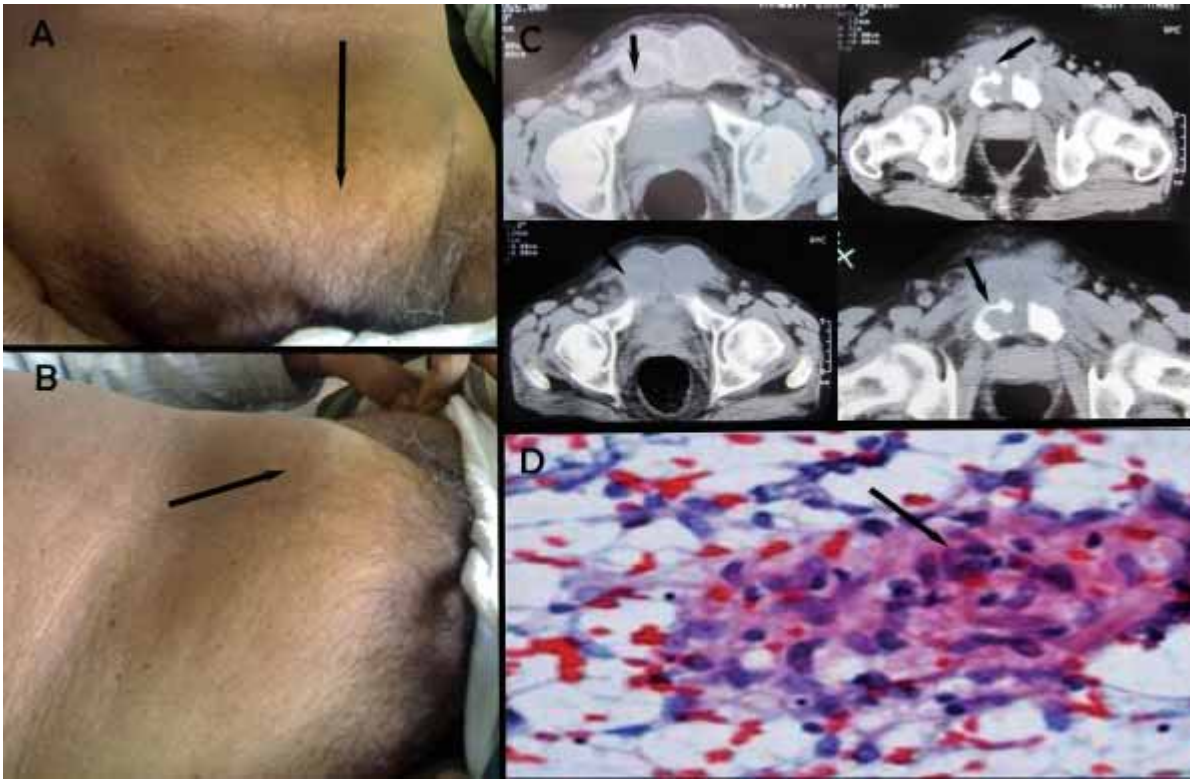

Figure 1
1A & B - Initial presentation of the patient with the lump at hypogastrium region.
1C - Computed tomograph of the lower abdomen showing lump – origin and erosion of pubic bone (pointer arrow) at four different sections.
1D - FNAC from the lump showing epitheloid cell granuloma with lymphocytes (Giemsa Stain, X40) [pointer arrow].

However, on ZN Stain, no AFB (acid fast bacilli) were found on the aspirate. Chest X-Ray, routine haematological tests, mantoux test, HIV I and II tests were within normal limits.

He was given Cat I Anti Tubercular Treatment (ATT) according to national programme for six months (isoniazid 600 mg, rifampicin 600 mg, pyrazinamide 1500 mg and ethambutol 1200 mg- each thrice in a week for the first two months; isoniazid 600 mg, rifampicin 600 mg- each thrice in a week for the next four months;— total six months' ATT). During the course of ATT, the swelling regressed. But after two months of completion of ATT, the patient came with a bulging in the same region, which increased due to strenuous activities and coughing. On examination, there was a reducible swelling over hypogastrium just left to midline and 1 cm above the left pubic bone with positive cough impulse. Repeat CT scan revealed it to be herniation of omentum through anterior parietal wall defect (4.34 X 3.17cm) at left pubic region (Figures 2A & B). Repair of the ventral hernia with prolene mesh placement was done. Hernial opening (0.5 X 1 cm) was found at anterior rectus sheath just above the left inguinal canal. During the surgery, one inguinal lymph node was suspicious and it was taken out for histopathogical examination. On histopathological test, this lymph

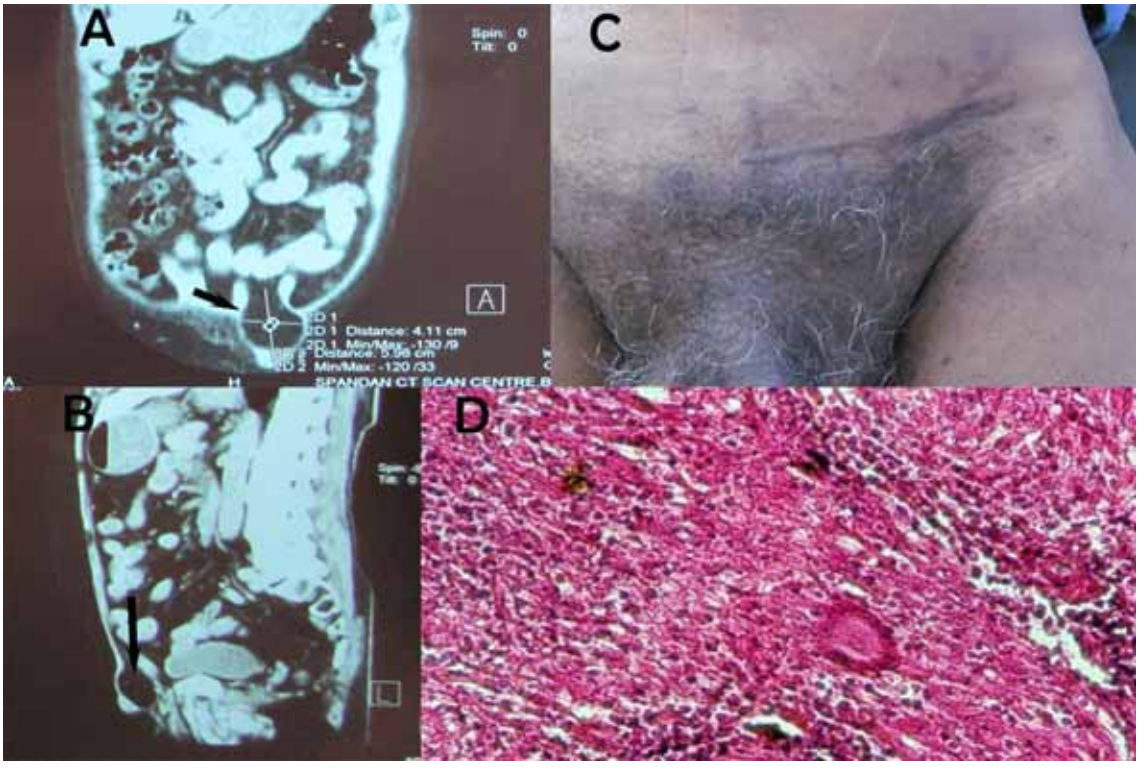

Figure 2

2A & B - Computed tomograph of the lower abdomen of patient at second presentation showing herniation of omentum through the gap at anterior abdominal wall (pointer arrow). A - antero-poterior view, B - lateral view.

2C - Post-operative photograph of the patient's hernia site after completion of ATT on follow up visit.

2D - Histopathology of excised lymph node showing features of tubercular lymphadenitis - epithelioid granuloma, caseous necrosis, Langhan's giant cells (Hematoxylin & Eosin stain, X200).

node showed features of tubercular lymphadenitis (Figure 2D).

Therefore, he was given Cat II ATT according to national programme (streptomycin 500 mg, isoniazid 600 mg, rifampicin 600 mg, pyrazinamide 1500 mg, ethambutol 1200 mg - each thrice a week for two months; isoniazid 600 mg, rifampicin 600 mg, pyraziminde 1500 mg, ethambutol 1200 mg - each thrice a week for the next one month; isoniazid 600 mg, rifampicin 600 mg, ethambutol 1200 mg - each thrice a week for the next five months - total eight months therapy) and is doing well without any recurrence on one year follow up visit after the completion of ATT (Figure 2C).

DISSCUSSION

The common sites of extra-pulmonary tuberculosis are Lymphadenopathy, Pleural effusion, bone and joint involvement, intestinal disease, pericardial, meningitis and milliary disease[6]. The involvement of skeletal muscle/abdominal wall musculature is very rare. Possible explanation for this rarity of muscle involvement in tuberculosis may be high lactic acid content, lack of reticulo-endothelial tissue, relative lack of lymphatic tissue, abundant blood supply and highly differentiated state of muscle tissue[1,2,7,8]. Petter[8] recorded only one case of primary muscular involvement of tuberculosis in over 6000 cases of all types of tuberculosis and Culotta[9] found

only four cases in his 2224 autopsies. On the other hand, preperitoneal space contains only loose areolar tissue, thus theoretical chance of TB bacilli infection is very less.

Tuberculosis can affect any organ in the body, especially in endemic areas. The incidence of extra-pulmonary tuberculosis is rising with increasing incidence of immuno-compromised states like AIDS. However, in our case, the person was immuno-competent, and no other tubercular foci could be discovered and that is why it is a very rare case. Tuberculosis can involve skeletal muscle from bone, synovial joints or tendon sheaths; by mainly three ways - A) direct inoculation by any means; B) lymphatic spread from primary foci; C) rarely haematogenous spread[1].

A tuberculous focus in the muscle/any tissue in closed space usually manifests as swelling and pain; infection is usually restricted to single muscle, several muscles involved rarely[10,11]. There may be frank abscess formation or nodular sclerosis followed by calcification[10]. It must be remembered that all atypical extraosseous extra-pulmonary presentations may be caused by florid disseminated tuberculosis, as was reported by Batra *et al*.[12]. Hence other diagnostic tests (X-rays, sputum examination, Blood tests, etc.) must be performed to rule out pulmonary and osseous involvement[13].

Diagnosis is very difficult, strong clinical suspicion and tissue diagnosis by FNAC and/or incisional biopsy is the mainstay[13]. **With effective ATT, the disease responds very well to the medical treatment. However large abscess may need drainage and there are also cases of multi drug resistant variety of tubercle bacilli (MDR TB)[13,14].**

On the literature search, we found only one report in 1971, that showed tuberculous abscess at space of Retzius, although presentation was dystocia in a female patient[5], unlike our presentation. **Here we saw tuberculosis affecting preperitoneal space (space of Retzius) leading to lump formation and poorly responded to ATT due to possible poor blood supply and leading to local weakness of adjacent fascial structure (here, anterior abdominal wall), thus resulting in hernia formation which needed surgical correction and ATT.**

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Case Report

A RARE CASE OF PRIMARY TUBERCULOUS OSTEOMYELITIS OF SKULL VAULT

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***Summary*:** In recent years, there has been a substantial increase in number of reports involving uncommon sites involving in tuberculosis. Rise in number of HIV positive patients has made the scenario worse. Calvarial tuberculosis has been reported very rarely in world literature till now. We are reporting a case of primary tuberculous osteomyelitis of frontal bone in a 15-year-old female. With prompt as well as careful diagnostic workup and treatment, we were able to halt the disease progression and excellent response to treatment was observed in follow up. **[*Indian J Tuberc 2014; 61:* 79-83]**

Key words: Calvarial tuberculosis, Tuberculous osteomyelitis of frontal bone, Tuberculous osteomyelitis skull vault, Primary extra-pulmonary tuberculosis.

INTRODUCTION

Occurrence of tuberculous osteomyelitis is about 1-6% among all cases of extra pulmonary tuberculosis[1]. Primary tuberculosis of skull vault is an extremely rare presentation[1] among cases of primary extra-pulmonary tuberculosis. Only a few cases of primary tuberculous osteomyelitis of skull vault have been reported in the world till now. Although precise aetiology behind rare incidence of calvarial tuberculosis (TB) is largely undefined, the peculiar pattern of blood supply in flat bones is sometimes implicated in causation of this rarity[2]. We are reporting the case of a patient, who presented with a chronic discharging sinus along superior orbital margin.

CLINICAL RECORD

A 15-year-old female presented in Department of TB & Chest Diseases, S. N. Medical College, Agra (Uttar Pradesh) with painless chronic discharging sinus along left superior orbital margin (Figure 1).

On detailed history taking, patient revealed that she was started with treatment by a general practitioner for a boil over affected area about four months back. With ongoing treatment, an obstinate discharging sinus appeared over the affected area which did not resolve even after continuing broad spectrum antibiotics for the next few months. The patient also gave history of low grade fever but there was no history of cough,

Figure 1: Fifteen-year-old female with chronic discharging sinus along left superior orbital margin

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breathlessness, loss of appetite and weight loss. There was no history of steroid intake by the patient.

On examination, the opening of sinus was found to be in the mid of left superior orbital margin, just beneath the overlying orbital ridge of frontal bone. Base of sinus was non-tender, on pressing around which, a few drops of cheesy material were extruded. Rest of systemic examination including chest was totally unremarkable except a 1 cm sized and freely mobile left post auricular lymph node, which was non-tender.

All routine blood investigations were within normal limits, except ESR which was 26 mm in first hour (Wintrobe's method). Mantoux test read 22 mm. Patient was Elisa for HIV I & II non-reactive. There was no history of diabetes mellitus or any such finding suggestive of any immuno-compromised status of the patient. No pleuro-parenchymal disease was noted on chest X-ray PA view of the patient (Figure 2).

Under full aseptic precautions, a blunt ended canula was inserted through sinus tract and 0.5 ml of pus was drawn {pus was subsequently found to be positive for Acid Fast Bacilli (AFB) in culture} followed by local contrast administration through canula. Sinograms were obtained which on Posterior antero (PA) and lateral views showed the contrast coursing through the orbital wall with irregular intracranial spillage (Figure 3).

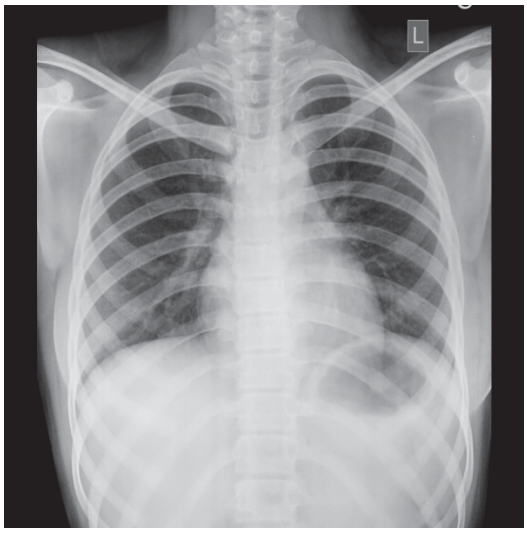

Figure 2: Chest X-ray PA view of the patient with no obvious pleuro-parenchymal disease

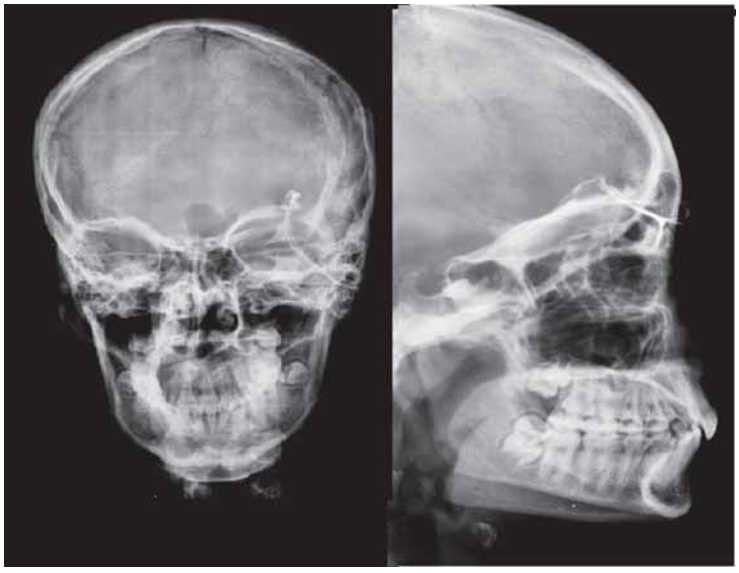

Figure 3: X-ray sinograms PA and lateral views showing sinus tract outlined by contrast extending through superior orbital bone defect with intracranial spillage

Pre-sinogram Non-Contrast Computed Tomographic (NCCT) Scan of head showed evidence of an irregular osteolytic defect along the roof of left orbit laterally with increased thickness and sclerosis of the orbital vault supero-medially. Post sinogram (after the removal of canula) CT showed the contrast within orbital roof along the soft tissues and within the defect with irregular pooling along osteolyzed inner vault in basi-frontal region (Figure 4).

MRI (Magnetic Resonance Imaging) findings revealed plaque like sclerosis along thickened skull vault involving inner and outer tables and intervening diploic space in left frontal region supero-laterally (Figure 5).

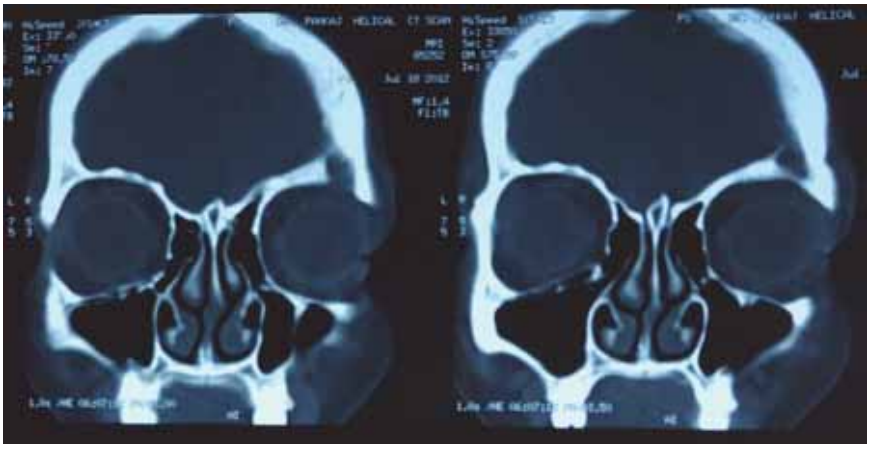

Figure 4: Pretreatment coronal non-contrast and post contrast axial CT sections revealing sclerotic thickening of left superior orbital wall surrounding a lytic area through which sinus tract is outlined by contrast extending in extra cerebral intracranial anterior frontal region with thickening of adjacent frontal skull vault

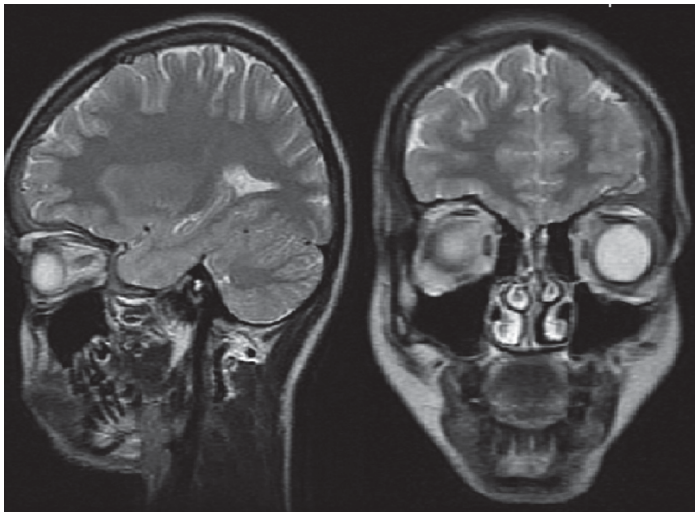

Figure 5: T_2 sagittal and coronal MRI sections corroborating the fluid signal hyper intense sinus and organized hypo intense epidural soft tissue displacing the dural margin without any intra cerebral signal abnormality

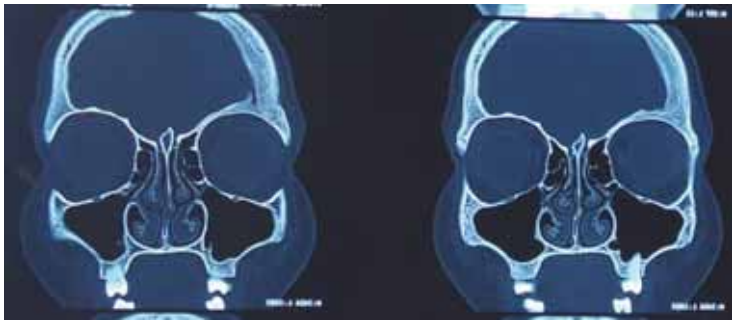

Figure 6: Post-treatment corresponding coronal CT sections (four months later) showing near total resolution of epidural soft tissue, lytic sinus tract with persistent sclerosis of superior orbital and frontal skull vault

On the basis of history, clinical presentation, Mantoux test and peculiar radiological findings, a presumptive diagnosis of chronic (primary) tuberculous osteomyelitis of frontal vault was made, which was confirmed by detection of AFB in pus culture (sensitive to all first line anti tuberculosis drugs).

The patient was put on World Health Organization (WHO) recommended 'directly observed treatment short course (DOTS) category-1' anti tuberculosis treatment (ATT) under Revised National Tuberculosis Control Programme (RNTCP). Patient showed considerable improvement during the first four weeks of treatment (fever and pus discharge subsided completely). A repeat CT scan was done after continuing the same treatment for four months which showed remarkable improvement (Figure 6). The patient is doing well in follow up and her treatment is continued.

DISCUSSION

The first case of calvarial TB was reported in 1842 by Reid *et al*. Among all the reported cases till now, about 70-90% patients were less than 20 years' old[3-5]. In majority of cases, the primary lesion lies elsewhere in body (lungs being the most common site)[6].

To the best of our knowledge, the present case is the first of its kind where direct evidence of AFB was found in the pus of a patient of primary tuberculous osteomyelitis of frontal bone.

Swelling and localized pain are the common early clinical presentations in tuberculous osteomyelitis of skull bones. Chronic discharging sinus may be a late manifestation. Other constitutional symptoms of TB are far less common unless there is co-existing pulmonary involvement. Important differential diagnosis may be eosinophilic granuloma, tumour and pyogenic osteomyelitis[7].

Radiological investigations like CT and MRI are particularly important in defining the extent of involvement of bony and soft tissue structures. However, diagnosis must be confirmed with staining/culture for AFB. Biopsy may be needed to confirm the diagnosis (by showing granuloma and/or caseation) where direct evidence of TB (by staining/culture) is absent. Mycobacterial DNA detection by PCR in paraffin-embedded tissue has also been used previously for aiding the diagnosis[8].

A possible explanation to causation of disease in this case may be direct inoculation of tubercle bacilli in a pre-existing skin lesion. Although far less common, this form of tuberculosis has been described in literature[9].

Main stay of treatment of calvarial tuberculosis is conservative with ATT. Surgical

intervention was considered to be the main line of treatment before advent of anti-TB drugs[10]. However, surgery should be considered in cases with large extradural collections causing neurological deficit or in cases with widespread secondary infection due to sinus formation[11]. We have successfully opted for conservative management with close follow up of the patient. Although sequestra of tuberculous osteomyelitis is supposed to be absorbed by adequate ATT, surgery can be considered as part of treatment plan if patient is not improving in the first four-six weeks of ensuing treatment.

CONCLUSION

Reports of involvement of rarer sites by tuberculosis are continuously pouring in, particularly after the rise in number of HIV cases all over the world. **Tuberculosis of skull vault must be considered in the differential diagnosis when a chronic infective pathology is suspected as timely intervention can save the patient from impending serious neurological complications or death. Successful treatment outcome in this case, further establishes the usefulness of WHO recommended DOTS treatment in rare extra-pulmonary forms of tuberculosis.**

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Case Report

THYROID TUBERCULOSIS: PRESENTING SYMPTOM OF MEDIASTINAL TUBERCULOUS LYMPHADENITIS - AN UNUSUAL CASE

Shirish S. Chandanwale[1], Archana C. Buch[1], Shruti S. Vimal[2] and Punita Sachdeva[3]

(Received on 4.3.2013; Accepted after revision on 10.9.2013)

Summary: Tuberculosis of thyroid gland is extremely rare. It spreads to thyroid by lymphogenous or heamatogenous route or from adjacent focus, either from larynx or cervical and mediastinal adenitis. We report an unusual case of a 33-year-old male with thyroid swelling. Fine needle aspiration (FNA) smears showed epithelioid cells without necrosis and acid fast bacilli (AFB). Subsequent investigation revealed mediastinal tuberculous lymphadenitis on Computerized Tomography (CT) scan. FNA confirmed the diagnosis of mediastinal tuberculous lymphadenitis. We conclude, when epithelioid cells are seen on FNA thyroid, tuberculosis must be ruled out especially in regions where there is high prevalence of tuberculosis. **[*Indian J Tuberc 2014; 61:* 84-87]**

Key words: Thyroid, Epithelioid, Tuberculosis, Lymph node

INTRODUCTION

Tuberculosis is a world-wide problem. It is estimated that approximately eight to ten million new cases and two to three million deaths occur due to tuberculosis every year. One third of all new cases of tuberculosis are in India and China.[1] Extra-pulmonary tuberculosis is on the rise world wide . Tuberculosis of the thyroid gland was first reported in 19th century. Primary or secondary thyroid tuberculosis is extremely rare even in countries with high prevalence of tuberculosis.[2] There are approximately 200 cases of thyroid tuberculosis reported in medical literature.[3]Tuberculosis spreads to thyroid by lymphogenous or haematogenous routes or from adjacent focus, either from larynx or cervical and mediastinal adenitis.[4] In patients of thyroid tuberculosis, signs of tuberculosis in the body are rarely found. [5] To the best of our knowledge, this is the first case of thyroid tuberculosis which is the presenting symptom of tuberculous mediastinal lymphadenitis.

CLINICAL RECORD

A 33- year-old male came with complaints of right thyroid swelling and dysphasia since 15 days. He gave history of fever on and off and weight loss since one month. There was no other significant medical history. On local examination, lower part of right thyroid lobe was enlarged and moved with deglutition. There were no palpable lymph nodes in the neck. Ultrasonography (USG) of the thyroid gland revealed a hypoechoic lesion measuring 1.2x 0.9 cm in the right lobe. Two small lymph nodes measuring 0.6x0.4cm each on same side were noted along the internal jugular vein. Routine hematological investigations were within normal range except increase in erythrocyte sedimentation rate (ESR) to 32 mm/1 hour. Free T 4 and thyroid stimulating hormone (TSH) were within referral range. Levels of antithyroglobulin and anti-thyroid peroxides antibodies were normal. Provisional clinical diagnosis of solitary thyroid nodule was made.

USG guided fine needle aspiration (FNA) of thyroid nodule was done. Blood tinged material was aspirated. Smears were prepared and stained with Leishman stain. Smears had low cellularity and showed dispersed and a few loose clusters of hyperplasic thyroid follicular cells with thin colloid on the background [Figure 1]. A few dispersed and occasional loose collection of epithelioid cells [Figure 2] with a

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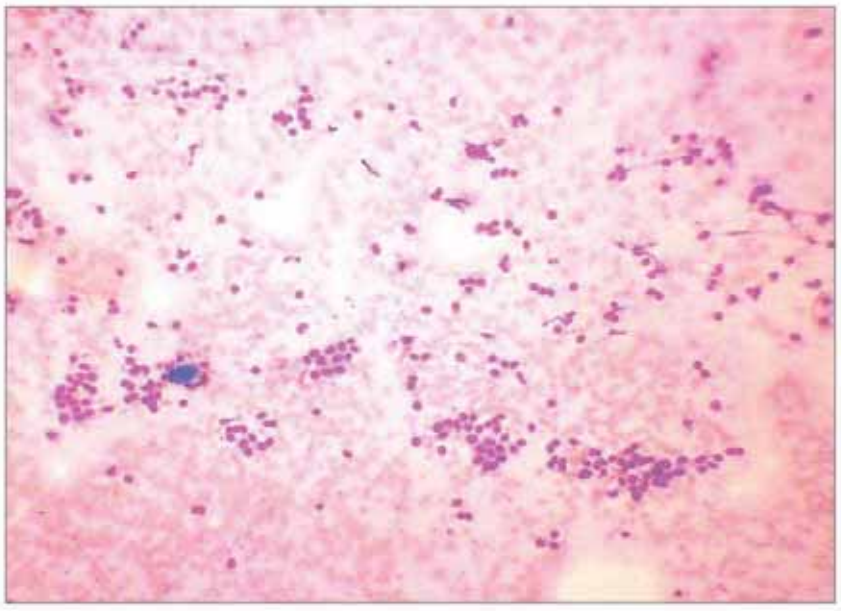

Figure 1: FNA of thyroid gland showing dispersed and a few loose clusters of hyperplasic thyroid follicular cells with thin colloid on the background (Leishman stain x 400)

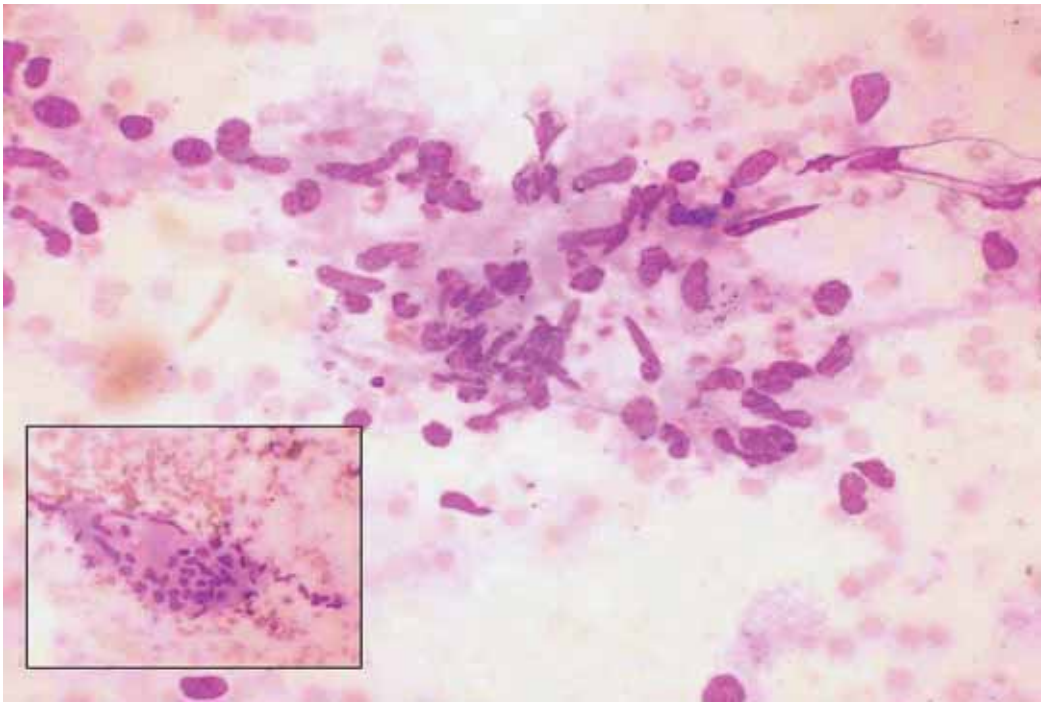

Figure 2: FNA of thyroid gland showing a few dispersed and occasional loose collection of epithelioid cells (Inset) showing histiocytic giant cell (Leishman stain x 400)

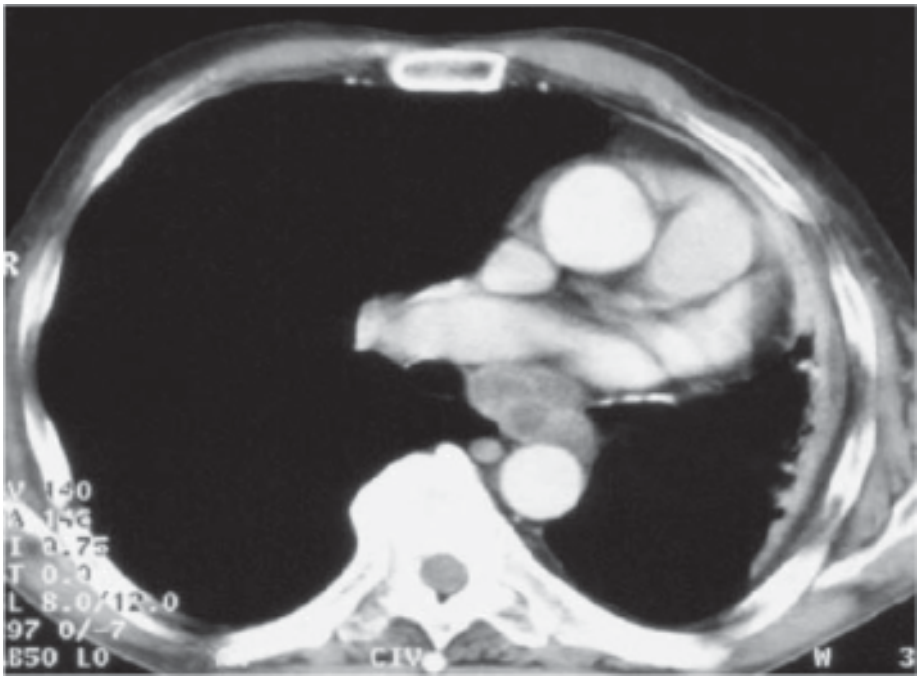

Figure 3: CT scan showing enlarged mediastinal lymph nodes having areas of central low attenuation with peripheral rim enhancement.

few histiocytic giant cells [Figure 2, Inset] were seen. Necrosis was not seen. A few lymphocytes were seen on the background. Ziehl Nelsen (ZN) stain did not show acid fast bacilli. Differential diagnosis of sub-acute granulomatous thyroiditis, tuberculosis and other infective causes of granulomas were considered. Patient was seronegative for human immunodeficiency virus (HIV). X-ray chest (PA view) showed mediastinal shift to left. Computed tomography (CT) scan showed matted enlarged mediastinal lymph nodes measuring 4.6x2 cm and having areas of central low attenuation with peripheral rim enhancement (Figure 3). A few areas of calcification were seen. Lungs had no lesions. Mantoux test was strongly positive (30x30cm). CT guided transthorasic FNA from mediastinal lymph node was done.

Aspirate showed many epithelioid granulomas and necrosis. ZN stain revealed many AFB. A definitive diagnosis of tuberculous mediastinal lymphadenitis with spread to thyroid gland was made. Standard anti tuberculous treatment (ATT) was advised (category I) as per Revised National Tuberculosis Control Programme (RNTCP).

DISCUSSION

Lebert in 1862 first reported thyroid tuberculosis in a case of disseminated mycobacterium infection. Definite incidence of thyroid tuberculosis is not known.[6] Rarity of primary or secondary thyroid tuberculosis is due to:1) Bactericidal action of colloid 2) High Vascularity of gland 3) High iodine content of the gland. Spread of tuberculosis to thyroid gland occurs through hematogenous, and lymphogenous route or extension from larynx or cervical or mediastinal lymph nodes.[7]

The symptoms of thyroid tuberculosis are non-specific and variable. The most common clinical presentation is solitary thyroid nodule which was also seen in our case. In some cases,

it may present as diffuse or multinodular goiter, acute or sub-acute thyroiditis or rarely as an acute abscess.[8] A few patients may present with pressure symptoms such as dysphagia, dyspnoea or recurrent laryngeal nerve palsy or with cervical lymphadenopathy. Some patients can be asymptomatic.[9]

Signs of tuberculosis elsewhere in the body are rarely found in thyroid tuberculosis.[5] In our case, patient had tuberculous mediastinal lymphadenitis. Thyroid dysfunction is rare with tuberculosis of thyroid and very few cases of thyrotoxicosis or hypothyroidism due to destruction of thyroid gland are reported in literature.[8] FNAC is an effective way of pre-operative diagnosis of thyroid tuberculosis.[10] Typically, tuberculous lesion on FNAC shows epithelioid granulomas, caseous necrosis and/or AFB.

Apart from tuberculosis, epithelioid cells in thyroid can be seen in sub-acute granulomatous thyroiditis, autoimmune thyroiditis, sarcoidosis and other infective causes of granulomatous inflammation.

In our case, FNA cytology smears showed only a few epithelioid cells and giant cells. Caseous necrosis was not seen. Thyroid tuberculosis presenting symptom of mediastinal tuberculous lymphadenitis is very unusual. This case is presented for uniqueness of its presentation in which thyroid tuberculosis was the presenting symptom of tuberculous mediastinal lymphadenitis.

CONCLUSION

Tuberculosis of thyroid, whether primary or secondary, is very rare. When epithelioid cells are seen in FNAC of thyroid lesions, tuberculosis must be ruled out at other sites in the body especially in countries where there is high prevalence of tuberculosis. Thyroid tuberculosis can be a presenting symptom of tuberculosis elsewhere in the body.

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CORRESPONDENCE

DELAY IN DIAGNOSIS AND TREATMENT AMONG TB PATIENTS

Beuy Joob* and Viroj Wiwanitkit**

Sir,

The recent report on delay in diagnosis and treatment among TB patients is very interesting[1]. Thakur and Murhekar studied on the situation in India and finally concluded that "educating private physicians about the need for maintaining a high index of suspicion of tuberculosis and sensitizing drug-store owners to refer the chest symptomatics to government health facilities would also help in reducing these delays[1]." In fact, the delayed diagnosis can further result in unsuccessful management of tuberculosis. This can be seen in any developing country. Nevertheless, the concern should also be given to the delay that is caused by the patients. Sometimes, the health care-seeking delay can be seen. Li *et al*. performed a meta-analysis for the China situations and determined many factors (such as "female sex", "living in rural areas", "low educational attainment" and "seeking care first from Traditional Chinese Medicine") that result in delayed visiting to the physicians[2]. To provide public health education to general population to increase their awareness on tuberculosis seems to be an additional requirement for successful disease control.

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MYCOBACTERIAL INFECTIONS - UPDATE FROM THE "INTERNATIONAL PULMONARY UPDATE"

Charles L. Daley*

Mycobacterial infections produce enormous morbidity and mortality throughout the world. While tuberculosis (TB), including drug-resistant disease, is a major health problem in India, non-tuberculous mycobacteria (NTM) have overtaken TB in the United States and many other industrialized countries. Both TB and NTM were discussed at the *International Pulmonary Update* held on 5 October 2013 at Santosh Medical Hospital in Ghaziabad. This was the first conference to be held jointly by Santosh University and National Jewish Health, a leading respiratory health centre in Denver, Colorado, USA. The conference was organized around three themes: 1) COPD, 2) Asthma, and 3) Mycobacterial Infections. A speaker from National Jewish Health and one from India joined forces to present on each topic. Attendees included Prof. P. Mahalingam, faculty and trainees from many institutions including Santosh University, Patel Chest Institute, Metro Centre for Respiratory Diseases, National Institute of TB and Respiratory Diseases, and All India Institute of Medical Sciences.

Mycobacterial infections were addressed in two lectures: 1) *Mycobacterial Infections* by Professor Charles L. Daley, Chief, Division of Mycobacterial and Respiratory Infections, National Jewish Health, Denver, Colorado, USA and 2) *MDR and XDR TB: Current Status* by Professor Rajendra Prasad, Director of the Patel Chest Institute, New Delhi. Professor Daley focused much of his discussion on the diagnosis and treatment of NTM infections noting that there are now more than 160 species of NTM. In the United States, pulmonary NTM infections are increasing at a rate of 8% per year among persons $\geq$ 65 years of age and the rates are higher than those of TB. Unlike TB, simply isolating an NTM from a respiratory specimen does not necessarily indicate that the organism is causing disease and thus, better diagnostic algorithms are needed. Treatment requires multiple drugs administered for approximately 18 months and except for a few notable exceptions, outcomes are generally poor when compared with drug-susceptible TB.

TB remains the most important mycobacterium globally with 8.6 million cases a year resulting in 1.3 million deaths. New rapid molecular tests are providing the opportunity to identify *Mycobacterium tuberculosis* and rifampicin resistance within two hours and research into shorter regimens and new drugs may alter the paradigm of TB control in the near future. New interferon-gamma release assays are available for the identification of latent TB infection and new short course regimens such as once weekly isoniazid and rifapentine administered for three months will hopefully improve adherence to preventive regimens. Unfortunately, the emergence of multidrug-resistant and extensively drug-resistant strains of TB threaten the success of TB control programmes globally and also in India. Professor Prasad reviewed the current epidemiology of drug-resistant TB and highlighted the fact that these strains of TB emerged in the setting of weak TB control programmes. While the new molecular assays and new drugs will improve our ability to diagnose and treat MDR and XDR-TB, we should aim to prevent further generation of drug-resistant *M. tuberculosis*.

The lectures were followed by additional lively discussion during a series of workshops involving trainees and post-doctoral students. These workshops provided the opportunity for closer interactions with the visiting faculty and were one of the highlights of the conference. The first International Pulmonary Update was quite successful and hopefully the first of many to come.

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ABSTRACTS

LED fluorescence microscopy increases the detection of smear-positive pulmonary tuberculosis in medical colleges of India

L. W. Reza, S. Satyanarayana, A. Pandey, S. Kumar, N. M. Devendrappa, L. Anand, G. Singh, A. M. V. Kumar, S. S. Chadha, N. Wilson, K. S. Sachdeva and S. A. Nair. *Public Health Action* 2013: **3(3)**: 240-42.

In July 2012, light-emitting diode fluorescence microscopy (LED-FM) replaced conventional light microscopy using Ziehl-Neelsen stain in the detection of sputum-positive pulmonary tuberculosis in 190 microscopy centres of medical colleges operating under India's Revised National Tuberculosis Control Programme. We compared the performance of LED-FM (July-December 2012) to that of conventional microscopy (July–December 2011) across 190 sites. Of 222658 patients examined using conventional microscopy, 28042 (12.6%) were smear-positive, while of 224714 examined using LED-FM, 33552 (14.9%) were smear-positive, an additional yield of 5251 cases after adjusting for the increase in patients examined. We recommend replacing conventional microscopy with LED-FM in high workload microscopy centres in India.

Drug-resistant tuberculosis in children in Thailand

K. Lapphra, C. Sutthipong, S. Foongladda, N. Vanprapar, W. Phongsamart, O. Wittawatmongkol, R. Saksawad and K. Chokephaibulkit. *The International Journal of Tuberculosis and Lung Disease* 2013; **17(10)**: 1279-84.

Few data on drug-resistant (DR) tuberculosis (TB) in children are available in Thailand. The objective was to evaluate the rate, clinical features and risk of DR-TB in children. It was an observational prospective study conducted in children diagnosed with TB at a tertiary care centre in Bangkok. Of 230 children diagnosed with TB, the median age was 6.5 years; 63% had identified adult source cases, and only 7% had received prior isoniazid treatment for latent tuberculous infection. Of the 195 (85%) specimens submitted, 57 (25%) were positive using culture or polymerase chain reaction. Of the 53 positive specimens available for drug susceptibility testing (DST), 18 (34%) had any resistance, 13 (24.5%) were mono-resistant, 2 (3.8%) polyresistant and 3 (5.7%) were multidrug-resistant. In multivariate analysis, prior TB treatment ($P < 0.001$), presence of atelectasis ($P = 0.039$) or lobar consolidation ($P = 0.012$) on chest X-ray were associated with DR-TB. DR-TB required longer treatment but there were no differences in rate of cure, treatment completion or death. The high rate of DR-TB underscores the importance of routine DST. History of treatment and drug susceptibility in source cases was useful in guiding initial treatment in children.

Xpert® MTB/RIF in pleural fluid for the diagnosis of tuberculosis

J. M. Porcel, R. Palma, L. Valdes, S. Bielsa, E. San-Jose and A. Esquerda. *The International Journal of Tuberculosis and Lung Disease* 2013; **17(9)**: 1217-9.

An automated nucleic acid amplification assay that simultaneously identifies *Mycobacterium tuberculosis* and rifampicin resistance, the Xpert® MTB/RIF test, has undergone extensive evaluation in sputum samples. Our aim was to define its diagnostic accuracy when performed on pleural fluid specimens. In 67 patients with pleural effusions, of whom half had tuberculous pleuritis, Xpert yielded 15% sensitivity and 100% specificity in the detection of tuberculosis (TB). Positive Xpert results tended to be more common in patients with microbiologically confirmed TB. Due to its low

sensitivity, Xpert testing of pleural fluids has a limited role in the work-up of pleural effusions.

Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: a meta-analysis

T. J. Hwang, D. F. Wares, A. Jafarov, W. Jakubowiak, P. Nunn and S. Keshavjee. *The International Journal of Tuberculosis and Lung Disease* 2013; **17(10)**: 1257-66.

Although cycloserine (CS) is recommended by the World Health Organization as a second-line agent for the treatment of multidrug-resistant tuberculosis (MDR-TB), safety concerns have impeded its uptake by several national TB programmes. Terizidone (TRD), a structural analogue of cycloserine, may be better tolerated. To assess the safety of CS and TRD for TB treatment, a systematic review and meta-analysis were conducted. From articles published up to December 2011, 27 studies with 2164 patients were included in our review of CS use. The pooled estimate for the frequencies of any adverse drug reaction (ADR) from CS was 9.1% (95%CI 6.4–11.7); it was 5.7% (95%CI 3.7–7.6) for psychiatric ADRs, and 1.1% (95%CI 0.2–2.1) for central nervous system (CNS) related ADRs. TRD showed no better to moderately better safety than CS in a systematic review of the available literature. The published evidence suggests that CS is associated with a higher frequency of psychiatric and CNS-related ADRs than other second-line drugs. While data were limited, treatment discontinuation rates appeared to be manageable. There were no significant differences in tolerability by region, study period or combination. As countries review and revise their treatment programmes, CS, and potentially TRD, should be included in MDR-TB treatment regimens. Adequate information on possible ADRs should be provided to patients, their families and attending health care workers. Greater attention to MDR-TB patients' mental health and a significant increase in resources devoted to pharmacovigilance and treatment of MDR-TB are essential.

No added value of performing Ziehl-Neelsen on auramine-positive samples for tuberculosis diagnostics

A. L. den Hertog, S. Daher, M. Straetemans, M. Scholing and R. M. Anthony. *The International Journal of Tuberculosis and Lung Disease* 2013; **17(8)**: 1094-9.

There is a push to switch from Ziehl-Neelsen (ZN) to auramine microscopy. Despite World Health Organization guidelines that one staining method is sufficient, in some countries national guidelines prescribe that auramine-positive samples should be confirmed by ZN. The objective was to investigate the added value of confirming auramine-positive samples using ZN. Using diagnostic data from 10276 respiratory samples collected from 5525 patients tested for tuberculosis (TB) at the Municipal Health Service of Amsterdam between May 2006 and October 2011, we determined the diagnostic accuracy of auramine alone and of confirmation of auramine-positive samples using ZN. Of 141 *M. tuberculosis* complex-positive samples detected using auramine on which ZN was performed, 32 (22.7%) were ZN-negative. A similar percentage (6/25, 24.0%) of negatives was found for samples containing non-tuberculous mycobacteria (NTM) species, thus making it impossible to distinguish between TB and NTM on the basis of ZN results. A positive auramine result followed by a negative ZN result could not be used to exclude TB or to indicate the presence of NTM species. Confirming auramine-positive samples using ZN in this setting thus provided no clinically informative information and was a waste of resources.

Yield of contact tracing from pediatric tuberculosis index cases in Gaborone, Botswana

S. Puryear, G. Seropola, A. Ho-Foster, T. Arscott-Mills, L. Mazhani, J. Firth, D. M. Goldfarb, R. Ncube, G. P. Bisson and A. P. Steenhoff. *The International Journal of Tuberculosis and Lung Disease* 2013; **17(8)**: 1049-55.

Contact tracing using pediatric index cases has not been adequately investigated in high

tuberculosis (TB) and human immunodeficiency virus (HIV) prevalence settings. The objective was to determine the yield of contact tracing in household contacts of pediatric TB index cases in Botswana. Index cases included all pediatric (age ≤13 years) TB admissions from January 2009 to December 2011 to Botswana's largest referral hospital. A contact tracing team identified cases, conducted home visits, symptom-screened contacts and referred those with ≥1 TB symptoms. The primary outcome was newly diagnosed TB in a contact. From 163 pediatric index cases, 548 contacts were screened (median 3 contacts/case, interquartile range [IQR] 2-4). Of these, 49 (9%) were referred for positive symptoms on screening and 27/49 (55%) were evaluated for active TB. Twelve new TB cases were diagnosed (12/548, 2.2%); the median age was 31 years (IQR 23–38); 11 (92%) were smear-positive. Ten (83%) had known HIV status: seven (70%) were HIV-positive. To find one new TB case, the number needed to contact trace (index cases/new cases) was 13.6, and the number needed to screen (contacts/new cases) was 46. This yield of contact tracing using pediatric index cases is similar to the traditional adult index case approach. Improving the proportion of symptomatic contacts evaluated may increase yield.

Multidrug- and isoniazid-resistant tuberculosis in three high HIV burden African regions

E. Sanchez-Padilla, E. Ardizzoni, D. Sauvageot, L. Ahoua, A. Martin, F. Varaine, F. Adatu-Engwau, G. Akeche, F. Salaniponi and M. Bonnet. *The International Journal of Tuberculosis and Lung Disease* 2013; **17(8)**: 1036-42.

Despite major progress in the surveillance of drug-resistant tuberculosis (TB), data are lacking for many low-resource countries. World Health Organization estimates of multidrug-resistant TB (MDR-TB) rates in Africa are low, and based on very limited data from the African continent. The objective was to measure MDR-TB prevalence in sub-Saharan African regions with a high prevalence of human immunodeficiency virus (HIV). We conducted three anti-tuberculosis drug resistance surveys in sub-Saharan African regions with high HIV-TB coinfection prevalence: Homa Bay (Kenya), Chiradzulu (Malawi) and West Nile region (Uganda). The prevalence of MDR-TB in new patients was found to be low in the three regions: 1.4% (95%CI 0.2–2.6) in Homa Bay, 2.0% (95%CI 0.4-3.6) in Chiradzulu and 0.6% (95%CI 0.0–1.5) in the West Nile region. We found no significant association between MDR-TB and HIV infection. Nonetheless, ≥10% of the new cases surveyed were resistant to isoniazid (INH). The relatively high rate of resistance to INH highlights the need for rapid detection of INH resistance in addition to rifampicin (RMP) resistance, to allow rapid modification of treatment to avoid the acquisition of RMP resistance. Drug resistance should be monitored periodically.

Socio-economic patterning of tobacco use in Indian states

S. Agrawal, A. Karan, S. Selvaraj, N. Bhan, S. Subramanian and C. Millett. *The International Journal of Tuberculosis and Lung Disease* 2013; **17(8)**: 1110-17.

Studies in India have identified marked variations in overall tobacco use between socio-economic groups. We examined whether associations between socio-economic status (SES) and tobacco use varied across individual Indian states by tobacco type. It was a cross-sectional survey of 100855 households in 24 Indian states and Union Territories conducted in 2009-2010. Outcome measures were household tobacco consumption by type. Logistic and linear regression models were used to examine associations at the household level between education, income and use and volume of tobacco consumed. Overall, 52% of households used any form of tobacco product; the predominant form was smokeless tobacco (22%), followed by bidi (17%) and cigarettes (4%). Increasing household income and higher education level were associated with a higher likelihood of cigarette use but a lower likelihood of bidi and smokeless tobacco use in some Indian states. Increasing household income was associated with higher volumes of cigarette and bidi use among consuming households; however, association between educational level and volume of tobacco consumption was inconsistent. SES has a

varying impact on different types of tobacco use in Indian states. Policy makers should consider socio-economic patterning of tobacco use when designing, implementing and evaluating tobacco control interventions in different states of India.

Validation of sputum smear results in the Electronic TB Register for the management of tuberculosis, South Africa

A. Dilraj, C. C. Bristow, C. Connolly, B. Margot, S. Dlamini and L. J. Podewils. *The International Journal of Tuberculosis and Lung Disease* 2013; **17(10)**: 1317-21.

The accuracy of tuberculosis (TB) surveillance systems is paramount in TB control. In South Africa, information from the laboratory is not directly linked to the Electronic TB Register (ETR). The objective was to validate smear results recorded in the ETR with those recorded in the laboratory. A retrospective evaluation was conducted among all sputum smear-positive TB patients recorded in the ETR during the fourth quarter of 2009 in KwaZulu-Natal Province. Of 1036 smear-positive patients recorded in the ETR, 683 (65.9%) had positive results recorded in the laboratory register. Only 364 (53.2%) had their smear results recorded in the ETR at the end of the intensive phase of treatment; of 326 (89.6%) recorded as converted to smear-negative, 224 (61.5%) were confirmed as smear-negative in the laboratory. Of 331 patients with end-of-treatment results in the ETR, 302 (91.2%) were recorded as cured, but only 105 (34.8%) were confirmed in the laboratory. Over a third of TB patients registered as smear-positive in the ETR could not be confirmed based on laboratory results. Many patients did not have a laboratory record, leading to uncertainty as to the validity of the smear results and treatment outcomes recorded in the ETR.

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