INDIAN JOURNAL OF TUBERCULOSIS

EDITORIAL BOARD

Indian Journal of Tuberculosis

Volume 67 Number 1 January 2020

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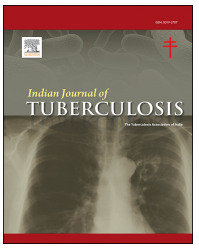

Editorial

Artificial intelligence and TB management – The way forward

The National TB Elimination Programme (NTEP) has been at the forefront of adoption of newer technologies in management of TB cases. The Artificial Intelligence (AI) provides a unique opportunity for the health sector, bringing efficiency, saving resources and bringing accuracy in interpretation and enhancing quality of service delivery. Its use in this sector has an ample scope to improve outcomes, especially in situations where resources are limited. Prime Minister of India has taken a bold decision to end TB in India by 2025, five years ahead of the Global Sustainable Development targets. A recent study published in ERJ open research journal[1] in association with the Global TB Programme, World Health Organization (WHO) stated that countries aiming to reduce their TB burden by 2035 to the levels envisaged by the WHO End TB Strategy need to innovate, with approaches such as digital health (electronic and mobile health) in support of patient care, surveillance, programme management, training and communication. It also mentioned that many experts forecast the imminent transformation of the delivery of healthcare services. Keeping this in mind, programme managers in India will need to take up these digital technologies in a big way.

Digital technologies can make our efforts to end TB more effective and efficient.[2] Access to the internet and affordable mobile devices is becoming increasingly widespread in low- and middle-income countries. In the past few years, WHO and its partners identified a set of priority electronic and mobile health products and concepts which were advantageously positioned to have a high impact on different domains of TB care and prevention.[3] Target product profiles (TPPs), consisting of descriptions of how these tools should work, were developed in order to communicate the product attributes to all partners involved in advancing them. The TPPs are intended to be dynamic documents which are updated regularly to incorporate the latest in the technology and remain relevant to TB practitioners and patients who should benefit from the finished product.

Digital technologies can support efforts against TB in four ways: patient care, surveillance, programme management and e-learning.[2] A number of currently available digital products already address one or more of these functions, but to achieve the ambitious goals of the End TB strategy these tools need to be rolled out more extensively. Moreover, their performance needs to be augmented by incorporating innovations such as artificial intelligence (the branch of computer science concerned with the automation of intelligent behaviour[4]) and machine learning (the subfield of computer science that gives computers the ability to learn without being explicitly programmed[5] into the future successors of today's technology. Artificial intelligence is already embedded in common applications that recognise voice and visual patterns, such as speech transcription software and computer-aided diagnostic platforms.

While treatment adherence has attracted much focus, digital technology could improve TB patient care through other approaches. For instance, "clip-on" hardware can convert a smart phone into a clinical instrument.[6] Cognitive computing (systems that learn at scale, reason with purpose and interact with humans naturally[7] could power algorithms within clinical decision support systems to help clinicians with diagnostic and treatment decisions. They could help, for instance, in the causality assessment of adverse events through the recognition of patterns and the association of various data. Artificial intelligence could enable rapid access to previously unreachable masses of data. These could include diverse sources ranging from cloud-based datasets that are not usually applied into clinical decision-making, as well as rich knowledge bases which usually remain locked up inside the individual patient's genome.[8] Access to this information helps both the human operator and the machine to learn. If an advanced artificial intelligence application can be incorporated into a mobile-based clinical decision support application, TB workers worldwide would not only benefit from its use, but also enrich it by the data and feedback they supply. Such a personalised approach to care is bound to challenge time-honoured practices, such as how new treatment regimens have been traditionally introduced in clinical care on the basis of observations extrapolated from drug trial participants. The demand for these resource-intensive studies, which can take several years to complete, could thus decrease.

Artificial intelligence could help to review the disaggregated patient clinical records. Where unique personal identifiers are commonly unavailable an intelligent system could still trace an individual person's "signature" over time within large datasets. This would be greatly important in TB surveillance, for instance to trace people with clinical manifestations suggestive of TB or disease relapse or adverse drug

reactions and to complete the monitoring of mortality and the linkage with HIV. In addition, this approach could identify predictors of treatment failure, which in turn could be useful in patient care as well as TB drug development.[9] Artificial intelligence has been proposed as a means to detect outbreaks of TB at the earliest.

Information has always been central to planning and management. In TB programmes the handling of diagnostic data is crucial to maximise coverage of services, identify discordance and limit the excess entries. "Connected diagnostics" is becoming a flagship concept in TB programme management, helping to monitor diagnostic machines remotely and to consolidate the results data. Successful implementation of such systems in low-resource settings has been given a boost by the advent of molecular diagnostics that generate their results digitally.[10] This is being used in India, at present. The next generation of products could go a step further by helping to interpret results data and match them with those from other diagnostic processes. Artificial neural networks have been applied to clinical situations that still pose diagnostic difficulties such as microscopy sputum smear-negative TB and pleural TB, in settings where diagnostic options are limited.[11] The potential contribution of computerisation to radiology, another important field in TB diagnostics was first recognised decades ago.[12] Nonetheless, the automated detection of TB on digital chest radiographs has yet to become more clinically relevant, although efforts are continuously being on to try it and collaborate with exiting clinical information.

While artificial intelligence has been incorporated in medical innovations since the 1970s, forthcoming advances such as cognitive computational systems will mark a radical departure from the previous order. Telemedicine and remote consultations can deliver healthcare via a home computer or mobile device, challenging the conventions of patient–carer relationships. Portable and wearable devices equipped with artificial intelligence-enhanced software can monitor patients and issue alerts fatigue-free to a degree which would be impossible even where trained workers are available. These developments will strengthen the trend towards home-based care and reduce healthcare facilities. The arrival of the smartphone in the past decade has given us a tool of how technology can rapidly transform lay persons into informed clients of healthcare services. This trend will keep expanding in future and will equip patients and their caregivers with more options to interact and to make the best possible clinical decisions.

Indian National TB Programme has already adopted many digital technologies in data management, treatment and surveillance. Still it needs to adopt artificial intelligence in a big way in smear diagnosis, radiology and molecular diagnostics. Efforts are on to utilize it in making clinical diagnosis especially in smear negative cases with radiological lesions. With these tools, India can hope to achieve TB Control in a faster way. There is enough scope of using artificial intelligence in Active Case Finding of TB cases, which is a key component of End TB Strategy. Similarly in National Disease Prevalence Survey presently being undertaken in India, radiological examination as well as smear examination can be read with better sensitivity with help of artificial intelligence tools. These tools are strongly recommended to be used in these two situations.

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https://doi.org/10.1016/j.ijtb.2020.02.002

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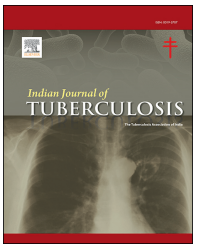

Original article

Hormonal changes and reproductive health issues in females with tuberculosis

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ARTICLE INFO

Article history:
Received 27 December 2019
Accepted 15 January 2020
Available online 23 January 2020

Keywords:
Menstrual abnormalities
Infertility
Hormone levels

ABSTRACT

Background/aims: The association between tuberculosis (TB) and female reproductive health issues usually remains unaddressed. TB is considered as one of the major causes of infertility in India. Because of the associated stigma, the suffering females do not discuss the problems they are facing. This may lead to disturbances in serum hormone levels also.

Hence, a study was planned to find abnormalities in menstrual patterns and fertility in women in childbearing age, who were suffering from TB, and evaluate disturbances in serum hormone levels of LH, FSH, Prolactin and testosterone, if any. It also aimed to evaluate if hormone levels, or some early disturbances in menstrual cycle, can serve as a predictor for infertility in future lives.

Materials and methods: 25 female patients each of child bearing age group from OPD/IPD: of pulmonary TB (PTB), extra pulmonary non genital TB (EPTB), extra pulmonary genital TB (GTB) and healthy controls were enrolled. Thus, a total of 75 patients with TB and 25 healthy controls were taken into the study.

Patients were questioned for any abnormalities of menstrual cycle. If married, fertility status, total number of live children, abortions etc and previous history of any reproductive health issues was asked. Serum FSH, LH, Prolactin and testosterone levels on the 3rd day of the menstrual cycle were done. Data so obtained was tabulated and statistically analyzed.

Results: TB patients (75/100) and healthy controls (25/100) were matched with respect to age, marital status and rural/urban background. Menstrual abnormalities, infertility and adverse events related to pregnancy were higher in patients with TB than healthy controls ($p = 0.176$, 0.571 and 0.005 respectively). TB patients had significantly higher levels of Testosterone and significantly lower levels of Prolactin than healthy controls ($p=<0.001$). Levels of FSH and LH were lower in TB patients than healthy controls ($p = 0.428$ and 0.274 respectively).

On categorization into different types of TB, the sub-groups were matched with respect to rural/urban background. GTB was significantly higher in patients who were married

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https://doi.org/10.1016/j.ijtb.2020.01.010

($p = 0.020$). Significantly higher GTB patients (10/25) reported menstrual abnormalities ($p < 0.001$). All the 3 infertile patients reported in the study belonged to GTB sub-group ($p = 0.044$). GTB had higher number of adverse events related to pregnancy followed by EPTB and PTB.

Levels of FSH, LH, Testosterone and Prolactin in the three sub-groups of TB patients did not show any significant difference ($p = 0.683$, 0.817, 0.781, and 0.187).

Since the total number of infertile patients in our study was only 3, relationship of menstrual abnormalities or serum hormone levels as a predictor of infertility could not be assessed.

Conclusion: Females suffering from TB experience significantly higher adverse events related to pregnancy than healthy controls. Menstrual abnormalities, infertility and adverse events related to pregnancy were more pronounced in females suffering from GTB than PTB/EPTB.

Female patients suffering from any form of TB need to be comprehensively managed. Because of highly sensitive issues related to infertility and reproductive health in today's era, it is imperative that any future complications of the same are kept into consideration in female patients with TB.

1. Introduction

Tuberculosis (TB) is a major health problem in India.[1] The association between tuberculosis and female reproductive health is well known but usually remains ignored.[2] Infertility is another serious health issue in India, and TB is one of the major causes of infertility.[3] In our country, because of the stigma associated with TB, and more so, with infertility and reproductive health, females don't come out to discuss the associated problems, and suffer in silence with the same. The ongoing disease and the other associated factors contribute to the disturbances in hormone levels as well. Thus, it becomes a vicious cycle, leading to added burden on health care services.

Hence a study was done to find the abnormalities in fertility and menstrual patterns of women in childbearing age, who were suffering from TB, and evaluate the associated hormonal changes in LH, FSH, Prolactin and testosterone, if any. It also aimed to find out if the hormone levels, or some early disturbances in the menstrual cycle, could be a predictor for some major fertility issues in the coming future.

2. Materials and Methods

It was a cross sectional, non interventional study. 25 female patients each of child bearing age group from OPD/IPD: of pulmonary TB (PTB), extra pulmonary non genital TB (EPTB), extra pulmonary genital TB (GTB) and healthy controls were enrolled. Thus, a total of 75 patients with TB and 25 healthy controls were taken into the study. Patients were recruited into the various said groups as per clinical and diagnostic protocol followed by the hospital, after adhering to the recommendations under the revised national TB control program (RNTCP).[1]

After informed consent, the patients were subjected to a questionnaire regarding any abnormalities of menstrual cycle. If married, fertility status, total number of live children, abortions etc and previous history of any reproductive health issues was detailed. Relevant history regarding TB was also noted, including the history of any anti tubercular treatment (ATT) in the past.

Infertility was defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.[4] Adverse events related to pregnancy included history of abortions, still births, problems with conception in previous pregnancies etc. Infertility and adverse events related to pregnancy were studied in total 100 patients. Analysis of these two parameters particularly was also done after exclusion of the patients who could not be evaluated for these two indicators specifically because of being unmarried or because they couldn't be labeled as infertile despite being married.

5 ml of venous blood was taken for estimation of serum levels of Follicle stimulating hormone (FSH), Luteinizing hormone (LH), Prolactin and testosterone on the 3rd day of the menstrual cycle from all the patients. The hormonal estimation was carried out by chemiluminescence (Advia Centaur-XP). The data so obtained was tabulated and statistically analyzed.

The study was approved by the institute's ethical committee.

2.1. *Statistical Analysis*

The normality of the variables was tested with the Shapiro–Wilk test/Kolmogorov Smirnov tests of Normality. Continuous data were written in the form of mean and standard deviation. Group comparisons of values of data were made with Kruskall Wallis test (for sub-groups of TB), Mann–Whitney test was carried out for comparisons of the two groups. Categorical variables were reported as counts and percentages. Group comparisons were made with the Chi–Sq test or Fisher's exact test as appropriate.

A P value < 0.05 was considered significant. All the statistical tests were two-sided and were performed at a significance level of $\alpha = 0.05$. Analysis was conducted using IBM SPSS STATISTICS (version 22.0).

3. Results

The patients of TB (75/100) and healthy controls (25/100) were matched with respect to age, marital status, rural/urban background, use of ATT in the past and history of contact with PTB patient in the past. Though statistically non-significant, menstrual abnormalities and infertility were higher in patients with TB ($p = 0.176$ and 0.571 respectively). Adverse events related to pregnancy were significantly more in patients suffering from TB when compared with healthy controls ($p = 0.005$) (Table 1).

After exclusion of patients who could not be evaluated for infertility and adverse events related to pregnancy, it was seen that a total of 69/100 patients were studied, out of which 52/75 patients belonged to the TB group, and 17/25 were from the healthy controls. All the 3 patients with infertility belonged to the TB group (3/52), and none had infertility amongst controls ($p = 0.570$). Patients who were suffering from TB had significantly higher adverse events related to pregnancy than healthy controls ($p = 0.003$) (Table 1).

Anemia was seen significantly more in patients suffering from TB. The patients who were suffering from TB had significantly higher levels of Testosterone and significantly lower levels of Prolactin than healthy controls ($p < 0.001$). Though non-significant, serum levels of FSH and LH were lower in patients suffering from TB than healthy controls ($p = 0.428$ and 0.274 respectively) (Table 1).

FSH and LH were lower and Testosterone and Prolactin were higher amongst TB patients who had some menstrual abnormality ($n = 11/75$), compared to those TB patients who did not have any menstrual abnormality, though this difference was statistically non significant ($p = 0.377$, 0.764, 0.725, 0.6 respectively).

There was no correlation of levels of FSH, LH, Testosterone and Prolactin amongst TB patients who reported adverse events related to pregnancy ($n = 18/52$, $p = 0.374$, 0.906, 0.441, 0.594 respectively).

On further sub-categorization of the TB patients into PTB, EPTB, and GTB, GTB was significantly higher in patients who were married ($p = 0.020$). It was followed by EPTB and PTB. In unmarried females, PTB was most common and it was followed by EPTB and GTB. There were no statistically significant differences with respect to rural/urban background amongst different subgroups ($p = 0.551$). 3 patients with GTB had history of ATT in the past whereas none of the patients of PTB/EPTB had any such history ($p = 0.004$). The three subgroups were matched with respect to contact with a pulmonary TB patient in the past (Table 2).

10 patients from GTB, 2 from PTB and none from EPTB suffered from menstrual abnormalities ($p < 0.001$). Infertility was seen only in the GTB subgroup, with all the 3 infertile patients belonging to it ($p = 0.044$). GTB had maximum number of adverse events related to pregnancy followed by EPTB and PTB ($p = 0.416$) (Table 2).

Table 1 – Showing various parameters in patients with TB and healthy controls.

Parameters		Patients with TB	Healthy Controls	P value
Age (in years)		28.92 ± 7.971	29.12 ± 5.826	0.488
Marital status	Married	53	18	0.899
	Unmarried	22	7	
Rural/Urban background	Rural	21	4	0.293
	Urban	54	21	
History of ATT in the past	Present	3	0	0.571
	Absent	72	25	
PTB contact	Present	8	0	0.195
	Absent	67	25	
Menstrual abnormalities	Present	12	1	0.176
	Absent	63	24	
Infertility	Present	3	0	0.571
(n = 100)	Absent	72	25	
Adverse events related	Present	18	0	0.005
to pregnancy	Absent	57	25	
(n = 100)				
Infertility	Present	3	0	0.570
(n = 69)	Absent	49	17	
Adverse events related	Present	18	0	0.003
to pregnancy	Absent	34	17	
(n = 69)				
Anemia	Present	34	1	0.001
	Absent	41	24	
Hormone Levels	FSH	6.4081 ± 5.99	6.1596 ± 6.16	0.428
	LH	5.0067 ± 4.95	5.5432 ± 5.54	0.274
	Testosterone	23.1640 ± 16.92	10.1720 ± 5.11	<0.001
	Prolactin	17.9783 ± 23.28	28.5360 ± 12.52	<0.001

TB: Tuberculosis, ATT: Anti tubercular treatment, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, (FSH and LH in mIU/mL, Prolactin in ng/ml, Testosterone in ng/dl).

Table 2 – Showing the various parameters in the 3 subgroups of patients suffering from TB.

Parameters		PTB	EPTB	GTB	P value
Marital status	Married	13	18	22	0.020
	Unmarried	12	7	3	
Rural/Urban background	Rural	8	5	8	0.551
	Urban	17	20	17	
History of Anti Tubercular treatment in the past	Present	0	0	3	0.044
	Absent	25	25	22	
Menstrual abnormality	Present	2	0	10	<0.001
	Absent	23	25	15	
Infertility (n = 75)	Present	0	0	3	0.044
	Absent	25	25	22	
Adverse events related to pregnancy (n = 75)	Present	4/25	6/25	8/25	0.416
	Absent	21/25	19/25	17/25	
Adverse events related to pregnancy (n = 52)	Present	4/13	6/17	8/22	0.943
	Absent	9/13	11/17	14/22	
Infertility (n = 52)	Present	0/13	0/17	3/22	0.114
	Absent	13/13	17/17	19/22	
Anemia	Present	18	7	9	0.004
	Absent	7	18	16	
Hormone levels	FSH	7.0980 ± 7.70	7.0164 ± 6.22	5.1100 ± 3.20	0.853
	LH	5.4700 ± 7.33	4.5768 ± 3.02	4.9732 ± 3.50	0.817
	Prolactin	24.0736 ± 35.68	10.6856 ± 4.51	19.1756 ± 16.77	0.187
	Testosterone	22.7120 ± 12.97	25.4240 ± 22.81	21.3560 ± 13.61	0.781

TB: Tuberculosis, PTB: Pulmonary TB, EPTB: extra pulmonary non genital TB, GTB: extra pulmonary genital TB, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, (FSH and LH in mIU/mL, Prolactin in ng/ml, Testosterone in ng/dl).

After exclusion of patients who could not be evaluated for infertility and adverse events related to pregnancy (n = 52/75), 3 patients suffering from GTB had infertility while none of the patients suffering from PTB/EPTB had infertility (p = 0.114). GTB patients had higher adverse events related to pregnancy (n = 8/22), followed by EPTB (n = 6/17) and PTB (n = 4/13), but the differences were statistically non significant (p = 0.943) (Table 2).

Anemia was seen to be most common in patients with PTB and least in EPTB (p = 0.004). There was no statistically significant difference in the serum levels of FSH, LH, Testosterone and Prolactin amongst the three sub-groups (p = 0.683, 0.817, 0.781, and 0.187).

4. Discussion

India is a high burden country for Tuberculosis.[5] Most commonly it involves the lungs, but it can infect almost any part of the body. The association between TB and female reproductive health problems, is well known, and yet, not well addressed.[2] Infertility is a major problem in India, and GTB is a major cause of menstrual abnormalities and infertility, accounting for a substantial proportion of cases.[3,5–7] High index of suspicion is required as many cases can be asymptomatic in early stages. It has been repeatedly advised that asymptomatic infertile women should undergo thorough investigations for silent GTB, especially in high burden settings like ours.[5,8] Early treatment can prevent significant damage to genital organs and permanent sterility.[9,10] Associated disturbances in the hormone levels have also been proposed.[2,5,11,12]

The patients of TB (pulmonary, extra pulmonary non genital and extra pulmonary genital altogether) and healthy controls in our study were age matched. These two groups were also matched with respect to marital status and rural/urban background. Matching of the marital status, in a way helped in eliminating the bias in result interpretation, since infertility cannot be evaluated in unmarried females.

Menstrual abnormalities and infertility were higher in patients suffering from TB in our study, when compared with healthy controls. Though the reasons for the same are poorly understood, but involvement of the hypothalamus, pituitary gland, ovaries etc or anti-gonadotropic effects of Mycobacterium may be responsible for such findings.[2,11] Some previous studies have also reported menstrual irregularities in patients with PTB, when compared with healthy controls.[2,13]

Adverse events related to pregnancy were more predominant in patients suffering from TB when compared with healthy controls. Since TB is known to silently affect multiple organs, though clinically manifesting only in one form or the other, the vicious cycle of infection with resultant unidentified and un-noticed irreversible fibrosis/damage may be responsible for such outcomes.

Role of female sex hormones in patients with TB has been overlooked in the past. In our study, the patients who were suffering from TB had significantly higher levels of Testosterone and significantly lower levels of Prolactin than healthy controls. Levels of FSH and LH were found to be lower in patients suffering from TB than healthy controls. FSH and LH have been reported to be higher as well as lower in patients with PTB in previous studies.[7,9,11,12] The physiological imbalance caused by disturbances in hormone levels may result in changes in the menstrual cycle, probably affecting the reproductive function in the long run.

When patients suffering from TB were further subcategorized, GTB was significantly higher in patients who were married (22/25). It is difficult to comment whether this reflects a truly high incidence, or it is because of the fact that GTB is mostly evaluated only in married females. In unmarried females, since GTB is usually asymptomatic and has a silent course, it remains unnoticed and undiagnosed. Early disturbances in the menstrual cycle or issues related to the same go unreported because of the psychosocial inhibitions regarding discussions related to reproductive health in the Indian setting. In our study also, PTB was seen to be more common in unmarried females (12/25) than EPTB/GTB.

3 patients with GTB had history of ATT in the past whereas none of the patients of PTB/EPTB had any such history. This finding again signaled that GTB may be a secondary infection from other organs, as hypothesized in the already available literature.[8]

As expected, menstrual abnormalities were significantly higher in our patients of GTB, because of the direct involvement of the genital tract. 2 patients suffering from PTB also reported menstrual abnormalities in our study. Menstrual disorders have not been studied extensively in patients with PTB or EPTB. It is said that menstrual disorders occur in non genital TB as well.[13] The findings from our study again point towards involvement of the alternate pathways and subsequent direct/indirect involvement of the female reproductive tract.[2,8,13]

All the 3 infertile patients belonged to the GTB group, resulting in a significantly higher infertility in this subgroup. Infertility is expected to be higher in patients with GTB, as already explained.

FSH and LH were lower and Testosterone and Prolactin were higher amongst TB patients who had some menstrual abnormality. This could be due to fluctuations in hormone levels which can affect the normal periodicity of the cycle. There was no such correlation of hormone levels in TB patients who reported adverse events related to pregnancy, suggesting that these changes in hormone levels may be for a short period of time, and do not cause long term affects. However, no conclusion could be drawn as the differences in hormone levels in the above comparisons were statistically non significant.

5. Limitations of study

Since the total number of infertile patients in our study were only 3, so the relationship between menstrual abnormalities or serum levels of FSH, LH, Prolactin and testosterone as a predictor of infertility could not be assessed.

6. Conclusion

There are increased chances of menstrual abnormalities, infertility and adverse events related to pregnancy in female patients with TB, and more so, if the patient is suffering from GTB. The risk of reproductive health issues at the time of diagnosis, management or in the coming future should always be considered by the treating physician. In addition to the treatment of TB, active involvement of the gynecologist, psychologist etc can help the females overcome the taboos and come out and discuss their problems openly. Subsequent early interventions can help in preventing irreversible damages over the years.

Conflicts of interest

The authors have none to declare

Acknowledgements

The authors gratefully acknowledge the financial assistance provided by the Department of Science and Technology, Chandigarh for carrying out this work.

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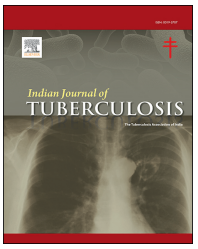

Original article

Strategies for smoking cessation (pharmacologic intervention versus enhanced motivation vs. standard motivation) in TB patients under treatment in the RNTCP, India - A cluster - Randomized trial

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ARTICLE INFO

Article history:
Received 2 August 2019
Accepted 9 January 2020
Available online 26 January 2020

Keywords:
Bupropion
Cessation
Enhanced counselling
Tuberculosis
Smoking

ABSTRACT

Background: Tuberculosis burden is still high and smoking prevalence among males has increased in India. It is found that increased morbidity, mortality and relapse among TB smokers.

Method: Setting: Patients from two Revised National Tuberculosis Control Program Centres of Tamilnadu form the study population.

Objective: To compare the effectiveness of Bupropion therapy along with standard counselling versus enhanced counseling versus standard counseling for smoking cessation among TB patients.

Study design: Cluster randomized effectiveness trial.

Procedure: Patients from each of the thirty-six Designated Microscopic Centres were randomly allocated to receive one of the three interventions using cluster randomization. Smoking cessation was assessed by self-reporting and confirmed by Carbon monoxide(CO) monitors, done at three-time points and TB treatment outcome at the end of ATT.

Results: Out of 517 male patients enrolled to the study, the smoking status is available only to 381 subjects. The proportion of patients who have quit smoking in drug, enhanced and standard arms at the end of treatment was 67%, 83% and 52% (P= < 0.001). There was no

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https://doi.org/10.1016/j.ijtb.2020.01.006

statistical significance in response to TB treatment between those who quit and those who did not (Favourable response 99.2% vs 97.6%).

Conclusion: Both enhanced counselling arm and drug arm are effective strategies for smoking cessation among TB patients and their implementation in the TB programs are recommended.

1. Introduction

Tobacco smoking is one of the major public health problems globally. Many studies have shown an association between smoking and tuberculosis (TB) and the association shows a strong dose-response relationship.[1] In 2017, TB caused an estimated 1.3 million deaths among HIV-negative people and three countries accounted for almost half of the world's cases of Multi-drug resistant (MDR)/Extensively-drug resistant (XDR-TB), India being on the top.[2] From our centre's experience, over 70% of male TB patients in the government health care system, are smokers(unpublished data), similar findings shown in another study.[3] It appears that there is evidence to conclude that smoking is causally associated with active TB.[4] Both passive and active exposures to tobacco smoke are associated with tuberculous infection.[5] Exposure to tobacco smoke both active and passive increases the risk of developing TB disease.[1,6] and also smoking leads to a faster and more severe progression of TB.[7] Smoking is an independent predictor of relapse of pulmonary tuberculosis adjusted odds ratio 3.1; 95% CI 1.6 to 6.0).[8] In a retrospective study of 43,000 adult male deaths and 35000 controls performed in both rural and urban areas in Tamil Nadu, India, mortality from tuberculosis was four times as great among smokers as among non-smokers.[9] Smoking was found to be associated with isoniazid resistance[10] and 'alcoholism with smoking' was associated with acquired MDR-TB.[11] WHO reports[12] a strong association of TB and smoking and also reports that smoking increases the risk of TB disease by more than two-and-a-half times and recommends to coordinate national TB and tobacco control programs. Joint efforts of WHO and Union, to control two related global epidemics released WHO/Union monograph on TB and tobacco control 2007.[13]

Around 80% of the 1.1 billion smokers worldwide live in low- and middle-income countries, where the burden of tobacco-related illness and death is heaviest[14] and India has one of the world's heaviest tobacco-related health burdens.[15] The National Family Health Survey (NFHS) surveys in India reports that the prevalence of smoking among males, illiterates, rural and lower socio-economic groups(predisposing factors for TB) has increased over years.[16]

The usual strategies adopted for smoking cessation include physician's advice, nicotine replacement therapies and pharmacological agents. On a literature search, limited studies existed on studies on smoking cessation in tuberculosis patients. Our centre's clinical study on physicians' advice on quitting smoking among TB patients had shown a success rate of 35–40% with or without counsellor's counselling.[17] We felt the need for a study to assess the effectiveness of using Bupropion-SR a safe drug and compare it with intensively trained enhanced counselling approach at TB program level, that could be effective than the standard care for smoking cessation that could be implemented. Studies assessing Bupropion SR intervention in smoking cessation in the general population done in India, reported encouraging results.[18,19] So we proposed to conduct a three-arm study with Bupropion SR, Enhanced counselling and compare with a standard counselling as per the TB program guidelines which were the control arm. The primary objective of the study was to compare the feasibility, acceptability, and effectiveness of pharmacologic therapy (Bupropion SR) versus enhanced motivation package versus standard motivation in smoking cessation among TB patients initiating treatment, under program settings in India and the secondary objective was to compare the TB outcome among those who quit and those who did not. The study registered clinical trial registry of India(no CTRI/2013/07/003830).

2. Methods

The study setting was Designated Microscopy Centres (DMCs) of the Revised National Tuberculosis Control Program (RNTCP) centres in two districts of Tamilnadu. The study design was a cluster-randomized effectiveness trial, with each DMC as a cluster unit for randomization. The study period was from 2013 to 2016. The study population was the smear-positive TB patients started on Anti-Tuberculous therapy (ATT) with a current history of smoking. We included sputum positive new or previously treated TB patients of eighteen years or older, who are current smokers and excluded patients with a seizure disorder, MDR-TB, HIV infected, past psychiatric illness and too sick (clinically judged) and with moribund status. Thirty-six RNTCP centres(DMCs) from two districts of Tamilnadu, (18 each from Villupuram and Kanchipuram districts) were randomly selected to receive any one of the interventions Bupropion SR(sustained-release) along with Standard counselling(T1), Enhanced Counselling arm(T2) or C- Standard routine counselling/Control arm(C). We ensured that rural and urban centres were equally distributed, that is nine centres from rural and nine centres from urban areas each from both Villupuram and Kancheepuram districts. Study participants with sputum AFB positive and ready to be started on anti-tuberculosis drugs (ATT), with smoking history and willing to quit smoking, after getting their consent were enrolled to the study. Smoking history details, nicotine dependence assessed using the Fagerstrom scale of Nicotine

Dependence was recorded. The Smoking Cessation intervention allotted to the study centre was delivered within a week of starting ATT by the RNTCP personnel of the centre concerned who were trained by the study team. The RNTCP personnel were the staff members available at the study centre, that included doctors, nurses, health visitors, lab technicians and others. Participants were reviewed at the second and sixth month or end of ATT when they come for giving sputum and smoking cessation was assessed by self-reporting and confirmed by Carbon monoxide(CO) Monitor test(reading <10 parts per million(ppm) considered quit). Wherever there were discrepancies, the final outcome would be still smoking when any of the methods said still smoking. Smoking cessation was defined as not currently smoking and a CO concentration of <10 ppm at the time of assessment(the 2nd month or at the end of treatment).

Sample size: Assuming the efficacy of quitting smoking by Bupropion to be 60%, the sample size was estimated to be 149 patients in each group in order to have a difference of 15% by Enhanced counselling with 80% power at 5% significant level. The sample size was projected to be 200 for a design effect of 1.16 for cluster sampling and coverage for the examination of at least 90%. Thus, a total sample size of 600 patients were calculated with 200 patients in each arm.

2.1. *Treatment arms*

2.1.1. *T1 -Bupropion SR along with standard counselling*

Along with the standard counselling for smoking cessation as per RNTCP guidelines, Bupropion SR 100 mg tablet was started once daily for a week and then twice daily for 7 weeks. Doctors at the study centres were to review the patient, counsel and prescribe the drug.

2.1.2. *T2 -Enhanced counselling arm*

This arm was a motivational package including.

1. Brochures on Smoking Cessation provision: Education material with information containing harms of smoking and information on how to quit smoking.
2. Flip charts: An extensive counselling by one to one sitting with the patient, using a flip chart prepared exclusively for the study purpose, explaining the hazards of smoking, the association of TB & smoking, how to quit smoking, withdrawal symptoms and family benefits on quitting smoking.
3. Posters: Three posters with two with details of harms of smoking, and one with TB - Smoking associations pasted in the study centres were shown.
4. Movie/video presentations: Movie clips on smoking and its harms were shown in the study centres wherever facilities were available.
5. Family counselling: Family members were also counselled and were sorted to extend their support in helping the subjects to quit smoking wherever possible

The intervention was to be delivered by the available staff member at the study centre, who were trained for the purpose.

2.2. *Control arm*

RNTCP guidelines modules to program managers[20] were followed. It recommends the 5 A approach (Ask, Advise, Assess, Assist and Arrange) and 5R approach (Relevance, Risk, Rewards, Roadblocks, and Repetition). The following were the instructions given to Medical Officers as spelt in the module: 1. The smoking status of the TB patient should be checked at every interaction. 2. It should be impressed upon the patient that smoking of tobacco will adversely affect the treatment outcome. 3. The Medical Officer has to help the patient with simple tips to quit smoking. However, if this does not yield any positive result, he should be referred to the smoking cessation clinic. 4. The patients should be protected from passive smoking. The environment of the patient has to be smoke-free at home/office and clinic. 5. To document the smoking status if any in the remarks column.

2.3. *Training and sensitization*

Before enrolling the subjects to the study, training on the smoking cessation strategies and sensitization of the related staff from different disciplines that included doctors, health visitors, lab technicians, senior treatment supervisors and others, under different sections of administrative heads (Directorate of Medical Education, Directorate of Medical Services, and Directorate of Public Health) with separate sessions for Villupuram and Kancheepuram districts was conducted, which was a challenging task as the staff were under different heads. Project staff including Social workers, Field Investigators meant for data collection but not to deliver the intervention were recruited for the study was trained first.

2.3.1. *Data Collection and analysis*

Socio-demographic and smoking details of the research subjects were captured and the interventions administered were documented in the prescribed study forms. The second and sixth month/end of ATT assessment of smoking cessation status both self-reporting and CO monitor reading was done the study project staff. TB outcome of the patients was captured from the TB register through the RNTCP personnel and documented in the study forms of each patient. Acceptability and feasibility of the interventions were assessed by the feedback of the research subjects, collected after two months after the intervention. If the intervention was delivered, as per the study norms, was considered as an 'acceptable' observation and if the intervention was delivered in steps as spelt out in protocol was considered as 'feasible' observation.

2.3.2. *Statistical methods*

Data was scrutinized to ensure accuracy, corrected for the discrepancy and missing information. The study data was entered in Epi Data (version 3.1). The data analyses were performed using SPSS version 20.0. Chi-square test was used to compare the difference in proportions between the arms. The level of statistical significance was fixed at 5%.

2.3.3. *Ethics approval*

NIRT Institutional Ethics Committee approval was obtained before the conduct of the study.

2.4. *Definitions*

2.4.1. *Current smoker*

Persons who smoked at least one or more cigarettes/bidis daily during the past seven days.

3. Results

A total of 517 patients were enrolled to the study, all were males. The Mean (SD) of selected characteristics of the subjects were as follows: (i) age:46.4(10.3) years,(ii) duration of smoking:24.6(11.5) years (iii) age at started smoking:21.8(7.1) and (iv) the number of cigarettes/bidis smoked per day:13.1(8.2). The demography and smoking characteristics of enrolled subjects at baseline under the three treatment arms are presented in Table 1. Of the total n = 381 subjects for whom the quit status was available, the proportion of patients who have quit smoking in drug, enhanced and standard arm at the end of TB treatment was 66.7%, 82.8% and 51.7% ($P < 0.001$), the quit rates among the treatment arms at 2nd month and 6th/end of treatment are presented in Table 2. A consort diagram to show the flow of enrolment and follow up of the study subjects are shown in Fig. 1. The data captured from the feedback of a total number of 418 research subjects showed that all those subjects have concurred that the interventions were delivered as per norms and done in steps as spelt in the study protocol, favouring that the delivery of the interventions was acceptable and feasible in RNTCP centres.

Out of the total 422 patients with favourable TB outcome(declared cured as sputum smears negative at the end of TB treatment), the quitting information was available in 367 cases. Out of these, 243 (66.2%), were quitters. However, there was no statistical significance in response to TB treatment between those who quit and those who did not (Favourable response 99.2% vs 97.6%).

Table 1 – Baseline demography and Smoking characteristics of subjects enrolled in the treatment arms details.

Variable	Drug arm	Enhanced counselling arm	Standard arm
Age			
≤45 years	61 (40.9)	81 (48.2)	96 (50.5)
> 45 years	88 (59.1)	87 (51.8)	94 (49.5)
Total	149 (100)	168 (100)	190 (100)
Education			
Illiterate	40 (26.8)	28 (16.7)	47 (24.9)
Literate	109 (73.2)	140 (83.3)	142 (75.1)
Total	149 (100)	168 (100)	189 (100)
Occupation			
Unemployed	8 (5.4)	6 (3.6)	8 (4.3)
Employed	141(94.6)	162 (96.4)	180 (95.7)
Total	149 (100)	168 (100)	188 (100)
Income/month			
≤ 5000 Rs	92 (61.7)	105 (63.3)	122 (64.9)
> 5000 Rs	57 (38.3)	61 (36.7)	66 (35.1)
Total	149 (100)	166 (100)	188 (100)
Marital status			
Unmarried	20 (13.4)	20 (11.9)	29 (15.4)
Married	129 (86.6)	148 (88.1)	159 (84.6)
Total	149 (100)	168 (100)	188 (100)
HIV status			
Negative	136 (97.1)	129 (96.3)	143 (97.9)
Positive	4 (2.9)	5 (3.7)	3 (2.1)
Total	149 (100)	166 (100)	188 (100)
Baseline Sputum			
Negative/1+	65 (43.6)	69 (41.3)	77 (40.7)
2+/3+	84 (56.4)	98 (58.7)	112 (59.3)
Total	149 (100)	167 (100)	189 (100)
Past H/O quitting #			
No	96 (64.4)	131 (79.9)	158 (84.9)
Yes	53 (35.6)	33(20.1)	28 (15.1)
Total	149 (100)	164 (100)	186 (100)
Duration of Smoking			
≤ 25 years old	78 (52.3)	93 (55.4)	101 (54.0)
> 25 years old	71 (47.7)	75 (44.6)	66 (46.0)
Total	149 (100)	168 (100)	187 (100)
Age Starting Smoking*			
≤ 20 years old	72 (48.3)	98 (58.3)	116 (62.0)
> 20 years old	77 (51.7)	70 (41.7)	71 (38.0)
Total	149 (100)	168 (100)	187 (100)
Type of Smoking			
Cigarette	48 (32.2)	54 (32.1)	71 (38.0)
Bidi	71 (47.7)	91 (54.2)	82 (43.9)
Both	30 (20.1)	22 (13.1)	32 (17.1)
Others	0	1 (0.6)	2 (1.1)
Total	149 (100)	168 (100)	187 (100)
No of Cigarette/Bidi per day*			
≤ 10 number	94 (63.1)	92 (54.8)	91 (48.7)
> 10 number	55 (36.9)	76 (45.2)	96 (51.3)
Total	149 (100)	168 (100)	187 (100)
Fagerstrom index score#			
Low dependant	112 (75.2)	144 (86.7)	126 (68.9)
High dependant	37 (24.8)	22 (13.3)	57 31.1)
Total	149 (100)	166 (100)	183(100)

*$p < 0.05$, #$p < 0.001$.
Only patients with complete information on demography are presented.

4. Discussion

Our study has shown that about 67%, 83% and 52% of the TB patients who were smokers given drug, enhanced counselling and standard counselling had quit smoking in the program conditions, the differences being statistically significant. We tried to ensure that all the interventions were given by RNTCP staff by themselves only This is an encouraging result and gives evidence to implement the strategies in the RNTCP centres for the management of TB patients who were smokers. The results of the studies have many implications. Firstly, enhanced counselling found to be very effective, between the arms, favouring the fact that intensive training on smoking cessation is likely to yield good results and should be scaled up in the RNTCP centres. Secondly, the drug arm could very well be an alternative strategy for smoking cessation for TB patients attending RNTCP centres, may not require very intensive training as Bupropion SR being a relatively safer, yet effective drug, easy to administer along with ATT. Thirdly, the effectiveness of the standard arm was about 50%, but it is to be

Table 2 – Quit rates among the treatment arms at 2nd month/end of IP and at the 6th month/end of treatment for TB.

Smoking Status	Treatment arm				p-values
	Drug arm n (%)	Enhanced Counselling arm n (%)	Standard Arm n (%)	Total n (%)	
At end of Intensive Phase(2nd month of TB treatment)					
Quit smoking	84 (57.5)[a,c]	99 (66.4)[b]	80 (47.3)	263 (56.7)	<0.005
Still smoking	62 (42.5)	50 (33.6)	89 (52.7)	201 (43.3)	
Total	146 (100)	149 (100)	169 (100)	464 (100)	
At end of TB treatment/6th Month					
Quit smoking	80 (66.7)[d,e]	96 (82.8)[f]	75 (51.7)	251 (65.8)	<0.001
Still smoking	40 (33.3)	20 (17.2)	70 (48.3)	130 (34.1)	
Total	120 (100)	116 (100)	145 (100)	381 (100)	

[a] Drug arm Vs Enhanced at 2nd month status – NS.
[b] Standard arm Vs Enhanced at 2nd month status – $p < 0.001$.
[c] Drug arm Vs Standard at 2nd month status – NS.
[d] Drug arm Vs Enhanced at 6th month status – $p < 0.01$.
[e] Drug arm Vs Standard at 6th month status – $p < 0.05$.
[f] Standard arm Vs Enhanced at 6th month status – $p < 0.001$.

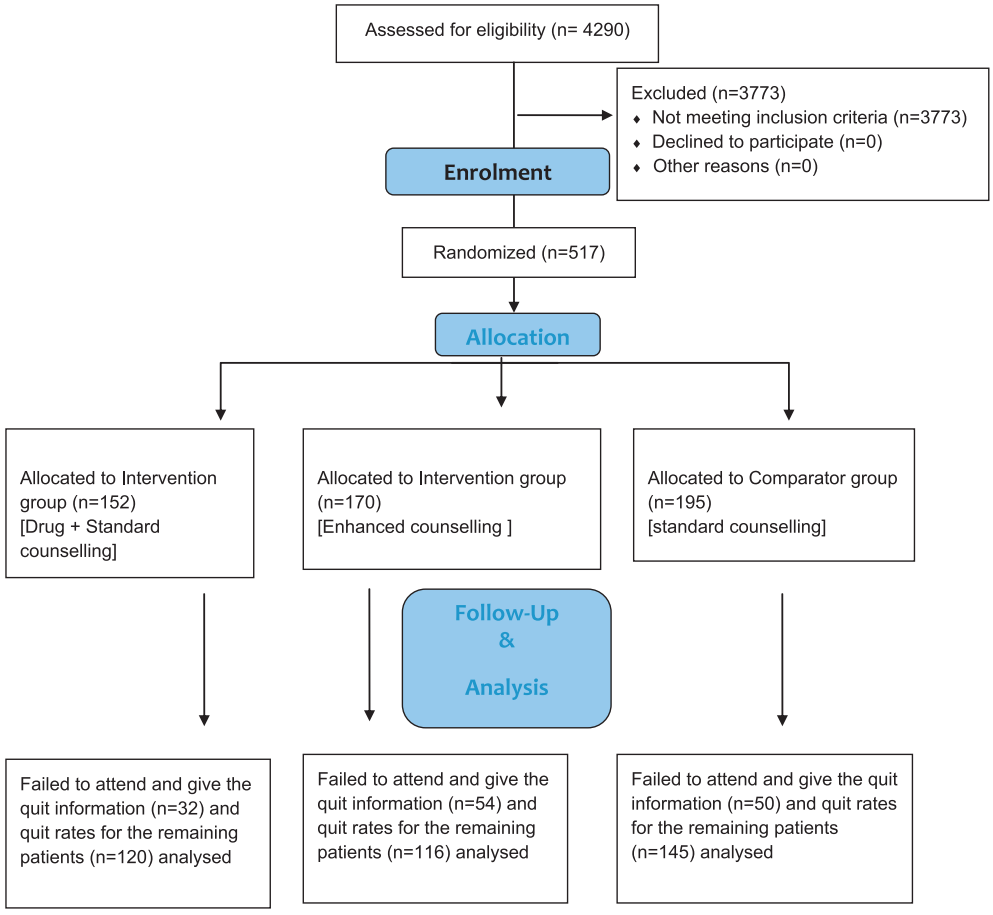

Fig. 1 – Consort Diagram to show the flow of enrolment and follow up of the study subjects.

noted that although no intensive training given to those staff of control arm study centres, we need to admit that a small part of sensitization of the RNTCP staff on delivering the smoking cessation motivation did take place due to the conduct of the study which would not have happened if the study did not take place in those centres. This shows that any amount of sensitization of the staff on smoking cessation would likely make some impact and attitude of staff in handling smokers.

Few studies on smoking cessation in TB patients have been done globally and overall all smoking cessation interventions increased smoking cessation between 15 and 82%[21] however there is significant heterogeneity of design, the definition of smoking and smoking abstinence, and implementation of the studies. A study done in Iran,[22]showed that the bupropion arm had abstinence rate at the end of six months to be 71.7% for combined intervention group, 33.9% for brief advice group and 9.8% for the control group ($p < 0.001$) and our study

intervention using Bupropion SR had resulted in a similar result with 67%. A study done in Pakistan[23,24] of the ASSIST trial(Action to stop smoking in suspected tuberculosis), with TB suspects being the study population, had some encouraging results with Bupropion.

Until the year 2017 as per the systematic review,[25] studies comparing TB outcome among quitters and non-quitters of the smokers were reported nil and listed our study among the limited ongoing studies. Recently conducted studies Sharma et al,[26] Goel et al[27] in India reported in the year 2018, found that TB outcome was not associated with the smoking cessation. The non-randomized trials in Malaysia,[28] and Sudan[29] had different findings, the former study showing higher rates of successful TB treatment outcome in the smoking cessation intervention group whereas the latter found no differences. In our study, there were more quitters among the patients with favourable TB outcomes, but we could not establish a clear relation with TB outcome and quitting smoking, as many with unfavourable TB outcomes were not available to give the smoking quitting status.

5. Limitations

The quit status of some of the patients, especially those who had unfavourable TB outcomes could not be collected, more so in later part of the study period, as they could not be traced for getting the self-reporting of quit status and CO monitor reading. Also, the regularity of taking bupropion tablets of the patients in the drug arm, could not be monitored, as the recording of the compliance of bupropion intake using 'Bupropion compliance card' to be filled by the staff who delivered the intervention were incomplete for many of the patients. If the actual compliance in taking the drug had been low, that could be one of the reasons for the quitting rate lower than enhanced counselling.

6. Conclusion

Enhanced counselling including giving one to one counselling using flip charts by the RNTCP health care workers to the TB patients attending the RNTCP centres for TB treatment as well as drug therapy using Bupropion SR with standard counselling are effective strategies for smoking cessation for TB patients treated in TB program. Implementing these strategies are acceptable and feasible at the RNTCP centres, we recommend both strategies to be implemented in the TB program for TB patients who are smokers, globally, especially in India.

Authors' contribution

RK, PAM contributed to study design, study implementation, analysis and interpretation of data. CKD contributed in study implementation, analysis, interpretation of data. VM contributed in study implementation, data management and in doing the analysis. VG contributed in study implementation with major contributions in fieldwork. VS contributed in study design, analysis, and interpretation of data. All authors had contributions to writing up the manuscript and read, approved the final version.

Funding

The study was funded by The United States Agency for International Development (USAID) through the World Health Organization(WHO) under the Model DOTS Project (MDP) reference number: 2013/313079-0.

Conflicts of interest

All authors have none to declare.

Acknowledgement

We would like to thank Dr. Soumya Swaminathan, former Director, ICMR-NIRT, former Director General of ICMR, who supported the research project and made it to happen. We would like to acknowledge the District TB Officers of Villupuram and Kancheepuram districts - Dr.R. Sudhakar and Dr Murugesan respectively whose support for the conduct of the study was commendable. The authors would like to thank Dr.Vidhubala, former head of Resource Centre for Tobacco Control, Cancer Institute, Adayar for the consultancy and support in training of the staff in smoking cessation. We are also thankful to Dr. M. Karthikeyan, Psychiatrist, for the support towards Consultancy and being a resource person for training the doctors. We are extremely thankful to the concerned RNTCP study centres staff including doctors, health visitors, and other health care staff involved in the study, who delivered the study interventions. We are thankful to M/s V. Mythily, NIRT for her support in statistical assistance. We are also thankful to the NIRT project staff who worked enthusiastically in the study. Not but not the least we thank every participant of the study.

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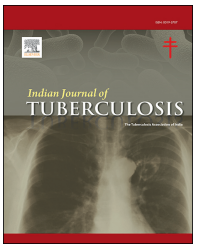

Original Article

Awareness & utilization of NIKSHAY and perceived barriers for tuberculosis case notification among the private practitioners in Udupi district, Karnataka

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ARTICLE INFO

Article history:
Received 3 August 2019
Accepted 3 January 2020
Available online 14 January 2020

Keywords:
Tuberculosis
NIKSHAY
Private practitioners
Barriers
Case notification

ABSTRACT

Background: NIKSHAY is a web-based TB case notification & management portal. The study aimed to assess the awareness and utilization of NIKSHAY among the private practitioners in Udupi district and identify the operational barriers to TB notification.

Methods: The study was conducted between January to May 2019. Allopathic doctors were included in the study. Interviewer-administered structured validated questionnaire was used. The doctors were interviewed at their clinics/hospital.

Result: Out of 206 doctors, 138 were included in the study. Most of the participants were males (88.4%).Whereas, majority of the doctors were specialists (73.2%). 99% of the doctors knew that TB notification is mandatory. The awareness of NIKSHAY was low (21.7%) among them. Of those aware, 51.9% of the doctors were registered on NIKSHAY. 92.7% of the doctors who were registered had notified at least one case in last 6 months. Training programs were effective in increasing awareness of NIKSHAY but not utilization. Factors like out-patient load, number of presumptive and diagnosed TB cases seen were associated with the awareness and utilization of NIKSHAY. The major perceived barriers for notification were difficult to treat TB, ignorance of TB burden, complicated notification system, patient stigma and loss to follow up, lack of acknowledgement from the government.

Conclusion: The awareness and utilization of NIKSHAY was low. Patient load was positively associated with the utilization of NIKSHAY. Private practitioners face various barriers which needs to be addressed to increase the notification rates.

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https://doi.org/10.1016/j.ijtb.2020.01.004
0019-5707/

1. Introduction

Tuberculosis causes high morbidity and mortality globally and is one of the top 10 killer diseases.[1] In India, almost half a million people die each year due to tuberculosis. Whereas about a million cases are missing that are either not notified, undiagnosed or wrongly diagnosed by the private healthcare providers.[2] Not notifying a TB case is an offence and may lead to imprisonment.[3] It is estimated that about 80% of TB patients consult a private practitioner before approaching the public sector, and about 40% of the TB patients seek treatment from the private sector.[4] Despite the legal provisions the notification rates are low among the private sector. In 2018, only 25% of the TB cases diagnosed in the country were notified by the private sector. The notification in Karnataka is lower than the national average with only 17.71% cases being notified by the private sector.[5]

NIKSHAY is a web-based online notification and patient management platform developed jointly by the Central TB Division and National Informatics Centre. This also enables the private practitioners to register and notify TB cases through this portal. Patient registration in NIKSHAY is mandatory to avail the monetary benefits for the TB patients and the doctors under the RNTCP.[2] Yet the awareness and utilization of NIKSHAY is low among the private practitioners.[6] RNTCP conducts various training programs among the private practitioners regarding the TB notification and programmatic updates. It is important to know the awareness of NIKSHAY among the private practitioners as they can contribute to reduce the TB burden by identification of the missing cases through notification through NIKSHAY and this would provide real-time data of the TB burden. NIKSHAY notification would also help the patient to get the monetary benefits as per the RNTCP program during their treatment course. Therefore, the study aimed to assess the awareness and utilization of NIKSHAY among private practitioners in the Udupi district.

2. Methods

2.1. Setting

The cross-sectional study was conducted in the private clinics/hospitals in the Udupi district of Karnataka between January 2019 and June 2019. The study was conducted the among the private practitioners in the Udupi district.

2.2. Inclusion & exclusion criteria

Allopathic private practitioners who have seen at least one presumptive TB case in the past two months or have treated any TB case in past with or without notifying the case were included in the study. Doctors who were working with the government and medical colleges were excluded from the study. The doctors who were not available for the interview even after 3 visit attempts were also excluded from the study. According to RNTCP presumptive tuberculosis case was defined as any individual with cough and fever for more than two weeks with or without weight loss, haemoptysis, and abnormalities in the chest X-ray.

2.3. Data collection method

A line list of 206 doctors practicing in the Udupi district was procured locally. The list was sorted as per the area of practice. An appointment was sought on telephone as per the doctor's convenience and a direct visit was made to the clinic/hospital of the doctor. 34 doctors had improper address/telephone number/couldn't be contacted; 22 doctors didn't meet the inclusion criteria or employed with medical college or government; while 12 doctors refused to participate. Therefore, the final sample size achieved was 138.

The doctors were interviewed at their clinics and data was collected using an interviewer-administered structured data collection tool. Data regarding the background information of the participants, their notification practices, awareness and utilization of NIKSHAY, awareness of the incentives, notification norms and operational barriers to TB case notification was collected.

2.4. Analysis

Data analysis was done in Statistical Package for Social Sciences (SPSS) version 15. The categorical variables were expressed as frequencies and percentages and the continuous variables as mean and standard deviation. Chi-square test and Fisher exact test were performed for categorical variables to look for associations. The level of significance was set at 0.05.

2.5. Ethical consideration

Institutional ethical clearance was obtained from Institutional Ethics Committee (IEC:628/2018). Indirect identifiers were used for all the study participants. Participant information sheet was provided to each participant and informed consent was obtained.

3. Results

Out of the 206 doctors, 34 had an improper address/wrong phone number/not answering the call, 22 doctors not having private practice/they didn't meet the inclusion criteria. 12 doctors refused to participate in the study. Thus, the remaining 138 doctors were included in the study.

The mean age of the participants was 53 ± 9 years. About 61% of the participants were less than 55 years old. Majority of the participants were males (88.4%) and were specialists (73.2%) and half of them were physicians and paediatricians. Most of the participants (75%) had seen 1 to 5 presumptive TB cases in past one month, while only 36% doctors had diagnosed TB in past six months (Table 1).

Almost all participants (99%) knew that TB is a notifiable disease. But, the awareness of NIKSHAY among the participating doctors (n = 138) was found to be low (21.7%). Only 10.9% of the doctors were registered on NIKSHAY and 10.1% of the doctors had notified at least one case on

Table 1 – Background information of the study participants.

Variable				N (%)
Age category		Less than 45 years		31 (22.5%)
		46–55 years		55 (39.9%)
		56–60 years		28 (20.3%)
		More than 60 years		24 (17.4%)
Gender		Male		122 (88.4%)
		Female		16 (11.6%)
Qualification of the participant	General Physician	37 (26.8%)		
	Consultants	101 (73.2%)	Cardiologist	4 (4.0%)
			Pulmonologist	1 (1.0%)
			Dermatologist	1 (1.0%)
			Otolaryngologist	4 (4.0%)
			Gynaecologist	13 (12.9%)
			Physician	32 (31.7%)
			Orthopedician	3 (3.0%)
			Paediatrician	24 (23.8%)
			Psychiatrist	2 (2.0%)
			Radiologist	2 (2.0%)
			Surgeon	15 (14.9%)
		138 (100%)	Total	101 (100.0%)
Number of out-patients per day		<35 patients		73 (53.3%)
		>35 patients		64 (46.7%)
		Total		137 (100%)
Number of presumptive TB cases per month		1-5 cases		103 (75.2%)
		>5 cases		34 (24.8%)
		Total		137 (100%)
Number of TB cases diagnosed in past 6 months		0 cases		88 (63.8%)
		1-5 cases		39 (28.3%)
		>5 cases		11 (8%)
		Total		138 (100%)

NIKSHAY. Only 45.7% of the participants attended advanced training on TB notification and programmatic updates provided by the Revised National Tuberculosis Control Program (Fig. 1). More than one-fourth of the General practitioners, Physicians of General medicine, Paediatricians, and Surgeons were aware of NIKSHAY (Table 2). About one-fifth of the Physicians of General medicine and Surgeons were registered on NIKSHAY.

The doctors who were seeing >35 outpatients per day and those who had seen more than five presumptive TB cases in a month as well as diagnosed more than two TB cases in past six months were more likely to be aware and

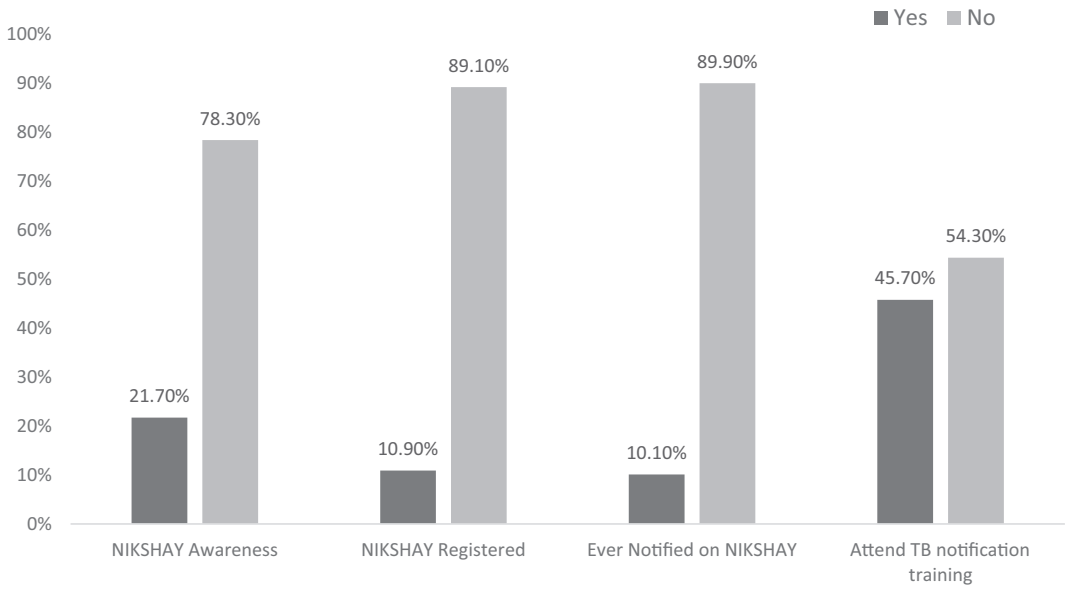

Fig. 1 – Awareness and utilisation of NIKSHAY among the participants.

Table 2 – Awareness and utilization of NIKSHAY among different designation of doctors.

Designation	NIKSHAY awareness		Registered on NIKSHAY	
	Yes	No	Yes	No
General Practitioner (n = 37)	4 (10.8%)	33 (89.2%)	0	37 (100%)
Physician (Medicine) (n = 32)	10 (31.3%)	22 (68.8%)	7 (21.9%)	25 (78.1%)
Paediatrician (n = 24)	6 (25.0%)	18 (75.0%)	3 (12.5%)	21 (87.5%)
Surgeon (n = 15)	4 (26.7%)	11 (73.3%)	3 (20%)	12 (80.0%)
Gynaecology (n = 13)	1 (7.7%)	12 (92.3%)	0	13 (100%)
Others (n = 17)	5 (29.4%)	12 (70.6%)	2 (11.8%)	15 (88.2%)

Table 3 – Factors associated with awareness and utilization of NIKSHAY among the private practitioners.

Variable		Aware of NIKSHAY		Total	p- value	Registered on NIKSHAY		Total	p-value
		Yes	No			Yes	No		
Number of out patients per day	<35 patients	9 (12.3%)	64 (87.7%)	73 (100%)	0.007*	2 (2.7%)	71 (97.3%)	73 (100%)	0.001*
	>35 patients	20 (31.3%)	44 (68.8%)	64 (100%)		13 (20.3%)	51 (79.7%)	64 (100%)	
	Total	29 (21.2%)	108 (78.8%)	137 (100%)		15 (10.9%)	122 (89.10%)	137 (100%)	
Number of TB case diagnosed in past 6 months	0-2 cases	22 (18.6%)	96 (81.4%)	118 (100%)	0.042*	8 (6.8%)	110 (93.2%)	118 (100%)	<0.001*
	3 or more cases	8 (40%)	12 (60%)	20 (100%)		7 (35%)	13 (65%)	20 (100%)	
	Total	30 (21.7%)	108 (78.3%)	138 (100%)		15 (10.9%)	123 (89.1%)	138 (100%)	
Presumptive TB cases per month	<5	18 (17.5%)	85 (82.5%)	103 (100%)	0.066	6 (5.8%)	97 (94.2%)	103 (100%)	0.002*
	>5	11 (32.4%)	23 (67.6%)	34 (100%)		9 (26.5%)	25 (73.5%)	34 (100%)	
	Total	29 (21.2%)	108 (78.8%)	137 (100%)		15 (10.9%)	122 (89.10%)	137 (100%)	
Attended training on TB notification	Yes	23 (36.5%)	40 (63.5%)	63 (100%)	0.001*	10 (15.9%)	53 (84.1%)	63 (100%)	0.083
	No	7 (9.3%)	68 (90.7%)	75 (100%)		5 (6.7%)	70 (93.3%)	75 (100%)	
	Total	30 (21.7%)	108 (78.3%)	138 (100%)		15 (10.9%)	123 (89.1%)	138 (100%)	

*P < 0.05, statistically significant.

utilize NIKSHAY (Table 3). Attending training program on TB notification was associated with better awareness about NIKSHAY but it was not related with the utilization of NIKSHAY. Participants who were aware of the incentives for the doctor and patient and also of the free availability of CBNAAT were better aware of NIKSHAY and were more likely to be registered on NIKSHAY (P < 0.001).

We also intended to identify the operational barriers to TB case notification among private practitioners (Table 4). Out of 138, only 106 doctors (76.8%) responded about their perceived barriers for notifying TB cases. Majority of the doctors felt that it was a challenge to treat TB and thus they preferred referring the case to the public sector. The other major barriers were misconception about TB epidemiology, patient stigma and lost to follow up, complicated notification system and lack of trust and acknowledgement from the government.

Table 4 – Operational barriers to TB notification.

Barriers to notification	N (%)
A challenge to treat TB (Refer the cases)	28 (26.4%)
Don't get TB cases	17 (16%)
Patient lost to follow up/Patient Stigma	17 (16%)
Complicated notification system (NIKSHAY)	16 (15.1%)
Lack of trust and acknowledgement from government	16 (15.1%)
Government treats TB better	6 (5.7%)
Lack of accurate diagnostic tests	4 (3.8%)
Lack of awareness about notification methods	2 (1.9%)
Total	**106 (100%)**

4. Discussion

In our study almost, all of the participating doctors (99%) were aware that TB is a notifiable disease. Whereas in Chennai only 73% of the doctors knew that they had to notify the TB cases,[7] while in Kerala, the awareness was 88%.[8]

NIKSHAY is a vital component of the RNTCP, which aids in TB case notification and management of the TB patient during the course of their treatment. Previously the access was limited to the public sector, but recently there have been efforts to make NIKSHAY accessible to the private sector. But we found that the awareness of NIKSHAY among the private doctors remains low (21.7%). While only 10.9% of the doctors were registered on NIKSHAY and were utilizing it. Another similar study conducted in the city of Mysore also demonstrated a low awareness of NIKSHAY (18%) among private practitioners.[6]

The utilization of NIKSHAY was also low among the private practitioners and only 10.9% of doctors were registered on NIKSHAY. Similarly, other studies have also demonstrated that the utilization of NIKSHAY among private practitioners was low (16.6%).[6]

In our study the training programs were effective in increasing the awareness and but they were inadequate to

increase the utilization of NIKSHAY. Other studies also similarly demonstrated that the training programs were effective in increasing knowledge but not effective in changing the practice.[9] The other factors that affect the utilization of NIKSHAY were outpatient load, the number of presumptive cases seen and number of TB cases diagnosed in the past 6 months. Similarly, another study conducted in Chennai demonstrated that the higher outpatient load and the number of TB case diagnosed by the private practitioner was indicative of better knowledge and practice.[10]

In our study, it was our intention to identify the operational barriers for TB notification that the private practitioners face. The common responses were: A challenge to treat TB (Refer), Don't get TB cases, Patient is lost to follow up/patient stigma, complicated notification system (NIKSHAY), Lack of trust and acknowledgement from the government. Datta K et al in their study found similar views in which the participating doctors did not have faith in RNTCP, and they wanted acknowledgement by the government to increase their participation in the program.[11] Philip S et al in their study in Kerala also found similar barriers such as misconceptions regarding notification, breaching of patient's confidentiality and causing stigma and discrimination among them, distrust and lack of coordination with the public sector.[8] Chadha S et al in their study in Mysore also had similar findings in which many private practitioners requested for enablers such as free drugs, and training program on the notification process through NIKSHAY, they also wanted timely feedback and acknowledgement from the government.[6] Thomas B E et al in their study in Chennai found similar barriers to notification of TB cases, such as lack of time, breaching patients confidentiality and offending the patients, they felt uncomfortable in reporting patient's personal information.[7] Yeole R D et al in their study in Pune came up with similar findings regarding the barriers for TB notification lack of awareness about notification of TB cases, scared of violating patient's confidentiality, complicated notification system and non-availability of a simple notification system, lack of faith and coordination with the public sector.[12]

5. Conclusion

Training provided by the RNTCP to the private practitioners is effective in increasing the knowledge about NIKSHAY and other programmatic updates. But, the coverage of the training remains low, resulting in many private doctors remaining unaware about NIKSHAY and the recent updates of the program. Even though, the training improves the knowledge, it was not found to be influencing the increase in utilization of NIKSHAY among private practitioners, with only number of daily OPD patients, number of presumptive TB cases seen in a month and number of TB cases diagnosed in past six months facilitating its utilisation.

In order to increase the TB case notification rates, it is essential to address the barriers faced by the private practitioners. Advanced hands-on training programs are needed to train the doctors regarding the notification process using NIKSHAY. It is important to bridge the gap between the public and the private sector through inter-sectoral collaborative activities and foster co-ownership of the program. Upscaling of the capacity building activities for the private sector is needed to improve their diagnostic, treatment and management practices of the TB cases.

Declaration of competing interest

All authors have none to declare.

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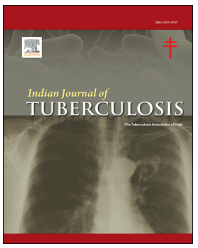

Original article

'Have we missed reporting adverse drug reactions under Revised National TB Control Programme?' - A mixed method study in Bengaluru, India

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ARTICLE INFO

Article history:
Received 4 June 2019
Received in revised form
27 August 2019
Accepted 3 January 2020
Available online 15 January 2020

Keywords:
Adverse drug reactions
Tuberculosis
RNTCP
Pharmacovigilance
India

ABSTRACT

Objective: Prompt identification, reporting and management of ADRs during anti tuberculosis treatment can ensure better compliance and treatment outcomes. The study was conducted to identify the gaps and associated factors in reporting of ADRs under RNTCP; assess knowledge, attitude and practice of RNTCP staff regarding pharmacovigilance programme and explore the barriers in reporting of ADRs from provider's perspective.

Methods: Mixed method research with sequential explanatory design was carried out in Tuberculosis Units of RNTCP administrative district of Bangalore city during July to December 2017. Quantitative study was carried out among 222 patients on intensive phase of Category I and Category II DOTS to study the incidence, severity and causality of ADRs; and records of these patients were analysed for gaps in reporting. Knowledge, attitude and practice (KAP) regarding recording and reporting aspect of pharmacovigilance programme was assessed among RNTCP staff. As part of the qualitative study, focus group discussion was carried out among RNTCP staff to study barriers for reporting ADRs from the provider's perspective.

Results: Record analysis at the time of recruitment showed documentation of ADRs in only five patients. Subsequent analysis of patient records during the middle and end of the intensive phase (IP) did not show documentation of any ADRs. Simultaneously interviews with patients revealed 116 (52.2%), 72 (32.4%) and 53 (23.8%) patients reported one or more symptoms of ADRs. The commonest ADR symptom reported were fatigability and gastrointestinal symptoms followed by musculoskeletal symptoms. KAP among 25 RNTCP staff showed that 96% of them felt reporting of ADRs was necessary and 92% reported the ADRs to their seniors, however 12% were scared to report. The main reason expressed for non-reporting was 'managing ADRs is more important than reporting' (52%). Also, 32% felt the need for retraining of staff on

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https://doi.org/10.1016/j.ijtb.2020.01.003

reporting and documentation. Barriers to reporting of ADRs were both health-system related like insufficient training and inadequate guidelines provided to RNTCP staff and patient-related factors like lack of awareness and reluctance to report ADRs.

Conclusion: Successful implementation of RNTCP and achievement of TB elimination requires provision of adequate information regarding ADRs to patients and intense follow-up and probing at each contact by programme staff to effectively manage ADRs.

1. Introduction

Globally, Tuberculosis (TB) continues to be the leading cause of death from a single infectious agent ranking above HIV/AIDS over the past five years (2012–2016) with 1.3 million deaths occurring among HIV negative TB alone. India accounts for 27% of the estimated global TB burden.[1]

Directly observed treatment short course (DOTS) is an accepted TB treatment strategy under Revised National Tuberculosis Control programme (RNTCP) for more than two decades in India. Evidences suggest that multiple drugs used for prolonged periods of time may result in undesirable adverse drug reactions (ADR) of varied severity.[2,3] Chances of non-compliance is higher whenever the patient experience ADRs thus leading to poor treatment outcomes. Repeated episodes of ADR during treatment may reduce confidence of patients over RNTCP leading to drop-outs, treatment non-compliance, treatment regimen changes and additional treatment cost.[4] Hence, intense monitoring, timely reporting, appropriate counselling and support to patients during episodes of ADR will improve compliance and treatment outcomes.[4]

Many studies report ADR incidence ranging 17–68% which mostly occur within first week of treatment initiation. Commonest ADR was gastrointestinal followed by CNS-related symptoms with most being mild to moderate.[2,5–8]

Pharmacovigilance Programme of India (PvPI) for monitoring of ADRs initiated in 2004 collaborated with RNTCP in 2013.[3] Patient guide and ready reckoner for health care providers (HCP) on prevention and management of ADRs among patients on anti-TB treatment (ATT) has been brought out by ICMR and RNTCP.[9] However, there are limited studies on understanding the ADR reporting system under RNTCP. Identifying the magnitude of ADRs among TB treated patients will help the programme in addressing and managing ADRs appropriately. We conducted this study to determine true incidence of ADRs during initial phase of ATT among TB patients under RNTCP, to identify gaps in ADR reporting and challenges faced by health care providers in implementation of PvPI.

2. Methods

A mixed method research (quantitative and qualitative) with sequential explanatory study design was conducted from July–December 2017. The Quantitative component included assessment of gaps in ADRs reporting; and assessment of knowledge, attitude and practice (KAP) of RNTCP staff on recording and reporting aspects in PvPI. Qualitative method included focus group discussions (FGD) among RNTCP staff to explore barriers in reporting of ADRs from provider's perspective.

2.1. Study setting

The study was conducted in a RNTCP administrative district [Bruhat Bengaluru Mahanagara Palike-BBMP] of Bangalore city located in Karnataka, a southern state of India. It is a densely populated (4351/km^2) urban district with 9.6 million population (2011 census). Under BBMP, fourteen tuberculosis units (TU) (with an average population of five million) are dispersed in three zones of the city namely East, West and South. TUs were randomly selected from all three zones for this study.

2.2. Part I: Quantitative study

All category-I and category-II TB patients registered under RNTCP on intensive phase (IP) of ATT were included in the study. Paediatric, drug resistant and transferred out TB cases were excluded. The key healthcare providers under RNTCP are Senior Treatment Supervisors (STS) and Senior TB laboratory supervisors (STLS) in addition to a TB health visitor (TBHV) exclusively in urban areas. The STS and TBHV in coordination with general health staff identify and educate a treatment supporter near to the patient's domicile for monitoring patient's treatment, counselling on adherence and documentation including ADRs.

Sample size was calculated based on previous studies considering the incidence of ADR as 48% under RNTCP.[5] The number was estimated to be 193 with 15% relative precision and 95% confidence level. Presuming 15% attrition rate, total sample size was calculated as 222.

After obtaining Institutional ethics clearance and necessary permission from concerned authorities, a medico-social worker was trained on data collection on identification of ADRs. Basic socio-demographic information (name, age, sex, residence), type of TB and treatment were captured from patient records and tuberculosis registers maintained at TUs and data was validated on patient's interview.

Line-list of all patients registered under the selected TUs during July–December 2017 were prepared and enrolled for

study. They were traced and interviewed personally or telephonically to elicit occurrence of any ADRs using a pretested semi-structured questionnaire. They were followed up prospectively on a weekly basis till the end of IP to ascertain for occurrence of any ADRs (Fig. 1). All reported ADRs were assessed for causality using WHO-UMC scale by the investigator.[10] If any ADRs occurred, the patients were asked if the same was reported to RNTCP staff. Further ADRs reported were validated at the start, middle and end of IP by scrutinising the treatment cards for any gaps in documentation of ADRs.

To assess the KAP, pre-tested semi-structured questionnaire was self-administered to all the Health care providers (HCP) present during the monthly review meeting.

2.3. *Part II -Qualitative study*

FGD was conducted among RNTCP staff to understand the barriers and reasons for the gaps in reporting of ADRs under PvPI of RNTCP.

FGD was conducted at BBMP District Tuberculosis Office with prior permission from the District Tuberculosis officer (DTO) on a convenient day and time for the participants and investigators which coincided with the weekly review meeting of RNTCP. Twelve STS/STLS from 14 TUs participated in the FGD and discussions were moderated by one of the investigators, trained in Qualitative research. Two investigators experienced in conducting FGDs documented the notes. FGD guide was used to aid the discussion and was

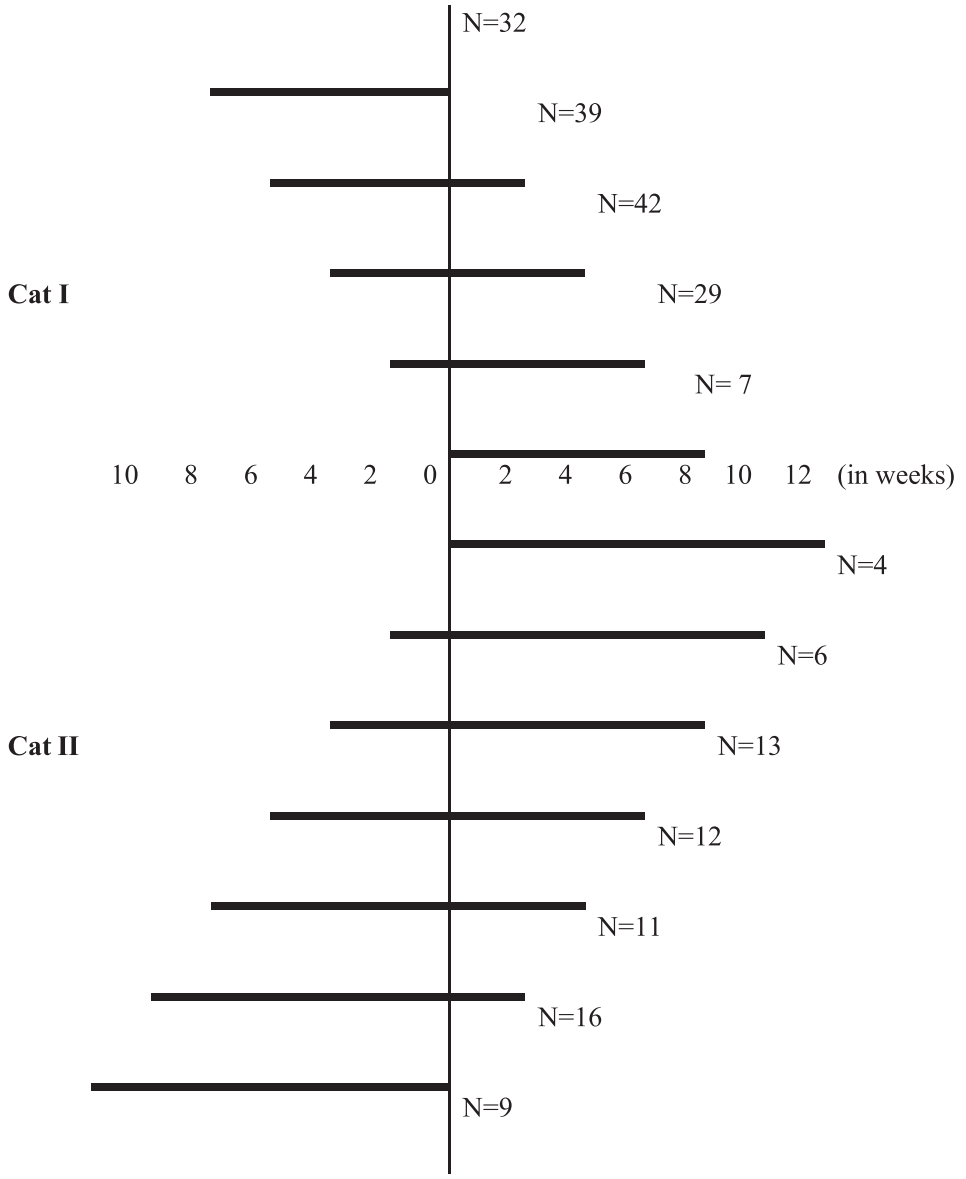

Fig. 1 – Showing different time point of ATT the patients were on at the time of recruitment (Point-0 is the point of recruitment).

conducted in local language *Kannada* in which all three investigators were well versed.

3. Analysis

3.1. Quantitative data

Data was entered in Microsoft excel and analysed using SPSS v18. Gaps in reporting of ADRs was calculated based on the difference in proportion of ADRs as documented in records and as per patient interviews. Descriptive statistics of ADR and KAP was analyzed and presented as numbers, proportions and percentages.

3.2. Qualitative data

Discussions were audio-recorded, transcribed to English and checked for translation accuracy by the third researcher. Manual descriptive content analysis was done to analyse the transcripts. The translated transcribed data was coded by inductive method by two independent researchers. The decision on coding rules and theme generation was done using standard procedures and based on consensus. Concurrence for codes was looked for and disagreement in codes were settled by discussion among investigators and final set of codes were prepared-training, guidelines, follow-up action for patients, involvement of private sector and awareness of patients on reporting ADRs. These were grouped as two broad themes-issues related to system and patients. Final report is a summary of the coded text and is collective understanding of text data by the investigators. Text that has been italicized are direct quotes from the respondents. The findings are reported by using 'Consolidated Criteria for Reporting Qualitative Research'.[11]

4. Ethics

Institutional ethics clearance was obtained from Ramaiah Medical College and Hospitals, Bengaluru. All the patients and HCPs were interviewed after obtaining written consent. Patients who reported ADR were appropriately counselled and referred to Medical-officer of TU or Peripheral health institute (PHI) for further management.

5. Results

Median age of the study subjects was 38 years (IQR: 27–47). Among them 59.9% were males; 70.3% were pulmonary cases, 27.9% had co-morbidities (Diabetes Mellitus –18.5%, Hypertension-5.8%, others- 3.6%), 3.6% were known HIV-positive cases (Table 1). Of the total, 147 (68%) patients were on Category I treatment, 96.8% on intermittent regimen and TBHV, the treatment supporter in nearly 79% cases (Table 2).

Table 1 – Baseline characteristics of study subjects (N = 222).

Variables		n (%)
Age groups (in years)	<25	45 (20.3)
	25–40	91 (41)
	41–60	66 (29.7)
	>60	20 (9)
Sex	Female	89 (40.1)
	Male	133 (59.9)
Possessed BPL card	Yes	90 (40.5)
	No	132 (59.5)
Site of TB	Pulmonary	156 (70.3)
	Extra pulmonary	66 (29.7)
HIV status	Positive	8 (3.6)
	Unknown	5 (2.3)
	Negative	209 (94.1)
Co –morbidities	Yes	62 (27.9)
	No	160 (72.1)

5.1. Gaps in reporting of ADRs

Record analysis at the time of enrolment revealed that ADRs were documented in five cases only but at subsequent analysis during the middle and end of IP, no ADRs were documented. Corresponding to record analysis, patient interviews at three different points of time revealed 52% (116), 33% (72) and 24% (53) of them reporting ADRs of varied severity (Table 3). Of them, 91% (106/116), 93% (67/72) and 94% (50/53), respectively stated that they had informed their treatment supporter. Proportion of them who sought treatment for ADRs at varied points of time were 37% (43/116), 42% (30/72) and 34% (18/53), respectively. Nearly 84% (36/43), 90% (27/30) and 89% (16/18) had sought treatment at public health facility for ADRs (Table 4).

Table 2 – Treatment characteristics of patients (N = 222).

Variables	Characteristics	Frequency n (%)
Category	Category I/New	151 (68)
	Category II/Retreatment	71 (32)
Type of patient	New	150 (57.6)
	Transfer in	11 (5)
	Treatment after failure	7 (3.2)
	Recurrent	28 (12.6)
	Treatment after loss to follow-up	15 (6.8)
	Others	11 (5)
Type of regimen	Daily	7 (3.2)
	Intermittent	215 (96.8)
DOTS provider/ Type of treatment supporter	Anganwadi worker (AWW)	5 (2.3)
	TB Health visitor	175 (78.8)
	Pharmacist	35 (15.8)
	Doctor	1 (0.5)
	Social worker	1 (0.5)
	ASHA worker	3 (1.4)
	Others	2 (0.9)
Type of treatment adherence	DOTS	180 (81.1)
	Family DOTS	26 (11.7)
	ICT supported	5 (2.3)
	Self-administered treatment	11 (5)

Table 3 – Gaps in reporting of ADRs (N = 222).

Time of review	Total ADRs reported as per patient (a)	Total ADRs as per records (b)	Gaps in reporting a-b (a-b/a*100)
At first contact (at recruitment)	116	5	111 (95.6%)
2nd contact (during IP)	72	0	72 (100%)
3rd contact (at end of IP)	53	0	53 (100%)

Table 4 – Reporting and treatment seeking pattern for adverse drug reactions.

Variable	1st contact (at recruitment) n/N (%)	2nd contact (during IP) n/N (%)	3rd contact (at end of IP) n/N (%)
No. of patients who reported ADRs	116/222 (52.2) *	72/222 (32.4)	53/222 (23.8)
No. of them who reported to STS/ treatment supporter	106/116 (91.3)	67/72 (93)	50/53 (94.3)
No. of those with ADR who sought any form of treatment for ADR	43/116 (37)	30/72 (41.7)	18/53 (33.9)
No. of those with ADR who sought treatment from public health care facility	36/43 (83.7)	27/30 (90)	16/18 (88.9)
No. of patients who stopped ATT following ADR	3/116 (2.6)	–	–

Causality assessment of reported ADRs belonged to the category of 'unclassifiable' or 'not assessable' as the information was insufficient and none of them were severe. None of them were certain, possible or likely. Commonest ADR symptoms reported were fatigability, gastrointestinal and musculoskeletal related (Table 5).

While the study was in progress, the programme was in the transition phase with daily regimen being introduced. Among 215 subjects on intermittent regimen, 119 (55.3%) developed one or more ADRs at some point of time during their IP while 44.7% never developed any ADRs which indicates that they tolerated the drugs well. Based on one or more ADR occurrence among 215 patients, incidence of ADR was estimated as 23.9 ADRs per 100-person months (95% CI, 19.6–28.2.). Similarly two out of seven patients on daily regimen reported one or more ADRs during IP phase. Since the patients on daily regimen were small in number, the results are not compared here.

With majority of patients on intermittent regimen, Incidence of ADRs was calculated only among those group.

Table 5 – Profile of symptoms as per patient's interview.

Symptoms of ADRs	1st contact (N = 116) n (%)	2nd contact (N = 72) n (%)	At end of IP (N = 53) n (%)
Fatigability	88 (75.8)	57 (79.2)	35 (66.0)
Gastrointestinal	73 (62.9)	47 (65.3)	25 (47.2)
Dermatological	49 (42.2)	25 (34.7)	12 (22.6)
Musculo-skeletal	38 (32.7)	20 (27.8)	12 (22.6)
Audio vestibular – vertigo	25 (21.5)	11 (15.3)	6 (11.3)
Neurological	23 (19.8)	15 (20.8)	10 (18.9)
Peripheral neuropathy	7 (6.0)	3 (4.2)	2 (3.8)
Visual disturbances	7 (6.0)	7 (9.7)	6 (11.3)
Sweating	6 (5.2)	1 (1.4)	1 (1.9)

5.2. *KAP of health care providers*

A total of 25 HCPs were assessed for their KAP regarding ADR reporting. Though majority (88%) were trained on ADR reporting, there were gaps in KAP as they had difficulty in comprehending the training content which was delivered in English. Many (96%) opined that ADR reporting was necessary and mandatory but HCPs self-reported that ADR reporting was missed in 4 (16%) cases. The study observed that 92% of the HCP had reported ADR to their immediate supervisors-Pharmacovigilance officer-7 (28%), DTO-7 (28%), STS/TBHV-6 (24%) and MO-3 (12%) (Table 6).

Operational barriers faced by the HCPs in reporting ADRs were (a) managing patients was more important than reporting ADRs (52%). (b) Not aware as whom and where to report (4%) (c) Most reactions being mild are manged at their own level (12%) (d) Patient do not report to the HCP(32%) and (e) afraid to report ADRs (12%). The HCPs felt that ADR reporting format needs to be simplified (48%), preferably in local language and 4% felt that training in local language would improve ADR reporting.

5.3. *Qualitative data interpretation*

On performing content analysis, we deduced 7 codes from the transcripts and categorised them into two broad categories as summarised in the box below.

BOX 1 – Broad themes emerging from FGD.

Broad Theme	Codes
1. Issues regarding system of PvPI	a. Training on PvPI b. Guidelines for reporting ADRs c. Follow-up action taken d. Involvement of Private Sector e. Motivation of STS/STLS
2. Patient related factors	a. Awareness level b. Patient behaviour

Table 6 – KAP of health care providers regarding ADR reporting (N = 25).

Knowledge related Questions	Correct response n (%)	Incorrect response n (%)	No response n (%)
Heard of Pharmacovigilance programme	23 (92)	2 (8)	–
Meaning of pharmacovigilance programme	18 (72)	2 (8)	5 (20)
Aware of system to report ADRs?	23 (92)	–	2 (8)
Aware of ADR reporting form	22 (88)	3 (12)	–
Reporting ADRs means admission that medical personnel caused or contributed to the reaction.	9 (36)	13 (52)	3 (12)
Attitude related questions	**Agree n (%)**	**Disagree n (%)**	**No response n (%)**
Is ADR reporting necessary?	24 (96)	–	1 (4)
Is ADR reporting mandatory?	24 (96)	–	1 (4)
Do you think ADR reporting will increase patient safety	24 (96)	–	1 (4)
Do you think ADR reporting will improve patient compliance	16 (64)	7 (28)	2 (8)
Do you think ADR reporting is a professional obligation	19 (76)	5 (20)	1 (4)
Do you think that you will be penalised if ADR is reported	6 (24)	19 (76)	–
Do you think ADR reporting system needs improvement?	24 (96)	1 (4)	–
Practice related questions	**Yes n (%)**	**No n (%)**	**No response n (%)**
Have you undergone training on ADR reporting	22 (88)	1 (4)	2 (8)
Have you ever seen ADR among your patients?	23 (92)	2 (8)	–
Is the suspected ADR reporting form available at your TU?	23 (92)	2 (8)	–
Have you ever reported an ADR in the reporting format?	23 (92)	2 (8)	–
Have you missed reporting an ADR?	4 (16)	19 (76)	2 (8)

1. Issues regarding system of PvPI

a. Training

One of the key issues that emerged was the need for more training on ADRs. Participants had attended training on PvPI conducted in English. They suggested training in local language would have been better. The discussions revealed that TBHVs who will be monitoring the treatment should be trained to report ADRs. TBHVs are appointed only in urban areas and at other places there were no such posts.

"We have been trained long ago, and only one training, we did not understand what we were trained for".

"Training was done in English and did not understand much."

"Please train TBHVs also as they are the first person who will be in touch with the patient."

"It would help if all health personnel are trained in identifying and treating ADRs, rather than training only one set of health care personnel. Specifically, medical officers also need to be trained."

b. Guidelines for reporting ADRs:

STS/STLS felt that guidelines were not clear regarding whether all ADRs irrespective of severity needs to be reported. Participants were aware that ADRs need to be reported, but felt reporting of mild ADRs and those symptoms which resolved within a short duration was not necessary. They opined that symptoms that take long duration to resolve are the ones that needs to be reported.

They expressed their limitation in comprehending some of the medical terminologies used in the PvPI reporting format and opined that reporting format should be in local language to aid better reporting. STS/STLS expressed that MO would be the right person to fill the PvPI format for ADR reporting. They also opined that awareness among MOs regarding ADR reporting was low who also prioritized maternal and child health over RNTCP.

"We do not understand the medical terminologies".

"We report ADRs only for the sake of reporting."

"Only ADRs that stay for long time are reported."

"What is the point of reporting ADRs when the patient is not benefited in anyway?"

c. Follow-up action taken in an event of ADR:

The key staff were not clear as to who would address the symptoms. STS/STLS are confused as to continue with the treatment or stop ATT due to ADRs. Symptomatic relief for the mild ADRs is mostly handled by STS/STLS themselves while severe ADRs referred for further management. They feel that the loop of reporting would be complete if they knew the treatment taken for ADRs at referred centres which seldom occurs.

"We don't get to know what treatment happens at referred centres".

d. Involvement of Private Sector:

Though private sector have recently started reporting TB under Nikshay, ADR reporting is still negligible. Patients often consult physician in private sector to seek care for ADR which most often goes unreported. Physicians from the private sector seek help of RNTCP staff only when patients on ATT are lost to follow-up and not for ADRs.

"Private Doctors call us only when there is lost to follow-up of patients. … …they do not report if they have treated any ADRs at their level."

e. Motivation of STS/STLS:

An important issue that might influence the programme itself was job insecurity of RNTCP staff. Most were contractual staff who do not get the benefits of a regular state government job in terms of job security or health protection.

"In 'A' class city like Bangalore it is difficult to make ends meet" "people who work for controlling Tuberculosis are not being looked after appropriately."

This could impact their motivation to carry out field activities which is critical in patient follow-up.

2. Patient related factors:

a. Awareness:

Awareness of the patients regarding ADRs would help in better reporting. Sometimes patients do not report ADRs as they are unable to correlate it with ATT. STS/STLS opined that all efforts are being made to counsel the patients before initiation on ATT about occurrence and reporting of ADRs. However, some report and some don't.

"If patients have any symptoms of ADR, they may approach the local neighbourhood physician for treatment but may not reveal that they are on ATT".

b. Patient behaviour in reporting ADRs:

The STS/STLS opined that some patients perceive them as persons who would only deliver ATT drugs and believe they are incapable of managing ADRs. They also revealed that patients do not like to be visited for follow-up due to the stigma attached. Patients are reluctant to reveal information on ADR if they have sought treatment outside the public health system. This calls for strengthening the rapport between RNTCP staff and patients which will improve their confidence in reporting ADRs.

"We ask the patients if they have any symptoms and are feeling sick, they do not reveal anything, they just take the medication and leave."

"Please do not contact us at our homes frequently, as neighbours might become suspicious of our diseases."

6. Discussion

This is one of the few studies conducted in India under programmatic settings to identify the challenges on reporting of ADRs. The incidence of ADRs was about 24 per 100 patient-months. Our study findings suggest that at least one in two persons have an experience of ADRs during the IP of treatment and majority had informed about the adverse events to their treatment supporters. There persists a huge gap in reporting of ADRs under programmatic settings for varied reasons. Under PvPI, spontaneous reporting and documentation of ADRs is expected to result in prompt action in terms of counselling, reassurance and appropriate treatment which will motivate patients to have trust and faith on the treatment provided under the system.

The study identified the following gaps which has programmatic implications. First, the proportion of ADRs reported in the beginning of IP was 52%, whereas other studies reported varied proportion ranging from 7.8 to 69%.[5,7,12–14] The commonest ADRs reported by these studies are gastrointestinal and hepatobiliary symptoms which is similar to our study. The symptoms of ADRs that occurred in this study shows that most of them are mild to moderate and many ADRs could be handled by treatment supporter if trained properly. It was noted that many patients had multiple ADRs which was reported to their treatment supporter but the evidence for the same were not reflected in the patient or system related documents maintained at the health facilities.

Second, the gap in reporting of ADRs was to the extent of 95–100% which may be due to varied perceptions of providers and patients regarding ADR reporting. Important reason by HCPs for non-documentation was that they felt that lack of clarity on the type of ADR to be reported. The programme has to come up with user-friendly, simple and feasible strategies with precise guidelines on reporting of ADRs. Extensive measures need to be undertaken to improve awareness among patients and HCPs. Patient factors included that majority of those who sought treatment for ADR from private sector did not reveal it to HCPs which could probably be due to poor knowledge on ADRs caused by ATT. At times, patients also hesitate to inform presuming that the symptoms are insignificant or can be treated locally through home remedies because of their non-aggravating nature.

Third, during FGD it emerged that training on PvPI was inadequate as it was complicated and delivered in English. The basic steps of what, whom, when and how to report was not understood. The programme has to come up with simple and effective training modules for HCPs.

Though, there are studies outlining the ADR profile of patients on ATT, there are no studies which have looked into whether all these ADRs are reported under PvPI among available literature. The study has following strengths[1]. It was

conducted under programmatic conditions and reflects the ground reality of programme implementation[2]; All patients enrolled for the study were followed-up and there were no drop outs[3]; The COREQ guidelines has been adhered to for reporting qualitative data collection and interpretation. Limitations[1] there was no validation of the fact if the patients had reported ADRs to treatment supporters. Information bias could have occurred with active probing for ADR by the interviewer which could have probably missed during spontaneous reporting[2]; Due to the change from intermittent to daily regimen during the study, a small proportion of patients on daily regimen were excluded for incidence calculation. Hence the incidence could be an underestimate[3]; barriers of reporting ADRs from patient's perspectives is not studied here.

7. Conclusion

Under programmatic settings, at least half of the TB patients encounter adverse drug reactions during their intensive phase of treatment. There exists a huge gap in recording and reporting of these adverse events. The programme needs to prioritize the implementation of pharmacovigilance programme with simple, feasible and time-tested strategies giving due emphasis to basic health care providers and patients.

Conflicts of interest

The study was funded by state Tuberculosis Office (Government of Karnataka), Bengaluru. However, the office/ concerned officers had no role or influence in design, conduct or interpretation of the results of the data.

Authors contributions

LK involved in the conception of the research idea; LK, SG, AHV, PC and SNS contributed to conception and design of the work. PRN, AD, SN and SBN gave inputs for improvement of the protocol and implementation. LK, SG, PC and AD undertook data acquisition. LK, SG, PC, AHV and SNS undertook the data analysis and interpretation. LK and PC interpreted the results and drafted the manuscript. SG, SNS, AHV, PRN, SN and SBN revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The study was undertaken as a part of the "Operational Research for Medical College Faculty under Revised National TB Control Programme (RNTCP)" conducted by RNTCP State Task Force Operational Research Committee, Karnataka with the funding support from the State Tuberculosis Office (Government of Karnataka), Bengaluru. The project and manuscript was developed during the "protocol development" and "scientific paper writing" workshops respectively. We acknowledge all the facilitators at the OR workshops who helped us develop the protocol and come out with the first draft of the manuscript. Our sincere thanks to our Principal & Dean, Nodal Officer-RNTCP, Professor and HOD, Community medicine of Ramaiah Medical College, Bangalore in extending all support and encouragement in conduct of this study. Our heartfelt gratitude to the RNTCP staff of BBMP and the patients for their unconditional support during the conduct of the study.

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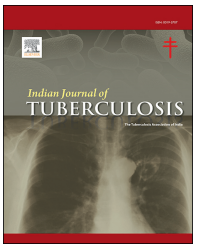

Original article

Effectiveness and safety of bedaquiline under conditional access program for treatment of drug-resistant tuberculosis in India: An interim analysis

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ARTICLE INFO

Article history:
Received 8 September 2019
Accepted 10 October 2019
Available online 16 October 2019

Keywords:
Bedaquiline
Field settings
Culture conversion
Safety and toxicity
Pharmacovigilance

ABSTRACT

Background: India accounts for a quarter of the world's multidrug-resistant tuberculosis (MDR-TB); with less than 50% having successful treatment outcomes. Bedaquiline (BDQ) was approved for use under conditional access program in India in 2015.

Objective: We evaluate the effectiveness, safety, and tolerability of a BDQ containing regimen used under field settings in India.

Method: Interim analysis of a prospective cohort of MDR-TB patients on a BDQ containing regimen at six sites in the country.

Results: Six hundred and twenty MDR-TB patients [349 (56%) males; 554 (89%) between 18 and 50 years and 240 (39%) severely malnourished] were started on BDQ containing regimen between June 2016 and August 2017. There 354 (57%) patients had MDR-TB with additional drug resistance to fluoroquinolone (MDR_{FQ}); 31 (5%) with additional resistance to second-line injectable (MDR_{SLI}) and 101 (16%) extensively drug-resistant TB. After 6 months of treatment, culture conversion was achieved in 513 of 620 (83%) patients. The median time to culture conversion was 60 days. Higher body mass index was the only factor associated with faster culture conversion (HR 1.97; 95% CI 1.24–2.9). Around 100 patients (16.3%) experienced a ≥60-ms increase in QTc interval during the treatment. Seventy-three (12%) deaths were reported, the majority of them (56%) occurring within the first 6 months of treatment.

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https://doi.org/10.1016/j.ijtb.2019.10.002

Conclusions: BDQ with a background regimen has the potential to achieve higher and faster culture conversion rates with a lower toxicity profile among DR-TB patients. Use of BDQ with additional monitoring may be safe and effective even in the field settings.

1. Introduction

The emergence of drug-resistant strains of *Mycobacterium tuberculosis* has become a significant public health problem and has led to a setback in efforts to end TB in many countries. World Health Organization (WHO) estimates that 160684 cases of multidrug-resistant TB (MDR-TB) were detected and notified in 2017 globally. Three countries accounted for approximately half of the world's cases of MDR/RR-TB: India (24%), China (13%) and the Russian Federation (10%).[1]

In 2017, of the MDR-TB cases detected and notified, only 87% were initiated on treatment with a second-line regimen; with China and India accounting for 40% of the global gap.[1] Also, the treatment success of MDR-TB remains low globally, at 55%, which further reduces to 40% in the presence of additional drug resistance to fluoroquinolones or/and second-line injectable (MDR_{FQ}/MDR_{SLI}) (extensively drug-resistant TB) with 8% failure or relapse, 15% death and 23% default.[2,3] The treatment success rate in India has been consistently below 50% in MDR-TB and below 30% in XDR-TB patients.[4] In order to close the gap between diagnosis and treatment of drug-resistant TB (DR-TB) and to increase the treatment success rate, we require newer diagnostics, higher coverage of drug susceptibility testing, easy access to appropriate treatment, and new medicines/treatment regimens that have higher efficacy and better safety.

Bedaquiline (BDQ), a new anti-TB drug with a different mechanism of action – was given accelerated approval by the United States Food and Drug Administration in 2012 and the European Medicines Agency in the year 2014. Trial results showed considerable potential for this drug to treat MDR-TB. WHO also released interim policy guidance on the inclusion of BDQ in combination therapy for treating MDR-TB patients.[5]

Considering the increasing number of DR-TB cases reported in India and as there was only limited experience available globally on the safety and efficacy of BDQ used under programmatic conditions, this drug was introduced under conditional access program (BDQ-CAP) in the country in six tertiary care centers in line with the recommendations from the drug regulatory authority of India. We present here the effectiveness, safety and tolerability profile of patients on BDQ-containing regimens treated under the BDQ-CAP in India.

2. Study population and methods

The Apex Committee under the Ministry of Health and Family Welfare, Government of India approved the use of BDQ-CAP in November 2015.

2.1. Site selection

BDQ-CAP was initiated in six sites in the country in June 2016, after rigorous training on guidelines for use of BDQ under CAP in India including cohort event monitoring (CEM) and pharmacovigilance/adverse events (AEs) reporting, which were recommended in the WHO interim policy guidance on the use of BDQ while introducing the new anti-TB drugs in a country. The six sites included Nodal DR-TB treatment centers at National Institute for TB and Respiratory Disease, New Delhi; Rajan Babu Institute for Pulmonary Medicine and Tuberculosis, New Delhi; Government Hospital of Thoracic Medicine, Chennai, Tamil Nadu; King Edward Memorial College & Group of TB Hospital, Mumbai, Maharashtra; BJ Medical College and Hospital, Ahmedabad, Gujarat; and Guwahati Medical College, Guwahati, Assam. These sites were selected based on the estimated patient load of MDR/XDR-TB patients, the geographical location of the center to represent all regions of the country and also based on the potential of the center to monitor drug safety at the time of initiation as well as during the course of treatment.

2.2. Patient selection

MDR-TB patients, defined as resistant to rifampicin alone or to isoniazid and rifampicin, with additional resistance to any or all MDR_{FQ}/MDR_{SLI}; or resistance to both FQ and second-line injectable (XDR-TB); or with mixed pattern resistance in MDR-TB being diagnosed at the culture and DST laboratories serving at these six sites were eligible to be initiated on a BDQ containing regimen. In additional patients declared as failures of prior MDR-TB or XDR-TB treatment were also re-evaluated and considered eligible for treatment with BDQ-containing regimen. At these six sites, any TB patient diagnosed through rapid molecular test (Cartridge Based Nucleic Acid Amplification test (GeneXpert) or First Line Probe Assay) and found as MDR-TB were further evaluated for the presence of second-line drug resistance to Kanamycin, Capreomycin, Levofloxacin (1.5), Moxifloxacin (2.0), Linezolid and Clofazamine by liquid culture drug susceptibility testing. If any RR/DRTB patient were found to be resistant to FQ or/and SLI drugs, they were considered for enrolment to BDQ-CAP.

2.3. Pre-treatment evaluation

Pre-treatment evaluation (PTE) consisted of a detailed clinical examination, blood tests including complete hematology, liver and renal functions, serum electrolytes, magnesium, calcium, lipase and amylase, urine microscopic examination, chest x-ray, electrocardiography, audiometry, urine

pregnancy test among women of reproductive age and specialist consults with psychiatrist, ophthalmologist and ENT. All PTEs were done at government Nodal DR-TB centers. Linkages with private laboratories were established if tests were not available at these centers, at no cost to the patients. The Nodal DR-TB center committee provided counseling and followed it with an informed decision-making process with the patients and their family members. These counseling sessions covered discussions on the benefits and potential side effects of all drugs including BDQ. Once an informed consent form was signed, the team initiated investigations related to drug safety monitoring including assessing the baseline history of known adverse/serious adverse events (AE/SAE), blood biochemical investigations, 12-lead electrocardiogram, audiometry, specialists consults, etc.

2.4. *Treatment initiation*

If all the PTEs were within normal limits, the patients were initiated an appropriate treatment regimen. Care was taken to correct any electrolyte imbalance before treatment initiation. BDQ was used along with a background regimen (BR), which was tailored to an individual based on his/her drug susceptibility test profile and prior drug exposure history by a group of experts in DR-TB center committee at the six sites. BDQ was administered as 400 mg once daily for 2 weeks, followed by 200 mg thrice weekly for 24 weeks, as per manufacturer's instructions. At the end of 24-weeks of treatment, BDQ was stopped and the rest of the drugs in the regimen were continued for 18–24 months as per standard of care. During the early part of the BDQ-CAP, all patients were hospitalized for 2-months and drugs administered under direct observation. Subsequently, as more experience was gained with this new-drug BDQ, the duration of hospitalization was reduced to 15-days. After discharge, from the hospital, patients were transferred to their respective districts to continue treatment and follow-up on an ambulatory basis with strict adherence to the follow-up schedule.

2.5. *Follow-up*

Patients initiated on BDQ-CAP were monitored with repeated sputum smear and culture examination every week for the first 2 weeks and monthly thereafter. Safety and tolerability to treatment were monitored through weekly complete blood counts for the first one month and monthly thereafter. Liver and renal function tests, serum electrolytes along with serum magnesium and calcium were measured monthly during the course of BDQ. An electrocardiogram was repeated daily for the first 2 weeks, weekly for the next 3 months and monthly thereafter. Corrective measures were taken immediately for any blood tests values above or below the given normal range.

2.6. *Study definitions*

Sputum culture conversion was defined as 2 consecutive negative culture at least 30 days apart during the course of treatment, in a patient with a positive specimen pre-treatment. Time to conversion was measured from the beginning of BDQ-containing treatment regimen to the date of specimen collection of the first of the 2 consecutive negative results. The severity of the AEs was graded as per the DAIDS criteria and their relatedness and causality to BDQ were assessed by the Causality Assessment Committee at the site, later confirmed by a central active drug safety monitoring committee (aDSM) committee.[6] QT interval was corrected for heart rate and the corrected QT interval was considered as prolonged if the absolute QTc was >500 ms or a difference of $\geq$60 ms from the baseline value and also monitored for any change within permissible limits.

2.7. *Data management*

The clinical-demographic details collected at the time of treatment initiation and during the follow-up period were captured in the CEM form, the data of which was subsequently entered in the e-portal of Revised National TB Control Programme called Nikshay. Data from Nikshay was shared with Vigiflow database of Pharmacovigilance program of India. A subcommittee periodically checked the correctness and completeness of the data entered and validated it before any analysis was carried out data entry, correctness, completeness, and validity. Statistical analysis was performed using SPSS software, version 21.0. Chi-square test was used to compare categorical variables; Wilcoxon Mann–Whitney test to compare the continuous variables while Kaplan–Meier analysis was used to evaluate the time to culture conversion. Patients with missing information were censored at the date of the last available bacteriological result. *P* values < 0.05 were considered statistically significant.

3. Results

3.1. *Patient characteristics*

BDQ-CAP in India enrolled 620 patients from June 2016 to August 2017 in the identified 6 sites. There were 349 (56%) males and 271 (44%) female patients enrolled. Age group distribution among <18 years, 18–25 years, 26–50 years and >50 years was 11 (1.8%), 272 (43.9%), 282 (45.5%) and 55 (8.9%) respectively. Majority of patients (424, 64%) were malnourished with body mass index (BMI) of <18.5, of whom 240 (39%) were severely malnourished (BMI <16). Eight patients were co-infected with human immunodeficiency virus. In this cohort, 8.4% were smokers while 6.6% were alcohol users (Table 1).

3.2. *Disease status*

Almost the entire cohort {600 (97%)} had a history of previous TB treatment, of whom 101 (16%) were treated previously for XDR-TB, 354 (57%) for MDR_{FQ} and 31 (5%) for MDR_{SLI}. At baseline, on liquid culture DST, a total of 385 (61%) patients showed RR/MDR-TB resistance with any or all FQ resistance, 101 (16.3%) had isolates resistant to both FQ and SLI (XDR-TB). Also, 26 (4%) patients were MDR-TB treatment failures, 13 (2%) were XDR-TB treatment failures, while 95 (15%) patients had mixed pattern resistance.

Table 1 – Demographic characteristics of 620 drug resistant tuberculosis patients in the Bedaquiline conditional access program.

S. No	Variables	Number (%)
1.	Gender (male)	349 (56)
2.	Age (in years)	
	<18 years	11 (1.8)
	18–25	272 (43.9)
	26–50	282 (45.5)
	>50	55 (8.9)
3.	Body mass index	
	<16	240 (38.7)
	16.1–18.5	184 (29.7)
	18.5–23.0	149 (24.0)
	>23.0	47 (7.6)
4.	HIV coinfected	8 (1.3)
5.	Injecting drug users (within past year)	1 (0.2)
6.	Tobacco Use (within the past year)	52 (8.4)
7.	Alcohol abuse (within the past year)	41 (6.6)

3.3. *Treatment effectiveness*

Patients in BDQ-CAP received a median of 4 companion drugs (range 3–6), with clofazamine and an injectable in 253 (41%) patients. Ninety-one (15%) patients had both an injectable and fluoroquinolone along with clofazamine in the BDQ containing regimen. At the end of 6 months of BDQ containing treatment regimen, sputum culture conversion was found in 513 (83%) drug-resistant pulmonary TB patients (Table 2). The median time to culture conversion was 60 days (range: 55.6–64.4 days). Patients with MDR_{FQ} or MDR_{SLI} showed a higher proportion of culture conversion and shorter time to culture convert (Fig. 1). Multivariable hazards model was used to find an association between various predictors like age, gender, BMI, type of regimen and time to culture conversion. Only higher BMI was found to be associated with faster time to culture conversion (HR 1–97, 95% CI 1.34–2.9).

3.4. *Safety and tolerability*

A total of 248 SAEs were reported in 620 patients during the study period.

3.4.1. *Deaths*

There were 73 (12%) deaths reported by 6 months of treatment during the study period. Of them, 49 occurred in patients with MDR_{FQ} or MDR_{SLI} TB, 13 in XDR-TB, 10 among mixed pattern and 1 in XDR-TB failure patient. Majority of the deaths (56%) occurred within the first 6 months of treatment, probably due to the advanced stage of the disease, as reported by treating physicians, with 48% of them being culture positive at the time of death. The regimen with BDQ, levofloxacin, an injectable and clofazamine had better survival rates than either of the drugs alone with or without clofazamine. Cause of death in the majority of them was attributed by the treating physician to respiratory failure and terminal stage of the disease.

3.4.2. *QTc prolongation*

Mean QTc in this cohort over 12 weeks of treatment was 430 ms. Fig. 2 shows the median QTc over the treatment weeks. Around 100 patients (16.3%) experienced a ≥60-ms increase in QTc interval during the treatment and BDQ was discontinued permanently in 27 (4%) patients.

3.4.3. *Other toxicity*

The most common AEs seen in this cohort were peripheral neuropathy (21%), vomiting (18%), breathlessness (13%) and thrombocytopenia (11%). Liver enzyme elevation occurred in 12 patients and serum amylase/lipase elevation was seen in one individual (Table 3). Electrolyte imbalance in terms of hypokalemia and hypomagnesemia was observed in 2% of patients in this cohort which was identified early and corrected by oral supplementation, without requiring termination of BDQ. BDQ was withheld temporarily in 18 patients with the reintroduction of the drug in all of them within two weeks. Permanent withdrawal of BDQ was done in 27 (4%) patients for various reasons like prolonged QTc (18), vomiting (2), septicemia (1), hemoptysis (1) and refusal by the patient for the restart of BDQ (5).

4. Discussions

In June 2013, the WHO published interim guidance for the use of BDQ in MDR-TB treatments that recommends adding BDQ to a WHO-recommended regimen in adult patients with

Table 2 – Culture conversion of 620 culture-confirmed drug-resistant tuberculosis patients in the bedaquiline conditional access program, categorized based on type of drug resistance.

Type of patient	Total numbers	Numbers converted	Culture converted				
			Till Mon 2	3 mon	4 mon	5 mon	6 mon
MDR_{FQ}/MDR_{SLI}	429	361 (84)	273	37	41	10	–
XDR	86	71 (83)	46	6	14	5	–
MDR (f)	26	21 (81)	13	3	5	–	–
XDR (f)	10	9 (90)	7	0	2	–	–
Mixed	69	51 (74)	40	4	5	2	–
Total	620	513 (83)	379	50	67	17	–

MDR (f): MDR-TB treatment failures; XDR (f) = XDR-TB treatment failures: MDR_{FQ} = MDR TB with fluoroquinolones resistance; MDR_{SLI} = MDR TB with second-line injectable resistance; Mixed = mixed drug resistance pattern; XDR = extensively drug resistance TB.

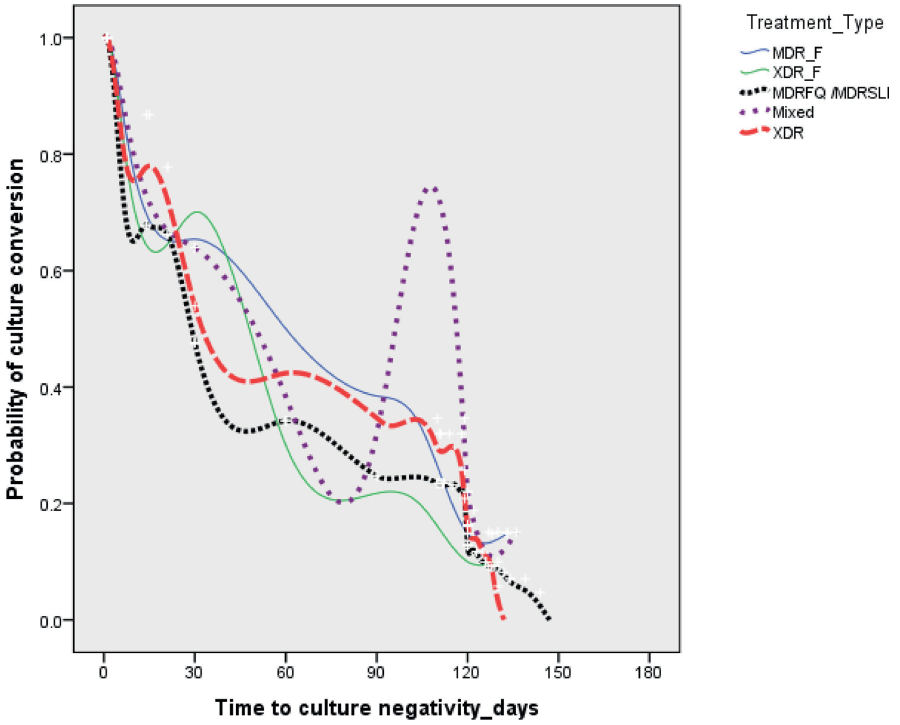

Fig. 1 – Kaplan–Meier analysis of time to culture conversion of Drug-resistant tuberculosis patients on Bedaquiline containing treatment regimen (n = 620). MDR_F: MDR-TB treatment failures; XDR_F = XDR-TB treatment failures: MDR FQ = MDR TB with fluoroquinolones resistance; MDR SLI = MDR TB with second line injectable resistance; Mixed = mixed drug resistance pattern; XDR = Extensive drug resistance TB.

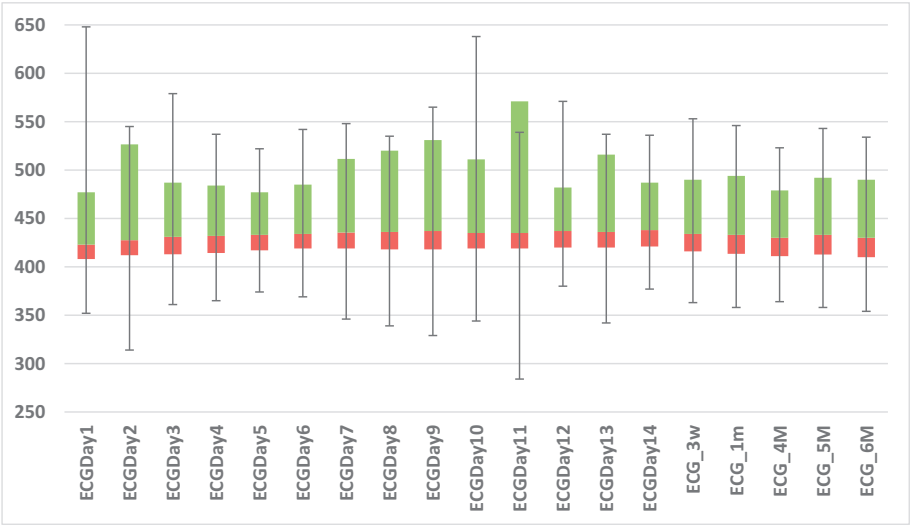

Fig. 2 – Box plot showing the median and quartile range of QTc values of patients on Bedaquiline-containing regimen in our cohort.

pulmonary MDR-TB.[5] In India, as the treatment outcomes of DR-TB patients in the field settings are very low, there is an urgent need to improve this, especially with the availability of newer drugs. BDQ-CAP was introduced in the country to be used under National program only and this interim analysis at 6-months of treatment with BDQ-containing regimen gave us an opportunity to assess the effectiveness and tolerability of BDQ in a cohort of DR-TB patients.

In our cohort, the culture conversion rate in these hard-to-treat MDR_{FQ} or MDR_{SLI} resistant TB patients and XDR-TB

Table 3 – System-wise classification of the 216 adverse events (death excluded) observed in the bedaquiline conditional access program.

S.No	System involved	Type of AE	N = 216 (%)
1	Nervous system	Peripheral neuropathy	26
		Seizures	3
		Loss of consciousness	2
		Headache	1
		Confusion	4
		Total	36 (17)
2	Cardiovascular	Prolonged QTc interval	14
		T wave inversion	3
		Infarct	3
		Complete heart block	2
		Chest pain	5
		Total	27 (13)
3	Gastrointestinal	Abdominal pain	6
		Diarrhea	5
		Vomiting	22
		Increased lipase	1
		Taste abnormality	1
		Total	35 (16)
4	Hepatobiliary	Abnormal LFT	12
		Increased uric acid	1
		Total	13 (6)
5	Renal	Renal failure	1
		Increased creatinine	3
		Total	4
6	Respiratory	Respiratory failure	2
		Breathlessness	17
		Hemoptysis	6
		Pneumothorax	1
		TB disease aggravated	6
		Total	32 (15)
7	Psychiatric	Psychosis	11
		Depression	2
		Suicidal thoughts	2
		Total	15 (7)
8	Hematology	Anemia	8
		Thrombocytopenia	12
		Eosinophilia	2
		Total	22 (10)
9	Ophthalmology	Blurring of vision	7
		Optic neuritis	1
		Total	8
10	ENT	Hearing loss	8
		Tinnitus	5
		Vertigo	1
		Total	14 (6)
11	Electrolyte abnormalities	Low potassium	2
		Low calcium/Magnesium	2
		Increased TSH	1
		Decreased TSH	1
		Acidosis	1
		Total	7
12	Dermatology	Itching	1
13	Others	Pedal edema	1
		Weakness	1

patients was 83% at 6-months of BDQ containing regimen. This is higher than that reported in clinical trials[7–9] as well as the South African Clinical access programme[10] but lower than the French cohort who reported a 97% culture conversion rate.[11] Similar results have also been reported from other countries where BDQ was used under compassionate grounds.[12] Culture conversions in our cohort were seen as early as 2-months into treatment with BDQ containing regimen. The median time to culture conversion was 60 days, faster than the trial scenario.[8] Our report is very similar to a

multicenter, multi-country study done in five continents among 428 culture-confirmed MDR-TB patients that showed a culture conversion of 57%, 81% and 91% at month 2, month 3 and end of treatment respectively.[7] Faster culture conversion was significantly associated only with a higher BMI in our cohort. Resistance to pyrazinamide,[9] lung cavitation and hepatitis infection[11] have been shown to be associated with slower culture conversion rate in other studies. BDQ was combined with clofazamine and linezolid in most of our patients. Studies have shown a good culture conversion rate when linezolid was used in regimens to treat MDR_{FQ} or MDR_{SLI} resistant TB and XDR-TB patients.[13,14] Also, a systematic review of 12 studies across 10 countries using clofazimine for the treatment of DR-TB patients showed a good treatment success rate with only mild skin and gastrointestinal AEs.[15]

As the occurrence of AE will prolong hospitalization and also affect treatment outcome, there is a need to regularly evaluate, monitor and emphasize prevention and management of ADRs. Treatment was overall well tolerated in our cohort, with few patients showing mild to moderate AEs including vomiting and electrolyte imbalance which were resolved with treatment. Majority of deaths reported in this cohort were not related to BDQ but to an advanced stage of the disease, similar to South African experience.[9] Though no severe hepatotoxicity or pancreatic dysfunction was seen in our cohort, drug toxicity should also be considered in such cases. The proportion of patients who experienced a QTc prolongation of $\geq$60-ms (16%) during treatment was similar to the French cohort.[11] However, BDQ discontinuation was higher in our cohort compared to other groups. This was seen in earlier days of the BDQ-CAP when physicians were still apprehensive about using BDQ with other cardiotoxic drugs in the regimen like clofazamine and moxifloxacin. With the gain in experience and confidence with BDQ-CAP, the discontinuation of BDQ decreased. Also, the QT correction was based on Bazzett formula as the ECG machines in the sites gave only Bazzett correction and not Fredrecia corrections, as generally recommended by the drug manufacturer. We may have had lesser BDQ discontinuation if Fredrecia correction was used. Concomitant use of moxifloxacin, clofazamine, and BDQ in our cohort showed AEs, including cardiac rhythm disturbances in approximately 20% of patients. Combination of drugs with BDQ like moxifloxacin and clofazamine has a role in increasing the QTc by 10–15 ms.[15] A recently published individual patient data meta-analysis also emphasizes that compared to failure or relapse; both treatment success and reduced mortality were positively associated with the use of linezolid, levofloxacin, moxifloxacin, BDQ, and Clofazimine.[16] Based on the safety and efficacy results from this meta-analysis, in the recent WHO treatment guidelines for MDR/RR-TB, BDQ and linezolid have been repositioned in the ranking, which also is in line with our findings in the BDQ-CAP cohort.

More than half of our cohort was malnourished with almost 40% in the severely malnourished category. Undernourished patients with MDR-TB have been shown to have significantly advanced disease with greater risk of drug toxicity and death.[17,18] Considering these factors, the Central TB Division, Ministry of Health and Family Welfare of Government of India has drafted a guidance document on nutritional care and support of TB patients in India.[19] The document provides an operational guideline to provide a protein-rich nutritional supplement to patients suffering from TB. Also, the Government has announced Direct Benefit Transfers to TB patients to meet their nutritional needs during the duration of their treatment.[20]

4.1. *Limitations*

This is a prospective cohort analysis of a BDQ-CAP done under observation in the field setting and not designed to show the differences between the existing standard of care in the national program and this new regimen. However, the improvement shown in the culture conversion rate with low toxicity, the BDQ-CAP is encouraging for scale-up of this drug in the country. Though there were strict eligibility criteria to include a DR-TB patient in the BDQ-CAP at the beginning of the program, with the passage of time and gain in confidence with this regimen, eligibility criteria were relaxed during midway of BDQ-CAP to allow more patients with mixed resistance pattern to start BDQ-CAP. Finally, this is an interim report at the end of the 6-months of BDQ-CAP. We cannot comment on the treatment outcomes at the end of the treatment (2 years) or the risk of culture reversion post stopping BDQ or relapse after treatment completion. These patients are under follow-up for treatment outcome indicators, the results of which will be published later.

4.2. *Impact of this study*

Experience learnt from this BDQ-CAP in India has helped the country learn first-hand the effectiveness, tolerability, and safety of this new drug in a TB endemic country where malnutrition, smoking, and air pollution are the main population attributable factors for fanning the TB endemic. Following the results of BDQ-CAP from these six selected sites, DSM Committee and the Revised National TB control programme were able to make recommendations to expand access to BDQ across the country under the programmatic settings, relax the strict eligibility criteria to initiate BDQ, come out with indications to initiate BDQ-containing regimen on out-patient basis and also relax the follow up investigations schedules to make it more field-friendly. Having seen the safety data from BDQ-CAP, country physicians are now more confident in using this drug for their hard to treat DR-TB patients. This program has also given an opportunity to train the country on pharmacovigilance and AEs recording and reporting for anti-TB drugs in a systematic manner. The program is also adopting the recommendations of the WHO consolidated guidelines for the treatment of DR-TB and preparing to introduce the oral longer MDR-TB regimen with BDQ in India.[21] Als, the country is currently involved in the conduct of a multicentric clinical study to evaluate the efficacy and safety of the combined use of BDQ and delamanid with linezolid in the management of adults with extensively drug-resistant pulmonary TB.[22]

5. Conclusions

In conclusion, this cohort study suggests that BDQ in combination with a BR has the potential to achieve higher and faster culture conversion rates in cases of advanced DR-TB including MDR_{FQ} or MDR_{SLI} resistance, XDR and mixed resistance pattern TB. The low toxicity profile in this cohort, especially the cardiac toxicity in terms of QTc prolongation is reassuring. These data support the scale-up of the BDQ-CAP in the country and to give access to a wider group of patients with MDR/RR-TB under the Programmatic Management of DR-TB in the country's national program. Also, health care providers and patients need to be educated about ADRs and preventability of ADR especially with the introduction of new drugs like BDQ and Delamanid.

Conflicts of interest

The authors have none to declare.

Acknowledgments

We greatly acknowledge the contribution of all the site Investigators, Medical officers, laboratory scientists, nursing staff and the entire team of the participating institutes of National Institute of Tuberculosis and Respiratory Diseases (NITRD), New Delhi; Rajan Babu Institute of Pulmonary Medicine and TB (RBIPMT), New Delhi; BJ Medical College, Ahmedabad, Gujarat; Government Hospital of Thoracic Medicine, Tambaram Sanatorium, Chennai, Tamil Nadu; Guwahati Medical College, Guwahati, Assam; and KEM Medical college and Group of TB Hospitals, Sewree, Mumbai, Maharashtra. We extend our gratitude to UNION office, New Delhi for supporting the BDQ-CAP program in terms of additional staff and Equipment; Pharmacovigilance Programme of India for the training and staff support for adverse events reporting, Staff of WHO Country Office, Central TB Division, Nikshay portal, and the Data Safety Monitoring Committee.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.10.002.

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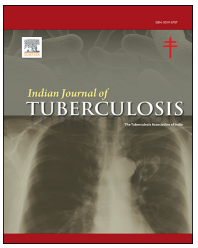

Original article

Active case finding for Tuberculosis among migrant brick kiln workers in South India

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ARTICLE INFO

Article history:
Received 11 July 2019
Accepted 13 September 2019
Available online 20 September 2019

Keywords:
Brick kiln workers
Migrant
TB symptoms
Active case finding
Health seeking

ABSTRACT

Background: "Active case finding among key populations" is one of the four main thrust areas under the National Strategic Plan for Tuberculosis (NSP) 2017–25.

Objective: This study aims to actively screen for TB symptoms and disease among migrant brick kiln workers and their care seeking behaviour for the symptoms through a private –public partnership effort.

Methods: This was a cross sectional study conducted among all migrant brick kiln workers working in the brick kilns in the field practice area of the Rural Health Centre of a medical college hospital. A pretested structured questionnaire was used for the interview. Productive Cough with or without other symptoms for 2 weeks or more was considered suggestive of TB. Sputum smear microscopy and Gene Xpert were used to diagnose TB among symptomatics. SPSS version 16.0 was used for analysis.

Results: Among 580 brick kiln workers, the prevalence of TB symptoms was 9.7%. Upon sputum examination, one was found to be positive for TB. Smoking was found to be associated with TB symptoms ($p < 0.05$). Only 50% of the symptomatics sought health care and the main reason for not seeking was low severity of symptoms.

Conclusion: Active case finding is helpful in screening and diagnosing TB among the marginalised community of brick kiln workers.

1. Introduction

"Active case finding among key populations" is one of the four main thrust areas under the National Strategic Plan for Tuberculosis (NSP) 2017–25. The program aims to *systematically screen* and encourages to scale up *public private partnership*. NSP mentions as key affected population – 3 groups of people namely, those having increased exposure to TB because of the place of work or living, those with limited

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https://doi.org/10.1016/j.ijtb.2019.09.003
0019-5707/

access to quality TB services and the people who are at increased risk due to their biological or behavioural factors.[1] Migrant brick kiln worker population fits in all the above categories to be marked as a Key affected group.

Brick kiln workers are one of the marginalised community who have come to work in different districts. They are economically vulnerable and belong to the lowest stratum of consumption quintiles. Majority of them are from socially disadvantaged backgrounds. They receive an advance payment for 6 months and then work as 'jodi workers' to repay for the money received. Thus they are de facto bonded labourers.[2] They live in kutcha houses with very poor lighting and ventilation and sanitary facilities are next to none.

Their constant exposure to dust, poor nutrition, long working hours combined with very poor environmental conditions make them a vulnerable target for chronic respiratory conditions and Tuberculosis. Around 40% of brick kiln workers were found to be having more than one respiratory symptom at a given time in a study from Egypt.[3] High dust exposures have been proven to lead to increased prevalence of respiratory symptoms from a study in brick kiln workers in Nepal.[4] A recent study from South India shows the prevalence of chest symptoms for TB among brick kiln workers to be 9.4%.[5]

Recognising migrants as marginalised population and having dedicated resources for TB control among them are some of the operational pillars of the 2008 World Health Assembly.[6] Identifying the cases early by active screening especially in the high risk groups are the first and foremost step in the elimination of TB. WHO suggests systematic screening for TB in workplaces with silica exposure.[7] In this way, the worsening of the condition, transmission to others and even mortality due to TB are prevented. Also knowledge on the health seeking pattern for their symptoms and what care they got at the health facilities will bring to light the level of TB awareness, investigation practices and care for TB symptoms by the practitioners in the local area.

Thus this study aims to actively screen for TB symptoms and disease among migrant brick kiln workers and their care seeking behaviour for the symptoms through a private–public partnership effort in the district of Thiruvallur in Tamilnadu.

2. Methods

This is a prevalence study done among migrant brick kiln workers who are staying and working in the brick kilns that are located in the field practice cum demonstration area (FPDA) of the Rural Health and Training Centre (RHTC) in Tiruvallur district attached to a medical college hospital in Chennai, Tamilnadu.

According to the study by Beena et al in their study on prevalence of chest symptoms among migrant brick kiln workers, the chest symptomatics constituted 9.4% of the study population.[5] Using this for sample size calculation, and an absolute precision of 3, a sample size of 363 was arrived at. Upon surveying, there were 12 brick kilns in the FPDA with an average worker population of 50. The owners of the brick kilns were residents of the villages in the study area, and the workforce was from different districts in Tamilnadu. They stayed and worked in the kilns for about 6–8 months in a year.

2.1. *Ethical considerations*

The Institutional Ethics Committee of Sri Ramachandra University approved the study (IEC-NI/16/AUG/55/66). Permission to conduct the study was obtained from Brick kiln Association of the district as well as from the individual owners of the kilns. After explaining the purpose of the study, written informed consent was obtained from all the participants before administering the questionnaire.

2.2. *Data collection*

After enquiring about the nature and duration of work and personal habits, information was sought about the symptoms specific for Tuberculosis and its duration. Then the details of health seeking for the reported symptoms namely, the health facility, and timing of visit since symptom onset and also whether any test for TB was performed on them were asked. Also the reasons for not seeking care were enlisted.

Any person who reported cough with sputum for 2 weeks or more with or without the other symptoms namely haemoptysis, night sweats, fever, chest pain, loss of appetite and loss of weight was considered to be a TB symptomatic. They were further given appointment within the next week for sputum examination and X-ray in the RHTC. Transport was arranged to bring the workers to the centre from each brick kiln.

Each of the symptomatic underwent X-ray Chest PA view. A trained lab technician collected a spot sample of sputum for smear examination and another sample of sputum for doing Gene Xpert test at Thiruvallur Government hospital. A container was handed over to them for early morning sample explaining them the procedure. The health worker handed over the samples for Gene Xpert at the district hospital on the same day. He also went to the kilns next day to collect the early morning sputum sample. TB was diagnosed if any one sample was positive by smear examination or by Gene Xpert.

2.3. *Statistical analysis*

Descriptive statistics namely proportion, mean, standard deviation, range etc. were calculated for the background variables. Test of significance for difference in proportion among groups was found using Chi-square test and if the p value is less than 0.05 it was considered as statistically significant. SPSS Inc. 16.0 was the statistical software used for analysis.

3. Results

There were 650 such workers in the FPDA area. Upon contacting each one of them, there was a non-response of 10% due to reasons like fear of medical check-up, busy with the work and unwillingness to participate. There were 580 participants in this study. Around 89% of the subjects were less than 50 years of age. The median age of the participants was 35 years. Males and females were in almost equal proportions (49% vs 51%). More than half of the workers were illiterates (52%). There was no difference in educational status among males and females ($p > 0.05$).

Two-thirds (66%) of the study population were engaged in moulding bricks and one-fourth (25%) in carriage and placement. The proportion of males working in baking was higher whereas more females worked in moulding and carriage and placement ($p < 0.05$). A higher proportion of females worked for less than 5 years in the kiln whereas there were more males who worked for more than 15 years ($p < 0.05$). There were more males who were smokers, consumed tobacco, alcohol ($p < 0.05$). Yet a high proportion of females consumed tobacco (12.2%).

Among the smokers ($n = 125$), 116 (93%) used only beedi while the remaining 9 (3%) used cigarettes and beedis. The median duration of smoking was 12 years and they smoked on an average 15 times per day. Very few (6) have stopped smoking and alcohol.

Among the study subjects, 64% were having normal BMI whereas 16% and 20% were in underweight and overweight – obese categories respectively. Close to 80% of them worked for about 10–11 hours per day. The moulding work was done during night (10 pm–6 am) whereas baking and carriage during day. Many of them used to smoke or use tobacco just to be awake during the nights.

The prevalence of the chest symptomatics in the study population was 9.7% (95% CI 7.4–12.4). Among those the proportion of subjects with other TB symptoms were haemoptysis 4 (7%), loss of weight 13 (23.2%), loss of appetite 16 (28.6%), chest pain 7 (12.5%), night sweats 6 (10.7%), and prolonged fever 17 (30.4%). Table 1 gives the prevalence of chest symptomatic among the study population and its association with their background characteristics.

When the background characteristics were cross tabulated with the presence of symptoms suggestive of TB, higher age >50 years, male gender, low educational status, long working hours and duration, tobacco use, smoking, alcohol use were all found to have a higher risk for developing symptoms. But only smoking was found to have a statistically significant association with TB symptoms ($p < 0.05$).

Table 2 gives the Health Seeking pattern of the symptomatic subjects for their complaints. Among the symptomatics ($n = 56$), 25 (44.6%) had sought health care. Majority of them (64%) waited for a week before seeking healthcare. More than half of the subjects who did not seek healthcare quoted low severity of symptoms as the reason. Among the people who had symptoms and sought health care, sputum test was done on 3 and X-ray on 2 at the place of visit.

The proportion of health seeking for chest symptoms was higher among literates compared to illiterates (48.3% vs 40.7%). Similarly more women (54%) sought health care compared to men (37%) for their symptoms. More people in under 50 years sought health care compared to those above 50 years of age (48% vs 30%). But these difference in proportions were statistically not significant ($p > 0.05$).

When the chest symptomatics were asked to come to RHTC, 43 (77%) came. Chest X-ray was taken for all of them and was read by a qualified chest physician at the District hospital. Table 3 shows the X-ray findings of the symptomatic subjects. The rest 13 (23%) didn't come quoting recovery from symptoms or busy with work schedule.

Among those who visited RHTC, 22 (51%) alone gave sputum for examination. The remaining subjects either recovered from chest symptoms or were unable to bring out sputum. The second sputum sample (early morning) was given by just 4 (18%). The sputum smear examination was negative among all the study participants whereas one subject was positive for sputum AFB by Gene Xpert test. The subject

Table 1 – Prevalence of Chest symptomatics among study population.

Background characteristics	Number ($n = 580$)	Prevalence ($n = 56$) N (%)	Odds ratio	P value
Age				
Up to 50 years	517	46 (8.9)	1	0.071
>50 years	63	10 (16.1)	1.957	
Sex				
Male	284	30 (10.6)	1	0.476
Female	296	26 (8.8)	0.818	
Educational status				
Illiterate	299	27 (9.1)	2.283	0.428
Primary schooling	99	8 (8.1)	2.044	0.510
High school	158	20 (12.7)	3.333	0.251
Higher secondary/ diploma/graduate	24	1 (4.2)	1	
BMI (kg/m^2)				
Underweight <18.5	94	10 (10.6)	1.306	0.487
Normal 18.5–25	371	31 (8.4%)	1	
Overweight and obese >25	111	14 (12.6)	1.583	0.179
Hours of work per day				
< or =8 h	121	8 (6.6)	1	0.210
>8 h	455	48 (10.5)	1.636	
Duration of work (years)				
<5 yrs	201	17 (8.5)	1	
6–15	262	27 (10.3)	1.237	0.513
>15	101	12 (11.9)	1.451	0.350
Smoking				
Yes	125	19 (15.2)	1.865	0.018*
No	455	37 (8.1)	1	
Tobacco				
Yes	153	13 (8.5)	1.209	0.566
No	427	43 (10.1)	1	
Alcohol				
Yes	202	19 (9.4)	1.048	0.874
No	378	37 (9.8)	1	

*p-value < 0.05.

Table 2 – Health seeking for TB symptoms ($n = 56$).

Health seeking for symptoms of TB	N (%)
Health care sought	25 (44.6%)
Timing since onset	
Within 2–3 days	4 (16%)
1 week later	16 (64%)
1 month later	5 (20%)
Place of visit	
PHC/Government hospital	7 (28%)
Rural Health and Training Centre	10 (40%)
Private hospital	8 (32%)
Reasons for not seeking health care ($n = 31$)	
Symptoms not severe	17 (55%)
Work pressure so no time	5 (16%)
Distance/no transportation	8 (26%)
Fear of treatment	1 (3%)

Table 3 – X-ray findings of the symptomatic subjects ($n = 43$).

X ray findings	No.	%
Normal	16	2.8
Increased broncho-vascular markings	19	3.3
Right hilar prominence	1	0.2
Emphysematous lungs	1	0.2
Right & left upper zone non-homogenous shape	1	0.2
Right lower zone emphysema and bronchiectatic changes	1	0.2
Upper pan-cortical enlargement	1	0.2
Upper pericardial enlargement	1	0.2
Dextrocardia with situs inversus	1	0.2

was sensitive for Rifampicin and was started on Category I (newly diagnosed) Anti-Tuberculous Treatment from RHTC.

4. Discussion

This study was done by a private public partnership to actively screen for Tuberculosis symptoms and disease among 580 migrant brick kiln workers in 12 brick kilns in the field practice area of RHTC of a medical college in South India. There were 56 symptomatics (9.7%) who were asked to further undergo sputum and X-ray examination, and one was positive for TB by Gene Xpert and started on treatment.

There were equal number of males and females and most were less than 50 years of age. More than half of them were illiterates. Among males, 43% were smokers and even among women 12% consumed tobacco. All the workers were from very poor socio-economic background. They worked for prolonged hours in a dusty environment. Close to two-thirds had worked for more than 5 years in brick kilns. Thus they had all the risk factors for developing Tuberculosis.

The prevalence of TB symptoms of cough and sputum more than 2 weeks was present in 9.7% of the study population. A study from rural and urban parts of South India reports the prevalence of Chest symptomatics to be 2.7% and 4.9% respectively.[8] But a study among brick kiln workers found it to be 9.4% which was similar to this study.[5] Thus the prevalence is clearly high among the migrant brick kiln workers when compared to urban or rural population. There is a self-selection in choosing to work in the brick kiln. Only those are free from any ailments opt to work in the kilns as most of them are aware from previous experience that it involves heavy long duration work for 5–6 months away from home. We may therefore infer that these people have developed these symptoms after started working in the kilns.

Apart from cough, the most frequent symptoms were prolonged fever and loss of appetite. Smoking was found to have a statistically significant association with development of TB symptoms. That smoking and heavy drinking increase the risk for Tuberculosis is well known.[9–11] But in this setting, the workers while continuing to smoke or use tobacco (rather excessively) to work in the nights didn't drink during the six working days and reported drinking only in the weekends. In the months when they don't work in kilns, many are daily and heavy drinkers. This change in smoking and drinking pattern might influence the association with TB among the workers.

Around 45% of the symptomatics sought health care for their symptoms in this study. This is comparable with the study from brick kiln in Tiruvallur[5] (50%) but very low compared to rural and urban areas where it ranges from 63 to 80% in different studies in India.[8] The reasons for not seeking care was low severity of symptoms (55%) which was similar to other studies.[8,12,13] Even when the symptomatics sought health care, sputum test was done on only a small proportion (3/25). Health workers while treating patients must ask about their background to know if they are from a key population and perform tests for TB at the first possible encounter in order not to miss them. Upon screening for 580 workers, one was identified as TB positive and started on treatment in this study.

The study is an example of successful private–public partnership in active screening for TB among high-risk population. Not only symptom screening, this study also attempted to do X-ray, test their sputum for TB bacilli by microscopy as well as Gene-Xpert to arrive at a diagnosis.

4.1. *Limitations*

Although 56 people had symptoms suggestive of TB, we were able to mobilise only 50% of them for sputum collection at RHTC. And out of them only 4 gave a second sample. This could have led to underestimation of the prevalence.

5. Conclusion

The prevalence of chest symptoms is high among brick kiln workers. Active screening is the only option in migrant workers who have a poor health seeking pattern and accessibility to health care. It is suggested that such people when they approach health facility, the health sector must be proactive and take sputum sample at the first meeting. Also awareness has to be brought on the association between smoking, alcohol and TB among the workers attempts made to decrease the exposure.

Author contributions

Vanishree Shriraam: Concepts, Design, Definition of intellectual content, Literature search, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor.

R. Srihari: Definition of intellectual content, Data acquisition, Manuscript editing, Manuscript review, Guarantor.

T. Gayathri: Design, Data analysis, Statistical analysis, Manuscript preparation, Guarantor.

Lakshmi Murali: Design, Definition of intellectual content, Manuscript editing, Guarantor.

Source(s) of support

Tuberculosis Association of India (2016–17) – Short term research project – Rs. 20,000.

Conflicts of interest

The authors have none to declare.

Acknowledgement

We thank TB Association of India for funding this study and the Brick kiln association of Thiruvallur district for giving approval to conduct the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.09.003.

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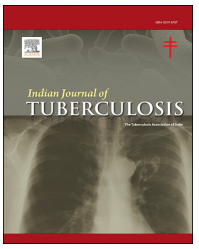

Original article

Profile of osteoarticular tuberculosis in children

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ARTICLE INFO

Article history:
Received 8 July 2019
Received in revised form
16 August 2019
Accepted 16 August 2019
Available online 22 August 2019

Keywords:
Bone
Children
Osteoarticular
Tuberculosis

ABSTRACT

Objective: To determine clinical profile of osteoarticular tuberculosis (TB) in children.
Methods: Cross-sectional analysis from 2007 to 2013. All patients diagnosed with bone TB, spinal TB or TB abscesses were included.
Results: Out of 1318 children with TB, 39 (2.96%) had osteoarticular TB, of which 16 (42%) had osteomyelitis, 8 (20.5%) had spinal involvement, 7 (17.9%) had TB synovitis, 2 (5.1%) had psoas abscess and 6 (15.4%) had abscesses. The mean age of presentation was 7.1 ± 3.5 years (range 2–14 years). Of the 33 cases in which a culture was done, 25 (64%) showed a positive culture. Drug sensitivity tests were done in 21 patients of which 10 (47.6%) tested were drug resistant, of which 4 (36.4%) were multidrug resistant (MDR), 2 (18.2%) were extensively drug resistant (XDR), 3 were pre-XDR (27.3%) and 1 was polyresistant (9.1%). Nine (23.1%) patients had TB in the past with a treatment duration of 8.3 ± 5.3 months. Contact with a TB patient had occurred in 10 (25.6%) cases. Associated pulmonary TB were seen in 6 (15.39%) and TB meningitis were seen in 1 (2.6%) patients. Surgical intervention was needed in 11 (28.2%) patients of which 5 (45.5%) underwent curettage, drainage was done in 1 (9.1%), arthrotomy in 4 (36.4%) and spinal surgery in 1 (9.1%) patient.
Conclusion: Drug resistant osteoarticular TB is an emerging problem in children.

1. Introduction

Bone and joint tuberculosis (TB) comprise a group of serious infectious diseases, whose incidence has increased in the past 2 decades, especially in the underdeveloped countries.[1] According to literature, spinal TB accounts for approximately half of all the cases of musculoskeletal tuberculosis.[2] A study in Chennai revealed that the prevalence of bone TB has been almost the same over the last 16 years and is more in the BCG non-vaccinated children.[3] The disease is common in the 1st and 2nd decades of life.[4] However, there is very little literature on prevalence of bone TB in children especially from Western India. We undertook this study to determine prevalence and clinical profile of osteoarticular and spinal tuberculosis (TB) in children affected with TB.

2. Methods

This cross-sectional analysis was done at the Pediatric TB clinic, at a pediatric tertiary referral center in Western India from 2007 to 2013. All patients who were diagnosed with bone

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https://doi.org/10.1016/j.ijtb.2019.08.014
0019-5707/

TB, spinal TB or TB abscesses were included in the study. Diagnosis was based either on histology, presence of acid fast bacilli (AFB) on smear or growth of mycobacterium tuberculosis (MTB) on culture. Drug sensitivity tests (DST) were performed in patients who had a positive TB culture and could afford the cost of testing. Patients were diagnosed to have multidrug resistant TB (MDR), extensively drug resistant (XDR) TB, partial XDR or polyresistant as per our previous classification.[5] Clinical and laboratory features of each patient were recorded. A detailed history of contact with a TB patient, prior BCG vaccination as well as occurrence and treatment duration of any past TB was recorded. Any associated organ involvement was recorded. ESR and lymphocytic counts were recorded. ESR was found to be elevated if it was greater than 20mm. Chest X-ray and HIV were done in all patients. Mantoux test, other radioimaging were done as and when required. A Mantoux reading more than 10 mm was considered as positive. The number of patients who were currently on treatment, who had completed treatment and who were lost to follow up was recorded.

Prevalence of bone TB among all patients with TB was determined. The association between bone TB (osteomyelitis and spinal) and age, gender, positivity of tuberculin skin test (TST), culture positivity, drug resistance, elevated ESR, BCG vaccination, past TB, TB contact, associated organ involvement and need for surgical intervention was determined. Data was analyzed using Graph pad software. Statistical methods used were Chi Square Test or Fishers exact test and unpaired 't' test. The association was considered statistically significant if the p value was <0.05.

3. Results

Out of the 1318 cases, 39 (2.96%) had bone TB. Mean age of presentation was 7.1 ± 3.5 years with a range of 2–14 years. Male: female ratio was 22:17. TB osteomyelitis was seen in 16 (42%), spinal TB in 8 (20.5%), TB synovitis in 7 (17.9%), psoas abscess in 2 (5.1%) and paravertebral, gluteal and axillary abscesses in 6 (15.4%) patients. Ten out of 11 (90.9%) patients has a positive mantoux test. Of the 33 cases in which a culture was done, 25 (64%) grew mycobacterium tuberculosis (MTB). DST was done in 21 patients and 10 (47.6%) were drug resistant, of 4 (36.4%) were multidrug resistant (MDR), 2 (18.2%) were extensively drug resistant (XDR), 3 were partial XDR (27.3%) and 1 was polyresistant (9.1%). Nine (23.1%) patients had been treated for TB in the past with a treatment duration of 8.3 ± 5.3 months (range of 2–18 months). Contact with a TB patient had occurred in 10 (25.6%) patients. Seven (18%) patients had associated organ involvement of which 6 (85.7%) had pulmonary TB and 1 (14.3%) had TB meningitis. In 19 (70.4%) out of 27 cases tested, the ESR was found to be elevated. The mean ESR was 43.9 ± 32mm (range of 5–142mm). Lymphocyte counts at presentation were 4073.1 ± 2248.6/cumm (range of 882–11368/cumm). Surgical intervention was needed in 11 (28.2%) patients of which 5 (45.5%) underwent curettage, drainage was done in 1 (9.1%), arthrotomy in 4 (36.4%) and spinal surgery in 1 (9.1%) patient. BCG vaccine was given in 32 patients (86.5%). On follow up, 7 (18%) patients were lost to follow up, 14 (35.9%) patients completed treatment and 18 patients (46.2%) were still on therapy. The average duration of current treatment was 8.9 ± 5.8 months, with a range of 1–21 months. Factors associated with spinal (including psoas abscess and paravertebral abscess) and osteoarticular TB (including synovitis and osteomyelitis are depicted in Table 1. Elevated ESR was more commonly seen in spinal TB as compared to osteoarticular TB (Odds ratio = 4.46).

4. Discussion

Bone and joint TB is an uncommon presentation of TB. According to literature, of all the patients suffering from TB, nearly 1–2% have involvement of the skeletal system,[6] which is consistent with the prevalence of 2.96% found in our study. In the pediatric age group, the 8% of the cases of extra pulmonary TB are those of osteoarticular TB.[3]

Vertebral tuberculosis is the most common form of skeletal tuberculosis, and constitutes about 50% of all cases of skeletal tuberculosis in the reported series.[6] Records of patients with multifocal osteoarticular TB have also shown that appendicular involvement is more common.[7] A study in Taiwan which analyzed the clinical characteristics of children with TB found that among 21 cases of TB osteomyelitis, tibia (33%) and spine (33%) were the most common sites of involvement.[8] Similarly, in our patients among osteomyelitis, spine was the most common site of involvement (23.1%) followed by the hip (12.8%).

A survey of 21 patients of spinal TB in London showed that MTB was isolated on culture from 14 (67%) patients, which is

Table 1 – Factors associated with spinal and osteoarticular TB.

	Spinal TB + psoas abscess (n = 12)	TB osteomyelitis + TB synovitis (n = 24)	P value
Age (years)	8 ± 3.6	6.2 ± 3.1	0.1118
Male	6 (50%)	15 (62.5%)	0.7199
Female	6 (50%)	9 (37.5%)	
Positive TB Culture	8/12 (66.7%)	14/18 (77.8%)	0.6779
Drug resistance	3/7 (42.9%)	7/12 (58.3%)	0.6499
Past TB treatment	2 (16.7%)	6 (25%)	0.6910
TB contact	1 (8.3%)	8 (33.3%)	0.2193
Associated organ involvement	2 (16.7%)	5 (20.8%)	1.0000
Elevated ESR	7/8 (87.5%)	11/18 (61.1%)	0.3602
BCG vaccination	10/11 (90.9%)	20 (83.3%)	1.0000

consistent with the results of our study (77.8% positivity). However, in their study, only 1 was an MDR strain.[9] A study on 93 specimens from patients of osteoarticular TB in Mumbai showed that culture was positive in 47 (53%), drug resistance was present in 15, of which 10 were MDR and 2 were XDR[10] which is similar to our study which suggests that drug resistant bone TB is highly prevalent in the city of Mumbai.

In the London study, 4 patients (19%) had a previous diagnosis of tuberculosis, which is similar to our results of 25% patients whereas 11 (52%) had a known contact with a TB patient.[9] This is significantly greater than the results seen in our study of 33.3% suggesting that bone TB in children can occur even without a significant exposure to a patient having TB.

Though bone TB is common in children who have not received BCG,[3,8] in our study 83.3% of the patients in our study had been vaccinated with BCG suggestive that in an endemic country such as India, BCG may not protect against skeletal TB.

As per a study in England, the mean age of occurrence of osteoarticular TB is 9 years.[11] Similarly, in our study, the mean age was found to be 7.1 years. Gender predominance has not been found in bone and joint TB, which is the same as that seen in our study.

A study in Qatar showed that ESR elevation was seen in 67% cases of childhood TB.[12] Our study shows elevated ESR in 70.4% patients. Hence, elevated ESR may be a good marker to determine bone TB.

Surgery may be required in selected cases like large abscess formation, severe kyphosis, an evolving neurological deficit or lack of response to medical treatment.[2] As per a study in Pakistan, spinal tuberculosis associated with any neurological deficit is usually treated by surgery. Medical treatment can reverse most of the neurological deficit and hence surgery should not be the first choice of treatment.[13] This is seen from our study, in which only 28.21% of the patients were managed surgically.

5. Conclusion

Osteoarticular tuberculosis is an emerging problem in children with commonest presentation being osteomyelitis followed by spinal TB. Mean age of presentation is 7 years. Drug resistant bone TB is highly prevalent. Surgical intervention is needed in a quarter of the patients. Elevated ESR was more commonly seen in spinal TB as compared to osteoarticular TB.

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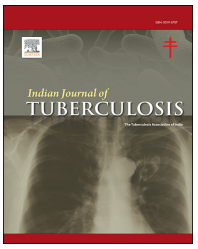

Original article

"99DOTS"techno-supervision for tuberculosis treatment – A boon or a bane? Exploring challenges in its implementation at a tertiary centre in Delhi, India

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ARTICLE INFO

Article history:
Received 22 July 2019
Accepted 14 August 2019
Available online 24 August 2019

Keywords:
HIV-TB
Adherence and monitoring
mHealth
Information and communication technology
Operational research

SUMMARY

Background: In India, daily regimen with fixed-dose combination along with 99DOTS adherence tool and one-stop service at Anti-Retroviral Treatment (ART) centres for HIV infected Tuberculosis (TB) patients was launched in 2017. No systematic evaluation of its implementation has been done so far in a tertiary care setting in urban India.

Methods: A mixed-methods study was conducted at National Institute of Tuberculosis and Respiratory Diseases, Delhi in 2018-19. Missed doses, average adherence and treatment outcomes were compared across 99DOTS dashboard and TB treatment card. In-depth interviews of patients and health care providers were conducted to explore the implementation challenges and benefits.

Results: Median of missed doses recorded during intensive and continuation phase were 56 and 68 respectively in 99DOTS as compared to 0 in the TB Treatment card ($p<0.0001$). Average adherence was observed to be 27% in 99DOTS versus 99% in the TB treatment card ($p<0.0001$). Technical issues like software malfunction, logistic difficulties such as missing custom envelops and patient's inability to give call were reported. Role clarity among ART and TB program staff was ambiguous, which contributed to poor information flow between them. Patient benefits such as reduced stigma, less travel costs and reduced work absenteeism were reported.

Conclusion: Success of 99DOTS program under programmatic condition needs webtool stability, uninterrupted logistic supplies (envelops), training of staff and better coordination between TB and HIV program personnel. Despite the challenges in its implementation, the benefit of this tool in terms of greater convenience and reduced stigma for patients is encouraging.

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https://doi.org/10.1016/j.ijtb.2019.08.010
0019-5707/

1. Background

Tuberculosis (TB) is one of the top 10 causes of death globally, with 10 million people falling ill with the disease and 1.7 million related deaths reported in 2017 alone. India tops the list of high TB burden countries accounting for about one fourth of the estimated global TB patients in 2017.[1] In the same year, there were ~0.1 million HIV-TB patients in India.

Like most countries, the National TB programme of India was following directly-observed intermittent Anti-Tuberculosis Therapy (ATT) i.e. thrice weekly for all drug sensitive TB patients irrespective of HIV status. There were concerns about emergence of TB drug resistance among HIV-infected TB patients treated on intermittent regimen. A systematic review showed that the relapse and failure rates were 2–3 times higher on intermittent regimen compared to daily regimen in HIV co-infected individuals.[2] In light of this evidence, World Health Organization (WHO) in 2010 strongly recommended daily regimen for drug sensitive TB patients, especially for HIV-infected TB patients.[3,4] In 2017, daily regimen for HIV-infected TB patients was introduced only in selected high burden Anti-Retroviral Therapy (ART) centres in India, wherein patients are given drugs for one month, which is self-administered.[5] Under daily regimen, patients must consume drugs daily which raise serious concerns about medication adherence. Hence, along with introduction of the daily regimen, the Information and Communication Technology (ICT) enabled adherence support system in the form of '99DOTS' was devised to support treatment adherence based on missed call, mobile reminder and smart pill box. In a pilot study by Cross et al., 99DOTS was found to be a promising approach for ensuring adherence to TB medications with over 90% of doses reported correctly by the patients.[6]

There are hidden phone numbers in each anti-TB blister pack, which are revealed only after the drug doses are dispensed. Patient makes a call to that hidden toll-free phone number, thus ensuring the intake of TB medication. In case of missed doses, the health care providers responsible for supporting the treatment adherence of the patient are alerted. Thus, enabling the virtual real-time monitoring of the treatment adherence. Despite this mechanism to improve adherence, a mixed-methods study in Karnataka, India revealed poor treatment outcomes among TB-HIV patients and also identified significant challenges in the implementation of this new care package in routine programme settings.[7]

The Anti-Retroviral Therapy (ART) Centre at National Institute of Tuberculosis and Respiratory Diseases (NITRD), a tertiary public health institute in Delhi, India also implemented 99DOTS along with daily regimen in 2017. There have been anecdotal reports about the implementation challenges faced by the beneficiaries and the provider. Many patients do not use the tool and do not give a missed call, although they take medication regularly, which is reflected in the patient treatment card records. Discrepancy in the reporting of drug adherence between 99DOTS dashboard and the patient treatment cards was also noticed. However, there has been no systematic evaluation of the same in a tertiary care setting in an urban locality.

Thus, in this operational research study, we evaluated the use of 99 DOTS as a monitoring tool for adherence to tuberculosis treatment and explored its implementation challenges and benefits.

2. Objective

Among TB-HIV patients registered on 99DOTS at ART centre, NITRD (March 2017 to February 2018), this study

1. Compares the median number of missed doses, mismatched doses and average adherence in the dashboard and the patient treatment cards
2. Understands the challenges in implementation and benefits of 99DOTS from both providers' and patients' perspectives

3. Methods

3.1. *Study design*

This was a concurrent explanatory QUAN-QUAL mixed methods study with a quantitative component (retrospective cohort study with review of existing programdata and 99DOTS dashboard data) and a descriptive qualitative component (in-depth interviews).

3.2. *Settings*

The study was conducted in the ART centre at NITRD, Delhi. ART centre is a fully equipped centre for providing comprehensive HIV counselling by trained counsellors and testing services such as CD4 testing as well as lifelong provision of free ART drugs. Both outpatient facility (with an average of 60 patients/day) and in-patient admission facility for HIV -TB cases is available in the centre.

3.3. *Management of HIV-TB patients (as per the new care package)*

All the socio-demographic, morbidity and follow-up details of the HIV patients on ART are recorded in a specific white card maintained at the ART centre. Diagnosis of TB is made by CB-NAAT (Cartridge based Nucleic Acid Amplification test) and sputum microscopy using standard RNTCP diagnostic algorithm.[8] Once diagnosed with TB, they are put on daily regimen containing fixed-dose combinations at the ART centre.

The details of initiation of TB treatment are documented in this Card. The staff nurse prepares the TB treatment card in duplicate. Original card is maintained and updated (once a month) by the nurse, when the patient comes to collect the ART and ATT together. A copy of this card is handed over to the patient. The ART counselor ensures proper counseling of all the HIV-infected TB patients regarding adherence, usage of 99DOTS, and possible side effects of ATT. Nurse administers the first dose and facilitates the first missed call for the patient. As soon as the Data Manager of the ART centre adds

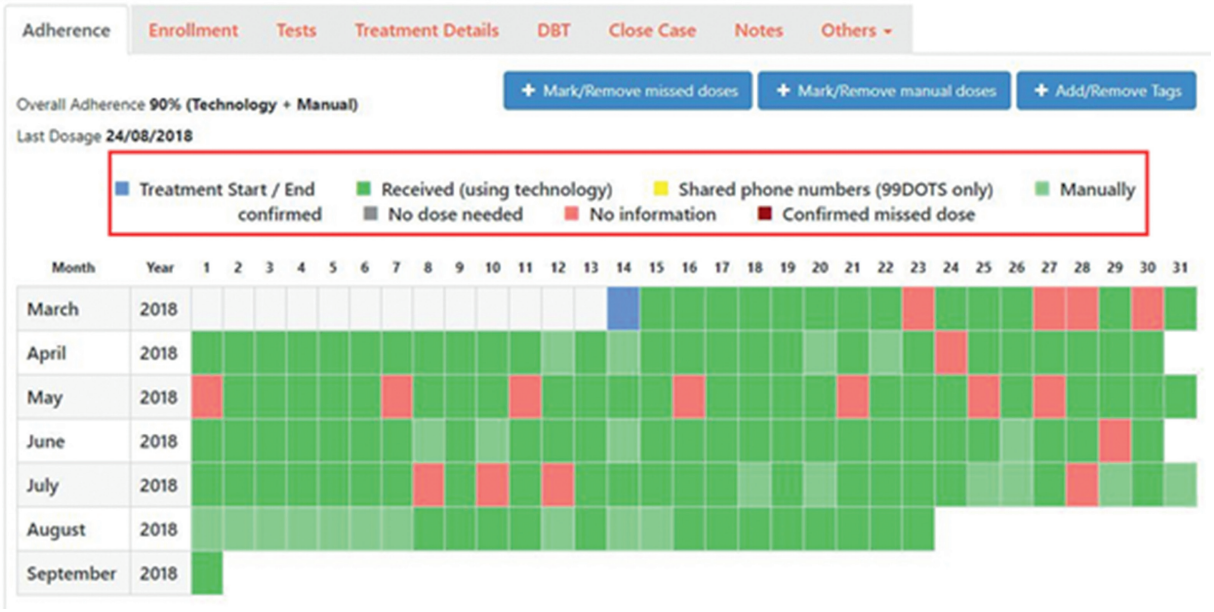

Fig. 1 – Screenshot of the 99DOTS portal.

the patient on the 99 DOTS website (and selects the correct district), a text message is sent to the District DR-TB & HIV Coordinator, provided his contact details are updated on website.[9] The coordinator will then link the patient to the correct TB Unit (TU) through the 99DOTS website. As soon as it is done, the field staff for that TU will start receiving text alerts for that patient. This will enable the TU staff to access the patient on 99DOTS website using their Nikshay (Unified ICT system for TB patient management and care in India) credentials.[9] In case of any missed doses (as seen on 99 DOTS dashboard), the staff visits the patients house and ensures retrieval action.[9] All such follow up actions are updated as notes on the website.

The treatment outcome is assigned by the ART Medical Officer in the White Card and updated in the TB treatment card by the ART staff nurse and in the Nikshay software by the concerned TU staff.[9]

3.4. *99 DOTS tool*

99DOTS is an innovative mHealth project to monitor and improve adherence to TB medications. After consuming the medicines, the patient is expected to give a missed call from the registered mobile number to the toll-free number printed on the flap of the blister pack. The phone call is considered as an indicator of tablet consumption. A missed call by the patient is indicated by a dark green color in the application dashboard. In case the patient fails to give a missed call, a red color is shown on the dashboard and a 'High attention' alert message is sent to the TB-HIV coordinator, Senior Treatment Supervisor (STS) and TB health visitor, who are facilitating the treatment of the patient. TB health visitor then visits the patient and carries out the retrieval action. They can also manually indicate in the dashboard that the patient has consumed the drug (indicated by light green color). The patient too gets reminder messages for consuming the drugs. The treatment adherence report for each of the patient can be extracted from the 99DOTS web dashboard or its mobile app. This adherence report contains number of missed doses, average adherence and classifies the patient as high-risk and low-risk based on the level of adherence. This stratification helps the healthcare providers to focus on high-risk individuals (Fig. 1).

3.5. *Study period*

This study was conducted between November 2018 and March 2019.

3.6. *Study population*

For the quantitative component, all TB-HIV patients enrolled under 99DOTS at the ART centre of NITRD, New Delhi during March 2017 to February 2018 were enrolled into the study.

For the qualitative component, a purposively selected sample of health care providers (involved in implementation of 99DOTS programme) and TB-HIV patients were recruited.

3.7. *Data variables, sources of data and data collection*

To evaluate the use of 99DOTS as an adherence monitoring tool, data variables were extracted from its website and the TB treatment card and were subsequently compared.

For the qualitative component, implementation related challenges were explored through in-depth interviews (IDIs) with health care workers (HCW) involved in 99DOTS implementation and TB-HIV patients.

Fifteen HCWs were selected purposively to cover all cadres of staff involved in 99DOTS implementation from both the programs i.e. RNTCP (01 Medical officer, 02 STS, 02 Senior Treatment Laboratory Supervisor, 01 TB-HIV supervisor, 01

Statistician, 01 Data entry operator and 01 TB-HIV field worker) and ART staff (03 Physician, 01 Staff nurse, 01 pharmacistand01 data entry operator). A total of 10 willing patients were selected to get their perspectives on the adherence tool. Saturation of findings decided the sample size.

The principal investigator (PI) conducted the interviews on a day and time convenient to the participants (post their consent). Interviews were done on a one-on-one basis, in a separate room in the health facility. Participants were informed of the purpose of the study before the interview. IDIs were done in local languages in which both the participant and the PI were comfortable. A pilot tested interview guide with broad open-ended questions was used to guide the interview. Audio recording of some interviews and field note were collected after obtaining consent. The summary was read back to the participant to ensure correct interpretation of what they said.

4. Data analysis and statistics

4.1. *Quantitative*

Data were double entered in EpiData (EpiData association, Odense, Denmark) and analysed using EpiData analysis. Number and proportions were used to describe the socio-demographic and clinical characteristics and the treatment outcomes of the patients. Median number of missed doses and median adherence were compared across 99DOTS dashboard and the TB treatment cards using Mann Whitney test.

A. Average adherence is calculated by: (number of doses marked as taken in 99DOTS dashboard/total number of doses in IP/CP)*100.
B. Average adherence by call: (number of doses marked green by patient's call in 99DOTS dashboard/total number of doses in IP/CP)*100.
C. Average adherence by manual: (number of doses marked manually as light green colour by the provider in 99DOTS dashboard/total number of doses in IP/CP) *100.

Mismatched dose: Any mismatch in dose in the 99DOTS tool versus the TB treatment card. For example, 99DOTS shows that the patient has consumed a dosage whereas the treatment card shows a blank box/cross mark for the same dosage suggesting that the dosage has not being consumed by the patient and vice versa.

4.2. *Qualitative*

Data from IDIs were transcribed by PI in *English* language. A coding framework was developed based on the themes emerging from the transcript. Manual descriptive content analysis was done to analyze the transcripts which was then reviewed by another investigator (KS) to reduce subjectivity in interpretation and improve credibility of the findings.[10] In case of any discrepancy, PI referred back to the transcripts or the audio files. The findings have been reported by using 'Consolidated Criteria for Reporting Qualitative Research' guidelines.[11]

Table 1 – Baseline demographic and clinical characteristics of HIV-TB patients attending NITRD ART Centre between March 2017 and Feb 2018.

Characteristics	Number	(%)
Gender		
Male	54	(75)
Female	16	(22)
Transgender	02	(3)
Age (years)		
15–29	21	(29)
30–44	37	(51)
45 and above	14	(20)
Level of Education		
Illiterate	20	(28)
Primary	20	(28)
Secondary	32	(44)
Occupation Status		
Employed	45	(62)
Unemployed	23	(32)
Not recorded	4	(6)
Marital Status		
Single	21	(29)
Married	47	(65)
Divorced/Separated	4	(6)
Income (in INR/month)		
≤10000	32	(47)
10001–20000	19	(28)
Above 20000	11	(16)
Not recorded	6	(9)
WHO Stage of HIV Disease		
Stage1	22	(31)
Stage2	3	(4)
Stage3	1	(1)
Stage4	40	(56)
Not recorded	6	(8)
CD4 count (cells/μL)		
<350	53	(78)
350–500	09	(13)
>500	06	(9)
Site of TB Disease		
Pulmonary	18	(25)
Extra-pulmonary	54	(75)
Type of TB Case		
New	60	(83)
Recurrent	12	(17)
TB Treatment outcome		
Treatment completed	49	(69)
Death	15	(21)
Lost to follow up	3	(4)
Transferred out	4	(6)
Not recorded	1	(1.4)

Abbreviation: NITRD – National Institute of TB and Respiratory Diseases; TB-Tuberculosis; HIV-Human Immunodeficiency Virus; ART-Anti-Retroviral Therapy.

5. Ethics approval

Ethics issues: Ethics approval was obtained from the Ethics Advisory Group of the International Union Against

Table 2 – Discrepancy in missed doses and adherence between 99DOTS dashboard and patient treatment card among TB-HIV patients.

Variable	99DOTS Dashboard	Patient treatment card	p value
Median missed doses in IP	56 (24–60)	0.4 (0–0)	<0.001
Median missed doses in CP	68 (28–122)	0.6 (0–0)	<0.001
Average adherence of patients (A + B)	27%	99%	<0.001
Average adherence by patient call	25.2%		
Average adherence by manual recording	1.8%		
Median mismatched doses in IP	55 (18–60)		
Median mismatched doses in CP	63 (28–122)		

Abbreviation: NITRD – National Institute of TB and Respiratory Diseases; TB-Tuberculosis; HIV-Human Immunodeficiency Virus; ART-Anti-Retroviral Therapy; IP-Intensive Phase; CP-Continuation Phase.

Tuberculosis and Lung Disease, Paris, France and the Ethics Committee of the NITRD, New Delhi.

6. Results

6.1. Socio-demographic and clinical characteristics

A total of 72 TB-HIV patients were recruited into the study. Majority of them were males (54, 75%) and adults in the age group (30–44 years). Most of them were new TB patients (83%. n = 60); three-fourths were extra-pulmonary TB (54, 75%) (Table 1).

6.2. TB treatment outcomes

Nearly 69% (n = 49) of the patients completed their treatment, death was recorded in 15 (21%) patients and loss-to-follow-up was seen in 3 (4%) patients (Table 1).

6.3. Discrepancy between 99DOTS dashboard and TB treatment card

Study revealed a significant discrepancy in the that the number of missed doses recorded by 99DOTS dashboard and the TB Treatment card. Median of missed doses, during intensive and continuation phase, in 99DOTS were 56 and 68 respectively as against 0 in the TB Treatment card ($p < 0.0001$). Average adherence was 27% in 99DOTS versus 99% in the TB treatment card ($p < 0.0001$) (Table 2).

6.4. Challenges in implementation of 99DOTS

Important themes related to challenges were deduced from the manuscript and were categorised into 3 main categories. It has been summarised in Table 3.

6.5. Challenges related to 99DOTS tool

HCW was largely appreciative of 99 DOTS as a "perfect use of technology" concept. However, they have faced multiple execution challenges using the tool. Primary issue was malfunctioning of the 99DOTS tool (patient's missed calls not getting registered). RNTCP staff didn't provide feedback citing

Table 3 – Challenges in the implementation of 99DOTS at a tertiary care centre in Delhi from patient and provider's perspectives.

Provider perspective
- No formal training to RNTCP staff
- Coordination challenges between RNTCP and ART staffs
- Operational Issues: Inadequate supply of medicine & specialized envelopes

Patient perspective
- Mobile phones unaffordable
- Unable to operate Mobile phones
- Lack of motivation to call
- Toll-free number concept misunderstood

99DOTS tool
- Software Bug
- Network Problems
- Deficieny in adding RNTCP staff as treatment supporter
- Inadequate SMS alerts

RNTCP – Revised National Tuberculosis Control Program; ART – Anti-Retroviral Therapy.

lack of formal training and practical experience on the usage of the tool.

6.5.1. *Provider-related challenges*

5 out of 6 ART HCW confirmed to have undergone formal training on 99 DOTS. However, RNTCP staff has had no formal trainings and expressed limited awareness about its methodology.

13 out of 15 HCW stated no patient information was shared between ART and RNTCP department. While, 2 of them stated minimal patient information was shared between departments.

DR-TB HIV Coordinator mentioned:

"Lot of coordination difficulty with 99 DOTS methodology as ART staff is neither sending patients to us for verification nor sharing their treatment cards with us"

On "retrieval action and supervision under 99 DOTS", 5 out of 6 ART health-care providers showed dissatisfaction with it.

A senior doctor at ART commented:

"The retrieval mechanism in case of missed doses, which was to be managed by RNTCP staff, never took off. So, no way to account for missed doses in real-time"

Another key implementation challenge that emerged was logistic difficulty in procuring smooth supply of medicine and their custom envelops. More than 10 out of 15 health-care providers confirmed to have faced this challenge at some point of time.

6.5.2. *Patient-related challenges*

One of the major challenges faced was lack of patients' motivation to call. They also had confusion regarding missed call procedures – toll-free number to call, time of call etc. One patient didn't own a mobile phone and another 3 had limited access to mobiles due to co-sharing of it with other family member or neighbours.

7. Discussion

This mixed methods study provides useful information about the use of 99DOTS as an adherence tool and its implementation challenges and benefits from the perspectives of different stakeholders. The key findings of the study are:

i) Software malfunction and other logistic challenges in getting medicines and custom envelops
ii) Substantial discrepancies noticed between the 99DOTS dashboard and the TB treatment card with respect to missed doses
iii) Poor coordination between ART and RNTCP staff resulting in no to minimal involvement of RNTCP staff and hence remarkably reducing the monitoring and supervision of HIV-TB patients.
iv) Benefits in terms of increased convenience to patients, less work absenteeism and less travel cost were remarkable.

It was felt by providers that transition to techno-supervision of 99DOTS was very sudden. Persistent software bugs along with limited technical knowledge of the staff led to misrepresentation of facts on 99 DOTS dashboard. It was reflected by falsely low adherence of most patients on this tool. This was augmented by frequent unavailability of 99DOTS custom envelops-encoding phone numbers on which patient had to call. Hence, the study observed gross mismatch between the 99DOTS and the TB treatment cards (in terms of missed dose recordings, treatment outcomes, treatment initiation dates and completion) which highlighted the inefficiency in adherence monitoring.

Another possible explanation for this finding was seen to be the challenges faced by the patient in giving missed calls despite having consumed the drugs. Some of the challenges that were explored in the interviews were: not owning a mobile phone, unable to operate a phone or dial a number, mobile network issues and mostimportantly lack of motivation to give missed call as they see any benefit out of it. Most of the patients gave missed calls only during the initial months of treatment, reflecting the need to reinforce the message during monthly visits. Another minor reason was in case of patient deaths; it was observed that 99DOTS dashboard remained active and hence, subsequent doses were still marked as missed doses giving rise to falsely low adherence.

It was also noticed that the adherence to drugs was high in the TB treatment cards. The 'treatment cards' were updated based on the information provided by the patient during their monthly visits (for pill re-fills). TB treatment cards have high dependence on self-reporting by patients. It was observed that most patients remain out of the system for a month and hence, no physical verification of actual drugs consumption is possible. In such cases, patients have high-chances to be non-adherent to medications and it may subsequently lead to treatment failure and drug resistance. This calls for proper patient communication on maintenance of duplicate treatment cards (which should be filled in real-time basis at home) as well as return all empty blister packs on monthly visits.

Another major revelation was lack of supervision and monitoring of patients registered under 99 DOTS at field level. "Directly-observed treatment" through field supervision, which was the hallmark of conventional DOTS, was missing as reported by the providers and patients. It was seen that RNTCP staff was not involved in the monitoring TB treatment of HIV-TB patients. This happened due to lack of information flow and coordination between ART and RNTCP staff.

DR TB-HIV coordinator mentioned:

"RNTCP staff is not provided with details and treatment cards for 99DOTS registered patients"

However, ART staff stated RNTCP health-workers get auto-generated messages from the Nikshay portal on new patient registration, but they do not take ownership of the patient.

Thus, lack of clarity around the roles and responsibilities of the ART and RNTCP staff coupled with lack of training has led to poor implementation. Similar concerns have also been

shared by a previous study in a rural programmatic setting in Karnataka, India.[7] This study concluded:

"*With new care package, TB treatment outcomes did not improve as expected and conversely declined compared to conventional care. TB and HIV programs need to address the operational challenges to improve the outcome*."

Despite these challenges and the drawbacks, certain benefits were also highlighted by providers and patients. Patients preferred 99DOTS due to fewer visits to the health facility (once a month), more time for work and hence, less expenses on travel costs. Similar insights were given by a study done that evaluated 99DOTS pilot project in Rajkot, India.[12]

A medical officer from the ART centre also reported "*reduction of stigma and discrimination because everything is digitized on the portal and is a major advantage*". Most of the ART staff appreciated the use of 99DOTS IT tool in treatment monitoring and liked the concept of real-time tracking of missed calls. They felt that if implemented well, this will ensure better drug adherence.

This study had a few strengths. Firstly, a mixed methods design allowed us to understand the important challenges related to the implementation of the 99DOTS package, which complemented thefindings from the quantitative findings. Secondly, the study adhered to the "Strengthening the Reporting of Observational Studies inEpidemiology (STROBE)"[13] guidelines and the COREQ guidelines[11] for reporting the quantitative and qualitative findings respectively. And finally, double data entry and validation was done which minimizes data entry errors.

However, the study also had a few limitations. Firstly, there are concerns regarding the use of TB treatment cards as a comparator for the 99DOTS dashboard because the entry of the number of doses taken by the patient as mentioned in the card is based on self-reporting by patients. Secondly, the health care providers and patients may have been reluctant to criticize the 99DOTS program as the PI is a service provider herself.

8. Conclusion

Success of 99DOTS program under programmatic condition needs webtool stability, uninterrupted logistic supplies (envelops), training of staff and better coordination between TB and HIV program personnel. Despite the challenges in its implementation, the benefit of this tool is in terms of greater convenience and reduced stigma for patients.

Funding

The training course under which this research was conducted and open access publication charges was funded by, The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interests

The authors have none to declare.

Author contribution

Ananya Prabhu: Principal Investigator and corresponding author, design of the protocol, acquisition of data, data analysis, drafting of the manuscript; Upasna Agarwal: design of the study, data acquisition, analysis and interpretation of data and reviewing the manuscript; Jaya Prasad Tripathy, Karuna Sagili, Pruthu Thekkur: design of the protocol, data analysis, critically reviewing the paper; Neeta Singla: data acquisition (facilitated interviews), critically reviewing the paper; Rohit Sarin: design of the study, data interpretation and critically reviewing the paper. All the above authors gave approval for the final version of manuscript submitted.

Acknowledgement

This research was conducted as a part of the 'National Operational Research Training Course 2018–19' organised by Project Axshya, funded by The Global Fund and implemented by The International Union Against Tuberculosis and Lung Diseases (The Union), South-East Asia Regional Office, New Delhi, India. The training course was conducted in collaboration with Revised National Tuberculosis Control Program, Ministry of Health and Family Welfare, Government of India and National Institute for TB and Respiratory Diseases, New Delhi, India.

The training is based on "The Union/Medécins sans Frontières (MSF)" model OR course and has been acknowledged/accredited by the Special Programme for Research and Training in Tropical Diseases at the World Health Organization (WHO/TDR) under SORT IT (Structured Operational Research and Training Initiative). Mentorship and facilitation for this course was provided through The Union South-East Asia Office, New Delhi; the Centre for Operational Research, The Union, Paris, France; Baroda Medical College, Vadodara; Médecins Sans Frontières, New Delhi; ESIC Medical College and PGIMSR, Bengaluru; North Delhi Municipal Corporation Medical College, Hindu Rao Hospital, New Delhi; GMERS Medical College, Vadodara; Postgraduate Institute of Medical Education and Research, Chandigarh, India; Yenepoya Medical College, Mangalore.

Also I wish to express my deep gratitude to Mr. Saurabh Kumar, my husband, for his valuable inputs, guidance and support in this endeavour.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.08.010.

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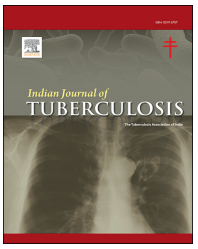

Original article

Comparison of front-loading versus spot morning sputum microscopy approach among suspected pulmonary tuberculosis cases in tertiary care centre in Uttarakhand

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ARTICLE INFO

Article history:
Received 16 April 2019
Accepted 13 August 2019
Available online 20 August 2019

Keywords:
Front loading
Sputum microscopy
Tuberculosis

ABSTRACT

Purpose: Comparative evaluation of front loading sputum microscopic approach versus standard Revised National Tuberculosis Control Programme (RNTCP) spot morning approach for diagnosis of pulmonary tuberculosis.

Methods: All cases coming to the designated microscopy centre, Microbiology in this tertiary care centre with presumptive diagnosis of pulmonary tuberculosis were enrolled for the study population after taking informed consent. The sputum sample collection, staining and reporting were done according to standard RNTCP guidelines.

Results: This study shows the probable non-inferiority of the frontloading sputum smear microscopy over the standard RNTCP approach.

Conclusion: The front loading smear microscopy could be considered a suitable alternate to standard RNTCP approach in an area with high drop out during diagnostic testing pathway.

1. Introduction

Tuberculosis (TB) is a major threat to the public health in India and world as well. India accounts for one-fourth of the global TB burden which is the highest in the world. In 2015, globally 104 lakhs estimated TB cases occurred and 14 lakhs died of TB, while this figure for India was 28 lakhs and 4.8 lakh respectively (excluding the cases of TB with HIV).[1,2] Pulmonary TB is commonest among different forms of TB. People with active TB disease, the symptoms (like cough, fever, night sweats, weight loss, etc.) may be mild for many months and it can lead to delay in seeking care and results in transmission of the disease to others.[3] For diagnosis of pulmonary TB, several diagnostic methods like sputum microscopy, culture on [solid Lowenstein Jensen media, Mycobacterial Growth Indicator Tube (MGIT)], molecular methods like GeneXpert etc. are now available. But in developing country like India with high TB burden, the widely followed method is microscopic demonstration of acid fast bacilli (AFB) in sputum smears by Ziehl-Neelsen (ZN) staining. Since it is a rapid and economical

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https://doi.org/10.1016/j.ijtb.2019.08.009
0019-5707/

method, hence recommended by World Health Organisation (WHO) and Revised National Tuberculosis Control Programme (RNTCP).

Conventional case finding approaches usually involve microscopic examination of 'spot-morning' sputum specimens (in countries with a two-specimen system) or examination of 'spot-morning-spot' (in countries with a three-specimen approach).[2] Most of the sputum results are therefore available only on the second or third day after the patient presents to a health service centre.[4] From the perspective of the health of individual and society, the major concern is patient dropouts leading to undiagnosed TB automatically reflecting on access and ease of treatment. It is estimated that people with active TB can infect 10–15 other people through close contact over the course of a year.[3] Hence, early diagnosis is required for prevention of transmission of infection.

In currently recommended standard approach (by RNTCP in India) for diagnosis of pulmonary tuberculosis by smear microscopy, the patients have to submit two sputum samples: one spot sputum specimen at the time of first visit (S) and another morning sputum specimen (M) collected at home in the morning and brought to laboratory the next day.[5] In this approach, patients have to spend a significant amount of money in travelling, stay, food etc. to reach the microscopy centre twice for giving samples only. In addition, it leads to loss of working days of the patients affecting their normal life. The only alternative in accordance to the feasibility in a developing country like India is same day diagnosis approach called front loading microscopy. In this method the patients have to submit two sputum specimens: one spot sputum specimen at the time of first visit (S) and another spot sputum specimen on the same day at least 1 hour later (Sx i.e. extra sputum sample).[5,6] We had observed low adherence rate for giving both spot and morning sample in designated microscopy center in our tertiary care centre. Keeping low adherence rate and limited studies in literature this study was planned with aim to compare the sensitivity of the front-loading microscopy with the current standard RNTCP approach.

2. Material and methods

The study was initiated after taking approval of Institute Ethics Committee. Information sheet (in language of participants) was given to the patients and written informed consent was taken before including the patient in the study.

This was a pilot prospective observational study conducted from 24th July to 30th September 2018 (approximately for 2 months) in a designated microscopy centre (DMC), Microbiology of a tertiary care centre in Uttarakhand. Patient with presumptive diagnosis of pulmonary tuberculosis submitted sputum sample in DMC were enrolled for the study population after taking informed consent.[7,8] Patient having any of the symptom or sign suggestive of TB including cough >2 week, fever >2 weeks, significant weight loss, hemoptysis, any abnormality in chest radiograph were considered as presumptive case of pulmonary TB. Demographic details were filled in predesigned ethically approved performa.

Patients with history of intake of anti-tubercular drugs for more than one month or history of known chronic diseases (like diabetes mellitus, hypertension, HIV) were excluded from the study. No intervention was proposed and all the procedures were followed as per the RNTCP guidelines.[8]

2.1. *Sputum specimen collection*

The patients were asked to submit three sputum specimens:

First -spot sputum specimen at time of first visit (S)
Second -spot sputum specimen on same day at least 1 hour later (Sx)
Third- early morning sputum specimen (M) collected at home in the morning and brought to DMC next day.

All patients were explained how to produce a good quality mucopurulent sputum specimen in the local language and asked to provide at least 2 ml of sputum specimen. Specimens S and Sx were collected under supervision and for M specimen the patients were given sterile, leak proof, disposable and appropriately labeled sputum containers and requested to bring specimens on next consecutive day. Specimens were transported to the laboratory as soon as possible and if delay was unavoidable, the specimens were refrigerated to inhibit growth of unwanted microorganisms.

2.2. *Smear preparations*

Sputum sample was examined for macroscopically and smear prepared from all 3 specimens. Ziehl Neelsen (ZN) staining was performed on sputum smears.

2.3. *Blinding*

The number portion of Sx slide was covered by opaque stickers and all slides of the day were mixed. Separate number was given by the person not involved in reporting of sputum smears to ensure blinding. To avoid inter-observer variations, all smears (S,Sx,M) were examined by the same person who was reporting smears routinely in the DMC.

2.4. *Reporting of smears*

Any patient with a smear positive sample (S/Sx/M) was considered positive for pulmonary TB. This was considered gold standard for this study for comparing results of front loading with standard RNTCP approach. Quality control was maintained as per RNTCP guidelines. All the information of the patients was kept confidential.

All the data was analyzed using Microsoft excel 2010 and IBM SPSS 23 version software. Continuous data was expressed as mean ± SD, range or as median with interquartile range as appropriate. Normality of quantitative data was checked by measures of Kolmogorov Smirnov tests of normality. For normally distributed data t-test was applied for comparison

between two groups. For skewed continuous variables Mann-Whitney U-test/Kruskal Wallis H test was used. Discrete categorical data was presented as n (%). For categorical data and gender comparisons were made by Pearson Chisquare test or Fisher's exact test as appropriate. All statistical tests were two sided and performed at a significance level of $\alpha < 0.05$.

3. Results

During study period of 2 months, 439 patient's sputum sample were received in the designated microbiology centre. Out of these 439 patients, 129 consented for the study. Among these 129 patients, 18 cases were excluded (16 cases with no symptoms or signs of pulmonary tuberculosis as defined in the inclusion criteria of the current study, one case of diabetes mellitus and one case on currently on anti-tubercular drug for >1months duration). One hundred eleven cases provided both spot and another spot sample after one hour. However, only 33 (29.7%) patients provided next day morning sample. The demographic profile, symptoms and expenditure details of study population is shown in Table 1. Among 111 patients 75 (67.6%) and 36(32.4%) were male and female respectively. Most common symptom for presentation was cough in 96 (86.5%), fever in 82 (73.9%), weight loss in 28 (22.2%) and blood in sputum in 21 (18.9%) cases.

In 23 patients' sputum sample revealed presence of AFB in one of the 3 samples as shown in Table 2. Among these 23 patients, 12 did not give morning samples. Result of morning samples were considered negative in cases where this sample was not received. On this assumptions same sensitivity, specificity, positive and negative predictive value of front loading and standard RNTCP approach was obtained to be 87%, 100%, 100% and 97% respectively against gold standard.

Only 33 patients provided all the 3 samples (S, Sx and M) and 11 were considered positive for pulmonary tuberculosis (as per gold standard defined in the current study). Among these 11 cases front loading detected 8 cases while standard RNTCP approach detected 10 cases. The sensitivity, specificity, positive and negative predictive value of front loading and standard RNTCP approach were 73%, 100%, 100%, 88% and 91%, 100%, 100%, 96% respectively.

Table 2 – Ziehl Neelsen's (ZN) smear result sample wise (S,Sx,M) (n = 111).

Smear microscopy result			
First Spot sample	Spot sample collected after 1 hours of first spot sample	Next day morning sample	Patients number n (%)
P	P	P	2 (1.8)
P	P	X	7 (6.3)
P	N	N	3 (2.7)
P	N	X	2 (1.8)
N	P	P	2 (1.8)
N	P	N	1 (0.9)
N	P	X	3 (2.7)
N	N	P	3 (2.7)
N	N	N	22 (19.8)
N	N	X	66 (59.5)

P and N represents acid fast bacilli found and not found in the ZN smear respectively. X indicates sample was not given.

4. Discussion

Tuberculosis being a global threat to the mankind in developing countries like India. Most patients in this study belong to low socioeconomic status. Sputum microscopy is most feasible method for TB diagnosis in such high burden and resource-poor country until newer better cost-effective methods get implemented. Variable dropout rate (6.3–95%) for TB smear diagnostic workup has been seen in various studies.[6,9–13]

In current study, 111 patients submitted both the S and the Sx sample while only 33 patients gave the next morning sample. Thus, the drop-out rate in this study was 70.3%. The probable reason for high dropout rate in comparison to other studies could be long distance to travel to reach the health care institution due to geographical terrain of the area. Among 111 patients included in this study, most of them were male (67.6%) as compared to female (32.4%). This could be due to less health seeking behavior of female population. Although in our study among confirmed TB cases almost equal males (52.2%) and females (47.8%) were found. The mean age of tubercular and non-tubercular patients in our

Table 1 – Demographic profile, symptoms and various expenditure of study subjects.

Characteristics		Tubercular cases (n = 23)	Non-tubercular cases (n = 88)	P value
Age in years mean (±SD)		37 (±18)	41.9 (±16.7)	0.71
Sex	Male n (%)	12 (52.2)	63 (71.6)	0.09
	Female n (%)	11 (47.8)	25 (28.4)	
Symptoms	Presence of cough >2 weeks n (%)	20 (87)	76 (86.4)	1
	Presence of fever >2 weeks n (%)	19 (82.6)	63 (71.6)	0.42
	Weight loss n (%)	8 (34.8)	20 (22.7)	0.28
	Blood in sputum	6 (26.1)	15 (17)	0.37
Expenditure in Indian Rupees Median (IQR)	Loss of income	400 (300,700)	500 (312,787)	0.26
	Additional expenses on food	100 (0,200)	200 (100,300)	0.13
	Additional expenses on accommodation	0 (0,0)	0 (0,0)	0.8
	Additional expenses in travel	300 (50,800)	400 (200,600)	0.09
	Total additional expenses	1200 (350,2000)	1275 (800,1975)	0.27

IQR= Inter Quartile Range 25, 75.

study was 37 (±18) and 41.9 (±16.7) years respectively which was similar to the study conducted by Cuevas et al.[5] Most common symptoms for presentation was cough followed by fever, weight loss and blood in sputum in the current study. However, no significant difference was seen in sign and symptom presentation among tubercular and non-tubercular cases in the current study. Multicentric study conducted by Cuevas et al had shown variable symptomatology among suspected tubercular cases. Although they had not calculated symptoms rate among confirmed tubercular and non-tubercular cases.[5] Total expenditure loss was comparable in tubercular and non-tubercular group of patients in our study. The anticipated monetary loss may be another major reason for high drop-out in current study. Among the 111 patients enrolled in this study, 23 (20.7%) were detected as smear positive by any of three sputum samples (S/Sx/M), while Firdaus et al and Myneedu et al had reported smear positivity to be 14.1% and 18.48% respectively.[6,14]

Out of 111 patients, 23 patients were found to be sputum smear positive (20.72%) in at least one of the samples. One patient showed sputum smear positivity only on Sx sample, although quality of morning sample was acceptable while that of both S and Sx were unacceptable quality according to Bartlett scoring. Among these 23 patients, 12 did not give morning sample, out of which 3 patients were positive only on Sx sample. These 4 cases (17.4%) out of total 23 cases were detected smear positive only in Sx samples which would have remain undetected by the standard approach.

Out of these 23 positive patients as defined by gold standard, 3 patients remained undetected by both the spot sample (but were of poor quality-unacceptable as per Bartlett Scoring) but morning sample was positive (graded as 1 + as per RNTCP grading). Similar results have been shown by Firdous S et al stating that the sputum smear positive cases that remained undetected in the S and Sx samples were paucibacillary in the morning sample and both the spot samples were of poor quality.[6] The rates of positive smears in S, Sx and M samples in our study were 12.61% (14/111) 13.51% (15/111) and 21.21% (7/33) respectively. While in study by Myneedu et al and by Firdaus S et al, these rates were 12.72%, 11.8%, 18.48% and 12.72%, 12%, 13.8% respectively.[6,14] The sensitivity of the front loading sputum microscopy verses standard RNTCP sputum microscopy approach in the current study was 73% and 91% respectively, if only patients who gave all the 3 samples (S, Sx and M) were considered. If we consider the missing morning samples to be reported as negative to include in analysis for additional yield as calculated in a study conducted by Ramsay A et al, the sensitivity of both the methods in current study is 87%.[15] Statistical significant differences could not be ascertained in the current study due to high number of missing morning samples and low number of sample size. The comparable sensitivity of S, M (94%) and S, Sx (93%) sample combination were shown by Ramsay A et al as seen in current study.[15] This indicates the probable non-inferiority of the frontloading sputum smear microscopy over the standard RNTCP approach.

5. Conclusion

The front loading smear microscopy could be considered a suitable alternate to standard RNTCP approach in an area with high drop out during diagnostic testing pathway. Although difference in sensitivity was noted in the current study between two approaches but due to low sample size no definite conclusion can be made from the current study with statistically significant confidence. However, considering the high dropout rate (70.3%), and detection of extra cases (17.4% of the total smear positive patients by Sx sputum smear microscopy only as compared to 13% of total cases detected only by morning sample) frontloading approach is favored in the current study. A larger multi-centric study with adequate sample size may validate or refute the issue of non-inferiority of front loading approach over standard RNTCP approach for sputum smear microscopy.

Conflicts of interest

All authors have none to declare.

Acknowledgement

This work was supported by Indian Council of Medical Research (ICMR) New Delhi as a Short Term Studentship Program for medical undergraduates (ICMR-STS reference ID 2018-01062).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijtb.2019.08.009.

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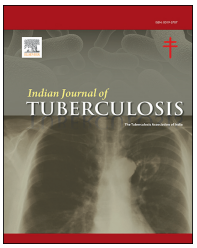

Original article

High prevalence of rifampin-resistant tuberculosis in mountainous districts of India☆

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ARTICLE INFO

Article history:
Received 31 May 2019
Accepted 10 August 2019
Available online 17 August 2019

Keywords:
Tuberculosis
Multidrug resistant tuberculosis
India
Himachal Pradesh

ABSTRACT

Background: India accounts for quarter of global rifampin-resistant/multi-drug resistant-tuberculosis (RR/MDR-TB). Knowledge on risk-factors and distribution of MDR-TB at district level is limited.

Objective: Study prevalence and risk factors of MDR-TB in tuberculosis patients in hilly districts of Himachal Pradesh, India.

Methods: Between July 2012–June 2013, TB patients registered under the Revised National Tuberculosis Control Program in Kangra and Una districts suspected of MDR-TB were referred for Xpert® MTB/RIF testing at the Delek Hospital, Dharamsala by the district TB Office.

Results: Of 378 patients enrolled (median age: 45 years; 85% males), 18% (n = 68) were rifampin-resistant. Among Xpert positives (n = 305), distributions of RR-TB were: 10% (n = 9/89) for recurrent cases who had received TB treatment for <2-months, 15% each for new (n = 9/59) or recurrent cases (n = 5/34) remaining smear positive between 2 and 4 months of treatment, 36% (n = 41/113) for treatment failures, and 40% (n = 2/5) for loss to follow-ups. Of the sputum-smear positives, 15% (n = 51/338) were Xpert negative. Seeking care in the private sector was associated with higher risk of RR-TB (OR:1.85; 95% CI:0.87–3.9).

☆ This paper is dedicated to the tireless service of late Dr. Kailash Chander Kaushal, MBBS, DIP, former WHO consultant for HP state, who had dedicated his life to the service of tuberculosis patients in the state of Himachal Pradesh.

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https://doi.org/10.1016/j.ijtb.2019.08.005

Conclusion: Prevalence of RR-TB is generally high in patients suspected of MDR-TB in the hilly districts of Himachal Pradesh. High prevalence during early phase of treatment can suggest primary transmission of DR-TB. Universal drug susceptibility testing and innovative case finding strategies will benefit patients living in mountain districts with inadequate access to healthcare. The high proportion of sputum-smear positive but Xpert negative cases may be due to non-tubercular mycobacterial disease.

1. Introduction

In 2016, India accounted for ~27% of the global tuberculosis (TB) incidence (2.79/10.4 million).[1] Approximately quarter (84,000/600,000) of the global rifampin-resistant or multi-drug resistant-TB (RR/MDR-TB) cases occurred in India in 2016.[1] Pooled MDR-TB estimates of 6% in new cases and 36% in previously treated cases were reported for India by combining study results from 2006-2015.[2] Recently, India's first national drug resistant survey conducted from 2014 to 15 was published that reported a prevalence of MDR-TB of 2.8% in new and 12% in previously treated cases.[3] However, state level inference on distribution of MDR-TB could not be made from the national survey due to limited sample size for individual states.[3] The prevalence and risk factors for TB drug resistance were insufficiently studied at state and district levels in India and studies that have been published were mostly from plain regions of the country.[2] Himachal Pradesh is a hilly state in India with difficult and mountainous terrains. Prevalence and risk factors for drug resistant-TB (DR-TB) have not been described before for the state. We report here the results of a project that was carried out to diagnose RR-TB and understand underlying risk-factors among previously treated patients under the Revised National TB Control Program (RNTCP) in two districts in HP.

2. Methods

2.1. Settings and population

The Tibetan Delek Hospital, a charitable institution in Dharamsala, HP, is a TB treatment center and an RNTCP designated microscopy center. In 2011, the Delek Hospital received the STOP TB PARTNERSHIP TB REACH wave 2 grant for active case finding of TB among Tibetans.[4] The grant included support for the hospital's GeneXpert cartridge supplies. The hospital decided to additionally extend its GeneXpert services free of cost to Indian TB patients in the state of HP in agreement with the RNTCP. Between July 1, 2012 and June 30, 2013, Indian TB patients at risk of DR-TB under the RNTCP in Kangra and Una districts of HP were consecutively referred by the District TB Officers of Kangra and Una to the Delek Hospital for Xpert® MTB/RIF assay. Initially, treatment failures, cases remaining smear positive at the end of 4th month of treatment, and contacts of known MDR-TB cases (formerly RNTCP DR-TB suspect criteria A)—were included. Subsequently, starting October 25, 2012, all patients registered as previously treated cases at diagnosis, patients with any smear positivity during a follow-up visit, and HIV co-infection at TB diagnosis (formerly RNTCP DR-TB suspect Criteria C) were additionally included for Xpert testing. Based on the inclusion criteria, the following risk groups were defined: 1) Cases registered as relapse (referred to henceforth as recurrent TB) who have received ATT for < 2-months or were not yet started on ATT, 2) new cases remaining sputum smear positive at a follow-up visit between 2 and 4 months of treatment, 3) recurrent cases remaining smear positive at a follow-up visit between 2 and 4 months, 4) patients who had failed anti-TB treatment, 5) treatment after lost to follow up, and 6) other previously treated cases. Standard WHO/RNTCP definitions were used in defining the risk-groups.[5] Treatment failure is defined as smear or culture positivity at month 5 or later during treatment.[5] While consecutive patients were systematically enrolled for Xpert MTB/RIF testing from Kangra and Una districts, select patients were later on randomly referred for Xpert testing from 6 other districts, results of which were separately presented here. The project was approved as a public health initiative by the RNTCP and the Delek Hospital and did not require separate ethics approval.

2.2. Study design and procedures

In a cross-sectional design, the risk of rifampin resistance was studied in consecutive patients suspected of DR-TB in districts of Kangra and Una of HP. Xpert® MTB/RIF assay was performed using GeneXpert® IV system (Cepheid, Sunnyvale, CA). Sputum smear microscopy with Ziehl-Neelsen staining was performed at the district TB center. Xpert testing on a second specimen was on random smear positive samples that tested Xpert negative on initial test. Xpert positive patients with indeterminate result for rifampin resistance on Xpert testing were not included in the analysis to calculate prevalence of rifampin resistance. Patients detected with rifampin resistance were started on MDR-TB treatment regimen at the district RNTCP DOTS Plus center as per national TB Programme. Information regarding demographic and clinical characteristics were extracted from the referral forms as well as by interview of patient at the time of visit for Xpert test.

2.3. Statistical analysis

Data were entered in Microsoft Excel (2010) spreadsheet by a trained nurse data manager. Data were processed and

analyzed in STATA version 13.1 (StataCorp, College Station, TX). Descriptive analyses and univariate logistic regression were carried out to assess the risk of rifampin resistance in the patients. In the logistic regression models, recurrent TB cases who have received ATT for <2-months were taken as the reference group based on a lower possibility of drug-resistance in them as compared to the other groups and also based on an observed lowest prevalence of rifampin resistance for this group in the data. The analyses for risk of rifampin resistance were restricted to districts of Kangra and Una.

3. Results

3.1. Patient characteristics

Between July 2012 and June 2013, 415 patients at risk of DR-TB were referred to the Delek Hospital for Xpert® MTB/RIF assay. Median age was 45 years (IQR: 32–58) and 81% (n = 337) were males (Table 1). Of the 415 patients, 69.4% (n = 289) were from Kangra, 21.5% (n = 89) from Una, and the remaining 9% (n = 37) from other districts including 5% from Mandi and 2% from Hamirpur districts. Twenty-four percent (n = 101) were laborers, 18% (n = 76) farmers, and 67% (n = 52) of the women were housewives. Fifteen percent (n = 63) reported contact with a TB case, 1% (n = 4) with DR-TB, and 3% (n = 12) were HIV-positive. Sixty-three percent (n = 225) were current or past smokers. Thirteen percent (n = 55) had reported they have visited a private practitioner at the start or during the project period. Of the 415 patients, 31% (n = 128) were recurrent TB cases who had received ATT <2-months, 11% (n = 44) were recurrent TB cases who continued to remain sputum smear positive between 2 and 4 months, 17% (n = 70) were new cases who continued to remain smear positive between 2 and 4 months, 37.5% (n = 155) were treatment failures, 2% (n = 8) were treatment after loss to follow-up cases, and 2.5% (n = 10) were other previously treated cases.

3.2. Risk of rifampin resistance

Of 378 patients suspected of DR-TB from Kangra and Una districts, 18% (n = 68) were rifampin-resistant (Tables 2 and 3), 20% (n = 57/289) from Kangra and 12.5% (n = 11/89) from Una. Among Xpert positive cases in the two districts, prevalence of RR-TB was 22% (n = 68/305), 25% (n = 57/226) for Kangra and 14% (11/79) for Una. Three cases from Kangra district showed indeterminate result for rifampin resistance. Despite an overall higher proportion of TB among males (81%), females had comparatively higher prevalence of RR-TB [32% (n = 15/47)] as compared to males [21% (53/280)]. Patients from Kangra district had higher risk (OR: 2.08; 95% CI: 1.03–4.22; p = 0.041) of rifampin resistance than patients from Una district. The prevalence of rifampin resistance in the various risk groups were: 10% (n = 9/89) for recurrent cases who had received ATT for <2-months, 14–15% for new (n = 9/89) and recurrent cases (n = 5/34) who had continued to remain sputum smear positive between 2 and 4 months of ATT, 36% for treatment failure cases, and 40% (n = 2/5) each for treatment after loss to follow-up cases and other previously treated cases. Compared to the recurrent cases that have received ATT for <2-months, patients who had failed TB treatment had higher risk of rifampin resistance (OR: 5.06; 95% CI: 2.30–11.13; p < 0.001). Lost to follow-up cases and other previously treated TB cases also had comparatively higher risk of rifampin resistance (OR: 5.93; 95% CI: 0.87–40.3; p = 0.069); a small sample size (n = 5 each) for the groups limit the discriminatory power for statistical

Table 1 – Demographic and clinical characteristics of tuberculosis patients suspected of having drug resistance in Himachal Pradesh state in India in 2012–2013.

Variable	n (%)
Median age (IQR)	45 (32–58)
Male sex	337 (81.2)
District	
Kangra	289 (69.4)
Una	89 (21.5)
Mandi	22 (5.3)
Hamirpur	8 (1.9)
Other	7 (1.7)
Occupation	
Farmer	76 (18.3)
Laborer	101 (24.3)
Driver	30 (7.2)
Student	26 (6.3)
Housewife	60 (14.5)
Other	122 (29.4)
Smoking history	
Current smoker	47 (11.3)
Past smoker	215 (51.8)
Non-smoker	153 (36.9)
Risk group (Reason of referral for Xpert test)	
Relapse case received ATT< 2-months[a]	128 (30.8)
New case smear + at 2–4 months' follow-up[b]	70 (16.8)
Relapse case smear + at 2–4 months' follow-up[c]	44 (10.6)
Treatment Failures[d]	155 (37.4)
Treatment after loss to follow up	8 (1.9)
Other previously treated patients[e]	10 (2.4)
History of contact with any TB case	
Yes	63 (15.2)
No	348 (83.8)
Unknown	4 (1.0)
History of contact with drug-resistant TB case	
Yes	4 (1.0)
No	383 (92.3)
Unknown	28 (6.8)
HIV status	
Negative	395 (95.2)
Positive	12 (2.9)
Unknown	8 (1.9)
Visit to private practice during treatment	
Yes	55 (13.3)
No	358 (86.3)
Unknown	2 (0.5)

[a] Freshly diagnosed relapse cases or relapse cases who had received treatment for < 2-months.
[b] New cases remaining sputum smear positive but had not yet failed treatment.
[c] Relapse cases remaining sputum smear positive at follow-ups between 2 and 4 months but had not yet failed treatment.
[d] Sputum smear positive at month 5 or later of treatment.
[e] Patients with outcome classified as treatment-after-default during last treatment or where information to assign a risk group was not available.

Table 2 – Relationship between patient characteristics and risk of rifampicin resistance among Xpert positive tuberculosis patients suspected of having drug resistant TB in Kangra and Una districts of Himachal Pradesh in India (2012–2013).

Variable	Rifampin resistance n (%)	Bivariate analysis OR (95% CI)	P value
Age, median (IQR)	42 (30, 55)	0.99 (0.97, 1.01)	0.157
Males (n = 280)	53 (20.5)	0.55 (0.28, 1.09)	0.088
Females (n = 47)	15 (31.9)	Reference	
District			
Kangra (n = 226)	57 (25.2)	2.08 (1.03, 4.22)	0.041
Una (n = 79)	11 (13.9)	Reference	
Risk Group			
Relapse case received ATT< 2-months (n = 89)[a]	9 (10.1)	Reference	
New case smear + at 2–4 months' follow-up (n = 59)[b]	9 (15.3)	1.6 (0.60, 4.30)	0.352
Relapse case smear + at 2 –4 months' follow-up (n = 34)[c]	5 (14.7)	1.5 (0.47, 4.95)	0.476
Treatment Failure (n = 113)[d]	41 (36.3)	5.06 (2.30, 11.13)	<0.001
Treatment after loss to follow up (n = 5)[e]	2 (40.0)	5.93 (0.87, 40.3)	0.069
Other previously treated (n = 5)[f]	2 (40.0)	5.93 (0.87, 40.3)	0.069
Occupation			
Farmer (n = 57)	15 (26.3)	Reference	
Laborer (n = 79)	12 (15.2)	0.50 (0.21, 1.18)	0.085
Driver (n = 21)	3 (14.3)	0.47 (0.12, 1.81)	0.111
Student (n = 13)	2 (15.4)	0.51 (0.10, 2.56)	0.922
Housewife (n = 39)	10 (25.6)	0.97 (0.38, 2.44)	0.654
Other (n = 96)	26 (27.1)	1.04 (0.50, 2.18)	0.515
Smoking history			
Current smoker (n = 105)	8 (22.8)	0.86 (0.35, 2.11)	
Past smoker (n = 165)	33 (20.0)	0.72 (0.40, 1.29)	0.330
Non-smoker (n = 35)	27 (25.7)	Reference	0.166
HIV status			
Positive (n = 7)	1 (14.3)	0.57 (0.07, 4.81)	0.541
Negative (303)	67 (22.4)	Reference	
Visited private practice during treatment			
Yes (n = 37)	12 (32.4)	1.85 (0.87, 3.91)	0.119
No (n = 267)	55 (20.6)	Reference	

[a] Freshly diagnosed relapse cases or relapse cases who had received treatment for < 2-months.
[b] New cases who remain sputum smear positive but had not yet failed treatment.
[c] Relapse cases remaining sputum smear positive at follow-ups between 2 and 4 months but had not yet failed treatment.
[d] Sputum smear positive at month 5 or later of treatment.
[e] Treatment interrupted for 2 consecutive months or more during the last TB episode.
[f] Patients with outcome classified as treatment-after-default during last treatment or where information to assign a risk group was not available.

Table 3 – District wise rifampin resistance among patients suspected of drug resistant TB in the state of Himachal Pradesh in India (2012–2013).

District (n = total patients)	Smear positive n (%)	Xpert Positive n (%)[b]	Rifampin resistance in all patients n (%)	Rifampin resistance in Xpert positives n (%)
Kangra (n = 289)	254 (88)	229 (79)	57 (20)	57/229 (25)
Una (n = 89)	84 (94)	79 (89)	11 (12.4)	11/79 (14)
Mandi (n = 22)	21 (95.5)	20 (91)	9 (41)	9/20 (45)
Hamirpur (n = 8)	8 (100)	8 (100)	3 (37.5)	3/8 (37.5)
Others (n = 7)[a]	7 (100)	6 (85)	3 (43)	3/6 (50)
Total (n = 415)	374 (90)	342 (82)	83 (20)	83 (24)

[a] Others include Solan, Shimla, Chamba, and Kullu.
[b] Xpert result showed indeterminate rifampin resistance status for 3 patients from Kangra.

significance. Recurrent and new TB cases who had continued to remain sputum smear positive between 2 and 4 months of ATT had higher prevalence of rifampin resistance as compared to the recurrent cases who had received ATT for <2-months but the risk did not reach statistical significance. Patients who had sought care at a private practice setting showed higher risk of rifampin resistance (OR: 1.85; 95% CI: 0.87–3.91; p = 0.119). Rifampin resistance status for patients referred from other states were described in Table 3; 9 of 22 (45%) DR-TB suspects referred from Mandi district were rifampin-resistant.

3.3. *Discordance in Xpert and smear positivity rate*

Forty-three of 254 (17%) smear positive patients from Kangra district and 8 of 84 (10%) smear positive patients from Una district were Xpert negative for *M.Tb*. Given this significant proportion of smear-Xpert discordant results, second sputum specimens from three random patients with initial Xpert negative results were obtained for repeat Xpert testing. Xpert results were negative for the second specimens. Chest x-rays of the smear positive Xpert negative cases that were reviewed showed findings suggestive of TB.

4. Discussion

We observed a prevalence of rifampin resistance of 18% among patients at risk of DR-TB in Kangra and Una districts of HP state. Among Xpert positives, the RR-TB prevalence was 22%. Of the risk groups for DR-TB, prevalence of rifampin resistance was highest for loss to follow-up and treatment failure cases (36–40%). Patients registered as new or recurrent cases continuing to remain smear positive between 2 and 4 months had higher prevalence of rifampin resistance (15%) as compared to recurrent cases that received treatment for <2 months. Because all patients were systematically included for Xpert testing between 2012 and 13, the sample would be representative of patients at risk of DR-TB in the districts. Kangra is the most populous district (~1.5 million) in HP with

~93% (~1.4 million) rural population.[6] As such, the results reflect the risk of DR-TB in rural population of HP and likely other hilly districts in the state.[6] To our knowledge, this is the first study to report the risk of rifampin resistant TB, a proxy for MDR-TB, in patients at risk of DR-TB in HP state of India.

A systematic review and meta-analysis of 75 studies reported a pooled MDR-TB prevalence of 36% among previously treated cases between 2006 and 2015 in India, ranging from 23% (95% CI: 15–31%) for Southern India to 43% (95% CI: 26–60%) for Western India.[2] There was no study from HP to be included into the review. The RR-TB prevalence in Una and Kangra was lower as compared to rates reported for other states. A state-wide drug-resistant survey in Gujrat in 2005–2006 showed an MDR-TB prevalence of 17% among previously treated cases, similar to that of this study.[7] The national TB drug resistance survey conducted in 2014–15 showed an MDR-TB prevalence of 12% in previously treated patients.[3] However, none of the 15 previously treated cases and only one of 23 new cases that were included in the national survey from HP had MDR-TB. Given the small sample from individual states, the results of the national survey, while nationally representative, are not generalizable to individual states.[3] We observed an RR-TB prevalence of 10% in recurrent TB cases that were newly diagnosed and had received TB treatment for <2-months. Also, 15% of new cases that had failed to achieve smear conversation after 2–4 months of ATT were detected with RR-TB. The high rate of RR-TB in early phase of treatment can suggest the burden of primary transmission. The prevalence of MDR-TB in new cases was 2.8% in the national survey.

We observed a higher prevalence of RR-TB (45%) in patients from Mandi district; however, we note that 55% of the patients referred to us from Mandi district were treatment failure cases that were at higher risk of DR-TB. To account for this selected referral, we compared the risk of RR-TB in the treatment failure cases from Mandi district [73% (n = 8/11)] to that of treatment failure cases from Kangra and Una districts [36% (n = 41/113)] and found a significantly higher risk for Mandi ($p = 0.018$). It is possible that there may be hotspots in each of the districts and therefore, targeted screening and active case-finding can help in early detection of the cases. The difficult terrains in Himachal Pradesh may hamper access to health care and delay diagnosis of TB and DR-TB in the state, underscoring the need for intensified case-finding. Innovative case-finding strategies including use of modern technology such as drones may be considered in parts of the mountain districts in Himachal Pradesh with poor road access, especially during Winter months. An early detection of DR-TB is also important in the light of the generally low treatment success rate (46%) for MDR-TB in the country and globally.[1] Females had higher proportion of RR-TB (32%) as compared to males (21%) in this study despite an overall lower disease burden in females; studies are needed to investigate this to guide prioritization of screening efforts.

The prevalence of RR-TB increased proportionately to the duration of TB disease/treatment: 10% in patients who have received TB treatment for <2-months (recurrent cases who have received ATT for <2-months) to 15% in those who have received treatment for 2–4 months (new or recurrent cases who have received treatment for 2–4 months and continued to remain smear positive) to 36% in patients who have received treatment for >5-months (treatment failure cases). The time dependent increase in prevalence of RR-TB in the risk groups may suggests acquired DR-TB as the mode of drug-resistance for patients in later months of treatment. However, a significant proportion of drug resistance also in the early treatment phase can suggest primary transmission of drug resistant strains. This highlights the importance of universal screening for MDR-TB at diagnosis for all patients as well as at follow-up time-points for at-risk patients and improving adherence.

We observed a 12% higher prevalence of RR-TB among patients who had reported seeking care at any private practice during the course of TB treatment. Studies in the past have shown a poorer treatment completion rate and outcome for patients treated in the private sector, where the large majority of Indian population, especially in rural India, seek care.[8–10] The ratio of public sector doctor to private providers in HP was found to be 1:5 in 2009–10.[11] Thirteen percent of the DR-TB suspect patients responded Yes to having sought care at a private practice. This may still be an under-reported estimate as TB patients are often not forthcoming in their responses regarding visits to private sector. A concerted effort to reach out and work with the private sector to improve case detection and treatment outcome of patients would be necessary.

A significant proportion (15%) of the patients who were sputum smear positive had tested negative for *M.Tb* by Xpert® MTB/RIF assay. Chest radiographs of these patients had findings suggestive of TB. It is possible that these patients were infected with non-tubercular mycobacteria (NTM). Culture results could help classify such patients and guide management.

Under the current RNTCP diagnostic algorithm, TB cases who are non-responders, MDR-TB contacts, previously treated cases, and co-infected with HIV are eligible for testing with Xpert MTB/RIF assay.[12] Meticulous implementation of this diagnostic algorithm vis-a-vis a rigorous contact tracing program would enable early detection of DR-TB and reduction of transmission. Implementation of a universal DST for all TB patients that is currently phased up in the country would greatly help in checking transmission.[12]

5. Conclusion

The high prevalence of RR-TB during early phase of treatment as well as later months warrants a thorough implementation of universal drug susceptibility testing at diagnosis and improving treatment adherence for TB patients. Innovative case finding approaches are necessary to overcome barriers to healthcare access arising from difficult terrains in the mountain districts. In the context of Government of India's commitment to end TB by 2025, improving TB services in the mountainous districts are particularly important.

Conflicts of interest

All authors have none to declare.

Ethics approval

The project was approved as a public health initiative by the Revised National TB Control Program of India and the Delek Hospital of the Central Tibetan Administration Department of Health. The project did not require separate IRB review or approval.

Acknowledgement

We thank the Tibetan Delek Hospital's administration for making the GeneXpert facility available to the TB patients under RNTCP in Himachal Pradesh and for providing Xpert testing free of cost to the patients. We thank the STOP TB PARTNERSHIP and the Johns Hopkins University for the TB REACH wave 2 grant that supported Xpert cartridge supplies for the Delek Hospital.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.08.005.

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Available online at www.sciencedirect.com

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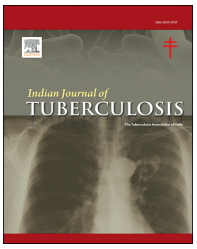
journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Original article

Map, know dynamics and act; a better way to engage private health sector in TB management. A report from Mumbai, India

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ARTICLE INFO

Article history:
Received 3 June 2019
Accepted 23 July 2019
Available online 29 July 2019

Keywords:
PPIA
PPM
Private-sector engagement
Tuberculosis care

ABSTRACT

Background: India, world's leading Tuberculosis burden country envisions to End-TB by optimally engaging private-sector, in-spite of several unsuccessful attempts of optimal private sector engagement. Private Provider Interface Agency (PPIA), a new initiative for private-sector engagement, studied the private-sector networking and dynamics to understand the spread, typology of providers and facilities and their relations in TB case management, which was critical to design an intervention to engage private-sector. We report the observations of this exercise for a larger readership.

Method: ology: It is a descriptive analysis of mapping data (quantitative) and perceived factors influencing their engagement in the PPIA network (qualitative).

Results: Of 7396 doctors, 2773 chemists and 747 laboratories mapped, 3776 (51%) doctors, 353 (13%) chemists and 255 (34%) laboratories were prioritized and engaged. While allopathic doctors highly varied between wards (mean ratio 48/100,000 population; range 13–131), non-allopathic doctors were more evenly distributed (mean ratio 58/100,000 population; range 36–83). The mean ratio between non-allopathic to allopathic doctors was 1.75. Return benefit, apprehension on continuity of funding and issues of working with the Government were top three concerns of private providers during engagement. Similarly, irrational business expectations, expectation of advance financing for surety and fear of getting branded as TB clinic were three top reasons for non-engagement.

Conclusion: A systematic study of dynamics of existing networking, typology and spread of private providers and using this information in establishing an ecosystem of referral

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https://doi.org/10.1016/j.ijtb.2019.07.001

network for TB control activities is crucial in an effort towards optimal engagement of private health providers. Understanding the factors influencing the network dynamics helped PPIA in effective engagement of private health providers in the project.

1. Introduction

India, world's highest TB burden country, accounts to 27% of the global incident TB cases and reported over 480,000 TB deaths in 2016 alone.[1] Of the 4.3million annual TB patients missing out of notification globally, India accounted to over a million, most of whom were presumably treated by the Private Health Sector.[2,3] India has a large Private Healthcare Sector which caters to most of the community irrespective of their socio-economic conditions.[4,5] Previous studies indicate that the proportion of TB cases being diagnosed and treated by these private healthcare establishments overshoots the NTP numbers.[3,4,6] TB treatment in Private Health sector is mostly un-notified, doesn't comply with national standards and is costlier to the patients.[6–8] Several attempts by NTP to engage these private healthcare establishments in TB care and surveillance through Private Public Mix schemes have not yielded optimal results.[9–12] There were many reasons for this letdown, important ones being, lack of mutual trust and pivoting force, limited knowledge of exact dynamics of private healthcare, including the number, networking and linkages, and little awareness on how to use this networking.[12,13] In spite of this failure, National Strategic Plan 2012-17 envisioned to optimally engage Private sector for effective management of TB.[14]

Realizing the need for innovation in this direction, Municipal Corporation of Greater Mumbai (MCGM) conceptualized and piloted a Private Provider Interface Agency (PPIA) model in consultation with Central TB Division (CTD) and World Health Organization in 2013. This PPIA project in Mumbai was implemented by PATH which worked to establish network of providers, organized free quality assured diagnosis, provided free quality assured drugs and notified TB cases diagnosed in this network. Before actual engagement, the initiative had to understand the spread, typology of providers and facilities and their relations in TB case management, The above information was critical to design a intervention to engage private sector. Mumbai has vast number of Private health establishments both, legally qualified to practice Medicine and un-organized under-qualified informal providers. The mapping exercise gave a platform for profiling of private healthcare providers, which provided several findings. We report these findings for the larger readership.

1.1. Design

It is a descriptive analysis of mapping data (quantitative) and perceived factors influencing their engagement in the PPIA network (qualitative).

1.2. Period of reporting

The mapping exercise was carried out between January to August 2014. For qualitative part FGDs were carried out with the PPIA service providers during October 2016.

2. Setting

2.1. General settings

Mumbai is a metropolitan city in west coast of India with approximately 603 sq. kms of surface area. It is highly crowded and accommodates nearly 12.4 million population. Nearly two thirds of the citizens live in urban slums.[15] The public-sector health infrastructure is severely deficient in the city with only 171 government hospitals/dispensaries catering to such a huge populace.[16] Reportedly over half of all TB patients seek care in Private health sector in Mumbai.[17] A report in 2012 about few "totally drug resistant TB" cases attracted Global attention on the situation of TB in Mumbai.[18] Much criticism followed on management of TB in private sector in Mumbai, and on sub-optimal engagement of private sector in TB control.[19–22] Having understood the need for innovation, the MCGM rolled out "Mumbai Mission for TB Control", which conceptualized and piloted the PPIA initiative for engagement of private sector in Mumbai.[23]

2.2. Mapping and engagement

Successful engagement of private providers to bring all TB patients under universal TB care and surveillance was the mandate of PPIA. This initiative realized the importance of understanding the spread, dynamics, networking and typology of private sector for establishing a meaningful engagement for TB control activities and undertook exercise of mapping to list all these healthcare professionals in its work territory. To start with, between March 2014 to July 2014, PPIA carried out this exercise in 12 administrative wards of Mumbai city, where it planned to roll out the "PPIA model of care". Slowly, the exercise was extended to other wards as well. As an exercise, field officers walked through the boundaries of their entitled areas, identified all the healthcare providers in the area using the sign boards, displays, clinic boards, name-boards etc., manually, using a pre-tested mapping form. The details of the health providers were also collected, including their title, qualification, clinic timings etc., as exhibited on the name boards. An updated list of mapped doctors (allopathic or non-allopathic, individual or multi-clinic/hospitals), chemists, and laboratories was prepared. The facilities thus mapped were followed through in person to study their client load,

networking with other doctors and laboratories for referrals, operating timings, linkage with chemists for dispensing, with special focus on TB. A prioritization matrix was followed with OPD loads, proximity to slums and pre-engagement with RNTCP, based on the feedback of this survey and suggestions from the public-sector TB managers. Probable facilities were thus identified for engagement. These probable facilities were deliberated for engagement by the PPIA staff and those ready to comply with the model of care under PPIA were formally engaged with an agreement. Operational definition of terms under mapping are explained in Box 1.

2.3. *Focus group discussions (FGD)*

Three FGDs were conducted with the Field officers (FO) (See Box 1 for operational definition of FO) in October 2016 to understand the perceived factors influencing the process of private provider engagement. A total of available 18 FOs were divided into two groups based on their year of joining the PPIA and their age. Each group was asked to enumerate the perceived concerns of private providers for engagement and reasons for non-engagement. These concerns/reasons were listed on the white board. After brainstorming for all concerns/reasons exhaustively, these points were printed and handed over to each FOs for individual ranking. FOs individually ranked these perceived barriers/reasons with rank one being most important and the last rank with least importance. These ranks were then weighed with effective score obtained by dividing the total score 100 by these ranks. The FO-wise weighed scores matrix was summated with mean score (with range) for understanding level of importance of each perceived challenge/reason.

3. Results

3.1. *Mapping of providers*

Mapping and engagement details of doctors, chemists and laboratories is summarized in Table 1. The initiative mapped 7396 doctors (3352 allopathic and 4044 non-allopathic), 2773 chemists and 747 laboratories. Of them, 3776 (51%) doctors (49% allopathic and 53% non-allopathic), 353 (13%) chemists and 255 (34%) laboratories were prioritized and formally signed for engagement.

Ward-wise distribution and density of private providers of initial 12 wards are shown in Fig. 1. While distribution of allopathic doctors had much variability among the wards (Fig. 1A: mean ratio 48/100,000 population; range 13–131), non-allopathic doctors were distributed more evenly (Fig. 1B: mean ratio 58/100,000 population; range 36–83). The mean ratio between non-allopathic to allopathic doctors was 1.75, and the ratio was unevenly distributed between wards (Range: 0.59–4,28. Fig. 1C.)

3.2. *Perceived barriers in engagement*

Common concerns of private health providers for signing into PPIA are summarized in Table 2. Return benefit, viability of funding and apprehensions in working with the Government

Box 1
Operational definitions of Mapping terminologies, Network, Human Resource under Private Provider Interface Agency, Mumbai, India, 2014-16

a. Terminologies used in mapping exercise	
Mapped	The facilities that are existing within the working boundary of the interventional area, which has been identified and line-listed
Targeted	Subset of "mapped", under serious consideration for engagement based on following criteria 1. TB client load, 2. prescription patterns, 3. linkage with a key provider, 4. infrastructure required for the intervention and 5. Input from local government authorities.
Engaged	Subset of "Targeted" list, who were formally signed for agreement for inclusion under the initiative. Essentially, they agreed for an undertaking to abide by the STCI for TB management.
Active	Active is defined as utilization of at least one service per month (reported every quarter considering previous one month activity)
b. type of doctors mapped	
Allopathic doctors	**Allopathic doctors** were defined as those having an MBBS (Bachelor of Medicine, Bachelor of Surgery) degree and/or medical post-graduation (Doctor of Medicine [MD]) or higher specialization.
Non-allopathic providers	**Non-allopathic providers** included healthcare providers with any government recognized health/medicine related degree other than allopathic, which included Ayurveda, yoga and naturopathy, unani, siddha, and homeopathy (abbreviated by the government as AYUSH). It also included health practitioners with some degree which could not be identified with any Government accreditations.
c. Cadres of field staff	
Field Officers:	They were medical representatives (detailers) involved in interacting with private providers (including private doctors, Labs, Chemist) for their engagement activities and networking under PPIA.

Table 1 – Details of Private health provider mapping and engagement under Private Provider Interface Agency for Tuberculosis care, Mumbai, India, 2014-16.

Private Providers by type	Mapped[d] – n (%)	Engaged[e] – n (%)
Non-Allopathic Doctors (AYUSH[b] & Unknown[c])	4044 (100%)	2132 (53%)
Allopathic Doctors[a]	3352 (100%)	1644 (49%)
Chemists	2773 (100%)	353 (13%)
Laboratories	747 (100%)	255 (34%)

[a] Allopathic Doctors: Doctors with modern system of medicine, registered under Indian Medical Council.
[b] AYUSH: Health providers with Indian system of Medicine - Ayurveda, Yoga, Unani, Siddha and Homeopathic.
[c] U n-known: Health providers with degree, which is not identified in India or without any known accreditation.
[d] Mapped: Number of providers identified and line-listed by the PPIA staff as denominators for inclusion under the initiative.
[e] Engaged: Number of providers formally signed memorandum of understanding for inclusion in the initiative.

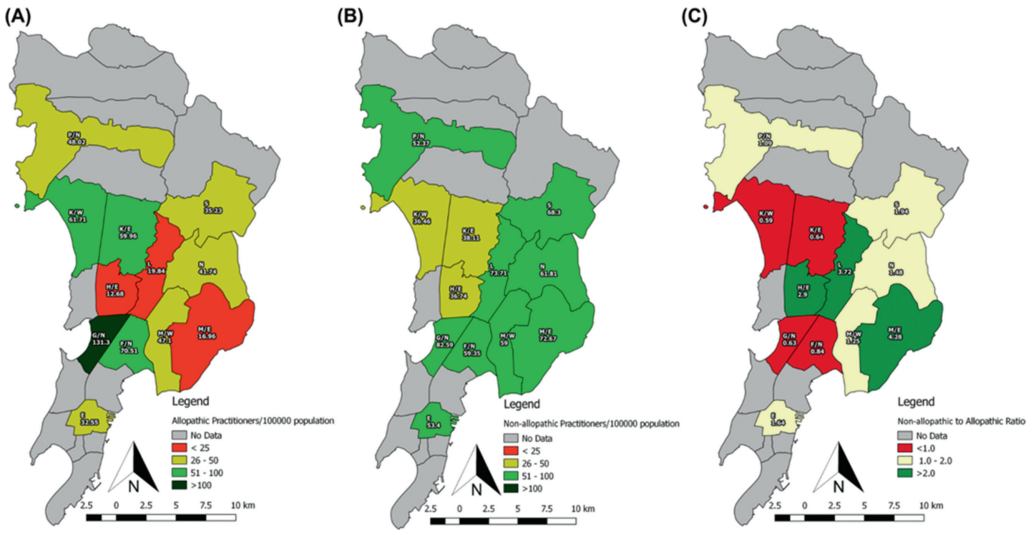

Fig. 1 – Ward-wise distribution and density of private health providers, Mumbai, India, 2014-16.

were the top three concerns of the private providers. Incentivizing patients, provision of nutritional support to patients and data confidentiality were their least priority concerns.

Common reasons for non-engagement of private providers in PPIA are summarized in Table 3. Irrational business expectations, expectation of advance incentives for surety (for incentivized services like Laboratories and X-Rays) and not wanting to get branded as TB clinic were top three reasons for non-engagement. Non-engaged providers were least bothered about price expectation mismatch, documentation/reporting and feasibility of payment scheduling.

4. Discussion

This is the first ever report to explain mapping of private healthcare providers for a public health initiative in India. The report highlights some important learnings. First, the exercise paved way to understand the spread, typology and existing relationship of private provider network with respect to TB patient management. Second, it highlighted the variations in doctors' ratio within the city between wards and between system of medicine, which indicates that one strategy may not fit all wards for a successful networking. Third, private providers mostly had self-centric concerns prior to engagement rather than patient-centric concerns. This finding is important for working out strategy for engaging providers.

Complete information on working domain is a prerequisite for success of any project. Since PPIA model had the mandate to effectively engage the private provider in the city in TB control, mapping to have a complete information on the denominator and inter-provider dynamicity is imperative. The exercise added many otherwise not in the list health providers to the denominator and paved way for studying the network more closely. Previous studies showed that many poor patients in India prefer informal providers as first point of care for their health issues.[24,25] This exercise of mapping gave an idea of their linkage with formal providers, which later was taken up by the PPIA for designing referral system for TB in the model.

Networking and referral mechanisms are important prerequisites for the success of any public health project. While networking depends on the dynamics of providers in that area, the ratios and dynamics are not the same in all the places. Mumbai is a crowded but geographically small city. The doctors' ratio changed rapidly within few kilometer radius in the city. This observation of variations in doctors' ratio between wards and between system of medicine within this

Table 2 – Concerns of private providers for engagement in PPIA prior to signing as perceived by the Field Officers, who were involved in mapping and engagement exercises, Mumbai, India.

Concerns of Private providers	Details	Mean Score	Range
• Return benefit	For engaging in the program and providing services to my patients, what is it that I will get in terms of monetary benefits or in kind.	15	6–100
• Source of funding	Providers were apprehensive about the credibility, legality and viability of funding (based on their previous experience with NGOs)	14	6–100
• Apprehension of working with Government	Providers felt notification may lead to loss of patients to public sector and may breach patient's confidentiality. Also mandatory notification process was perceived as unclear and time consuming	14	6–100
• Additional Paper work	Providers were worried about the additional paper work for documentation (in a voucher system) and to keep information for notification	12	6–50
• Duplicity of efforts	There is already a project of National TB Program what is this another program?	12	6–100
• Why no Incentives?	The project didn't provide incentives to the providers. Providers were concerned about the non-provision of incentives to them for diagnosis and treatment	12	6–100
• Why can't we treat? We are also doctors (IFP)	Informal providers perceive themselves competent to treat the TB patients. They were apprehensive about losing patients to referral network.	10	6–50
• Project will end what after that?	Whether the free services under the project will affect my practice after the end of project.	9	6–100
• Reimbursement mechanism is not sustainable	Providers concern about sustainability of the services and why engage if it is not sustainable	9	6–20
• Signing the MoU	Providers were concerned about the legal validity and their bindings once they sign the MoU.	9	6–33
• Advance payment for services	Apprehension of service providers (chemists and laboratories) on security of their payment for services as a reimbursement mechanism. They were insisting on advance payments	8	6–33
• Expectation for second line drugs	Few providers were expecting free second line drugs as well under the project. They were interested in treating DR-TB	8	5–100
• What is the credibility of NGO	When the mapping started, providers were not aware of the credibility of implementing agency	8	5–100
• Multiple stakeholders	Providers were confused about the role of multiple stakeholders (donors, implementing partners and the government) as the project was first of its kind.	7	5–100
• Who will be responsible for TB notifications	Providers were reluctant on extra work on notification. Hence were concerned about who will notify, whether project staff on their behalf or providers themselves.	7	5–50
• Lack of belief in DOTS	Few providers were apprehensive of treatment under project. They perceived that project will adopt intermittent DOTS therapy. Many providers were against DOTS..	7	5–50
• Who will pay?	Providers were confused about payment of their fees (by project or by patient?) Laboratories and chemists were confused whether the payment will be done by Government or the PPIA?	7	5–50
• Disclosure of consulting fees	Implementing agency's request for disclosure of fees for establishment of referral networks from informal providers was perceived as a concern by some formal providers	7	5–33
• Quality of medicines under the project	Provider perceived that PPIA is supplying the medicines to the chemists. If so, is the quality reliable? Which company products?	7	5–20
• Is this sustainable	Is the arrangement of referrals, notifications, free medicines to all, call centers etc., sustainable for long?	7	5–33
• Return benefit for referral (Informal provider)	Why should I refer to formal providers without any benefit and at the risk of losing my patient?	6	5–14
• Knowledge gap regarding newer diagnostics / WHO endorsed tests	Providers were unaware of the newer diagnostics and hence were apprehensive on using them in place of conventional diagnostic tests	6	5–11

(*continued on next page*)

Table 2 – (*continued*)

Concerns of Private providers	Details	Mean Score	Range
• Data Sharing Concerns	Providers were of the opinion that notification comes in way of confidentiality and follow up of their patients by public sector	6	5–14
• Whether you will provide nutritional support	Although not a concern, providers were of the opinion that nutrition plays a role in TB management and hence suggesting inclusion of nutritional supplements under the project	6	5–13
• Incentives to the patients	Some providers were concerned about their patients and suggesting to include some form of incentivizing patients during the treatment to motivate them to complete full course of treatment..	5	5–9

IFP: Informal Providers.
MoU: Memorandum of Understanding.
NGO: Non-Governmental Organization.
DOTS: Directly Observed Treatment Short-Course.
WHO: World Health Organization.
PPIA: Private Provider Interface Agency.

Table 3 – Common reasons for non-engagement of Private Providers in PPIA as perceived by the Field Officers, who were involved in mapping and engagement exercises, Mumbai, India.

Concerns of Private providers	Definition	Mean Score	Range
• Irrational business expectation	Providers were expecting reimbursements to additional tests like LFT, RBS, CBC and ESR	21	11–100
• Advance for security of reimbursable solution	Initially as PATH was not familiar to many providers, they were demanding security deposits	21	9–100
• Don't want to brand the facility as TB Hospital	Providers were initially apprehensive of the TB hospital tag being attached to them if they start notifying cases	18	9–100
• Clientele Affluent	Some providers didn't want their patients to be visited at home for some reasons	16	9–50
• I Don't want to refer the patient to CP	Some providers were under the impression that, once referred the patient and their family get lost	16	8–50
• Dummy prescription	Some providers showed dummy prescriptions just to show that they have seen TB patients.	14	8–100
• Existing pacts/Commitment/Charity/ relations		12	7–100
• Infection control apprehensions	Doctors were apprehensive about nosocomial infection in their hospitals	12	8–50
• Nonbusiness inclination	Some providers were not interested in doing any new ventures.	12	8–20
• Don't believe in NGO	Some providers were not believing in NGOs and hence were not interested	11	8–50
• Data Sharing	Providers were of the opinion that notification comes in way of confidentiality and follow up of their patients by public sector	10	7–50
• Payment schedule for feasible	Some service providers (Labs/chemists) felt that reimbursement schedule is not acceptable to them and hence remained non-engaged	10	7–100
• Paperwork	Providers were worried about the additional paper work for documentation (in a voucher system) and to keep information for notification	10	7–50
• Price expectation mismatch	Few service providers did not compromise on the service charges and hence could not accept the negotiated prices for re-imbursement	10	7–50

CP: Chest Physicians.
NGO: Non-Governmental Organizations.
PPIA: Private Provider Interface Agency.

city limit guided the project to strategize modalities for networking. FOs studied the pre-existing networking within doctors, chemists and laboratories. The exercise informed the PPIA about the private sector network ecosystem, which was retained in the model.

Many published literatures from India had observed that the reason for not notifying TB cases by private providers were concerns about their patients' confidentiality and other patient related issues.[26–29] In contrast, the PPIA mapping and engagement exercise showed that the private providers had mostly self-centered concerns for signing the engagement. One could also speculate this finding logically as well, for the "for-profit" private sector. This exercise provided much insights for designing the strategies for signing the providers for engagement in the project. PPIA designed marketing strategy based on these observations. PPIA FOs were trained in

behavioral change communication skills and they periodically met doctors and explained about indirect incentives they gain out of goodwill and assured inflow of patients. The supportive services like laboratories and chemists were reimbursed the expenditure for the services at pre-negotiated rates.

Internal improvement and review of strategies for evidence based modifications is key for the sustenance and longevity of a public health project. Periodic review with project staff is hence important to have constant feedback and internal improvements in policies and strategies. A similar inbuilt mechanism of FGDs in PPIA was helpful in bringing out the procedural and administrative shortcomings which were perceived to be key issue in engagement. This helped the project to fine-tune the policies. For example, one of the perceived barriers was paperwork involved in notification. Based on this observation, the program brought in two key changes in its strategy. First an IT platform was brought in for minimizing the paperwork involved in series of verification and notification processes (see Box 2 for details). Second, project staff assisted the engaged providers in remaining paperwork and administrative procedures for generating patient ID, payment vouchers and notification.

Box 2
Information Technology platform for handling Private Provider Interface Agency initiative, Mumbai, India.

Information Communication Technology (ICT) platform: Information and communication technology (ICT) platform: A web-based ICT platform, called UATBC, was developed under PPIA. This platform hosted end-to-end patient journey, starting with the identification of presumptive TB till the outcome of treatment. The services under UATBC included registering presumptive TB cases, notifying confirmed TB cases to "NIKSHAY" (online portal for RNTCP's electronic database), generating electronic vouchers for X-ray, providing CB-NAAT and first line anti-TB drugs, sending reminder messages to patients on treatment, and calling patients for periodic monitoring. UATBC is enabled to generate payment invoices and link electronic payment portals to service providers.

How It **work?** Presumptive TB cases identified were allotted beneficiary identification (BID) after registering in the UATBC platform. BID is tagged to the patient as an identifier throughout the management cycle. The doctor used the BID at the hub center to prepare vouchers for diagnostic tests for the referred patients and for walk-ins. These vouchers were used for verification and payments at the diagnostic centers (X-ray or CB-NAAT). Verification involved tele-confirmation with the ICT call center using the BID and patient details. Once verified, the service was provided to the patient free-of-cost and the provider retained the voucher for payment by PPIA. The field officers transported the sputum samples deposited at the hub centers to the CB-NAAT labs to begin the process.

Nevertheless, the exercise had some inbuilt shortcomings. Importantly, while project staff studied the existing networking within formal and informal providers in Mumbai, a systematic documentation of the nature, quantification, geotagging and dynamicity of these networks was lacking. A well-documented effort in this direction could have informed the policy in a much better way. A mixed method study is planned for informing the dynamics of private providers, the marketing strategy that worked to complement these dynamics, strategy adopted for behavioral change communication has been planned.

5. Conclusion

A systematic study of dynamics of existing networking, typology and spread of private providers and using this information in establishing an ecosystem of referral network for TB control activities is crucial in an effort towards optimal engagement of private health providers. Understanding the factors influencing the network dynamics helped PPIA in effective engagement of private health providers in the project.

6. Funding

The PPIA project is funded by the Bill & Melinda Gates Foundation, India, New Delhi. The manuscript writing was also supported by Bill&Melinda Gates Foundation Seattle, USA by funding the hiring of Medical Writer.

7. Conflicts of interest

The authors have none to declare.

Acknowledgement

We acknowledge the guidance and mentorship of district TB officers of 24 wards of Mumbai; efforts of the NGO staff working in the field; staff members of UATBC call center for their relentless efforts in smooth running of the initiative; and all the private practitioners, laboratories, and chemists. We thank BMGF for providing access to experts for course correction and funding. We thank Dr. Nimmy Dominic, Technical Officer, PATH, Dr. Sarang Deo, Indian School of Business, Earsnt & Young, Accenture, Clinton Health Access Initiative, Global Health Strategies, and Vertex for their contribution towards the success of the program. We would like to extend a special thanks to Dr. Madhukar Pai (McGill University, Canada), Jishnu Das (The World Bank), Ada Kwan, Ben Daniels, and Dr. Andrew Mcdowell for guiding us throughout the program. We also thank the beneficiaries of this initiative for their immense cooperation.

Write up for this paper is accomplished with the help of BMGF, who funded the hiring of our medical writer, Dr. Prashant Bhat. We sincerely thank Dr. Prashant for his valuable work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.07.001.

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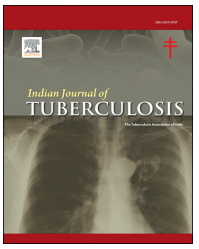

Original article

Tuberculosis in renal transplant recipients: Our decade long experience with an opportunistic invader

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ARTICLE INFO

Article history:
Received 4 November 2017
Received in revised form
26 April 2019
Accepted 8 May 2019
Available online 15 May 2019

Keywords:
Pulmonary tuberculosis
Organ transplant
Immunosuppressants
Type II diabetes mellitus
Calcineurin inhibitors

ABSTRACT

Aim: To study the incidence, pattern of tuberculosis, Its risk factors, and prognosis in renal transplantation recipients in Indian population.
Settings and design: This study retrospectively analyzed the patients who underwent renal transplantation at Ramaiah medical college Hospitals, India from 2004 to 2015.
Methods and material: The study enrolled 244 patients. Diagnosis was based on radio0-imaging, sputum smear, culture and polymerase chainreaction and histology.
Statistical analysis used: A descriptive univariate analysis was performed to identify the individual risk factors.
Results: The TB infection was present in 21/244 (8.6%) renal transplantation patients (mean age ± SD = 44.3 ± 12.9 years). Pulmonary tuberculosis was the commonest (57%) followed by extrapulmonary tuberculosis (43%). Type II diabetes mellitus (DM) (14.6%; p = 0.0169)was significant risk factor. Majority of the patients (n = 18, 10.7%) were on standard tripledrug immunosuppression. The median duration of anti0tubercular therapy was 14 months and crude mortality was 19%.
Conclusions: High index of suspicion for tuberculosis is require d in renal transplant recipients owing to their immunocompromised status and atypical presentations. Higher age, DM and use of immunosuppressants increase the risk for post0renal transplantation tuberculosis. Interactions between anti0tubercular drugs and immunosuppressants need to be considered in these patients.

Abbreviations: CKD, Chronic kidney disease; SRD, End stage renal disease; CVD, Cardiovascular disease; DM, Diabetes mellitus; TAC, Tacrolimus; MMF, Mycophenolate mofetil; PCR, Polymerase chain reaction; ATG, Antithymocyte globulin; CT, Computed tomography; CNS, Central nervous system; INH, Isoniazid; SD, Standard deviation.

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https://doi.org/10.1016/j.ijtb.2019.05.001

1. Introduction

Renal transplantation is the most preferred treatment option for the end stage of chronic kidney disease (ESRD).[1,2] As per estimates from the World Health Organization, 69,400 renal transplants are performed each year worldwide (46% from living donors).[3] In India 3500 renal transplantations are performed every year.[4,5] Patients with renal transplantation have improved survival rates and quality of life in comparison to the patients on dialysis.Cardiovascular diseases (CVD) are the common cause of mortality in the Western countries following renal transplantation.[6,7]

However, infections, in addition to CVDs, are the major cause of mortality in Indian renal transplant recipients.[8] Infections within first month after the transplantation are usually nosocomial, donor derived, or due to surgical issues. However, opportunistic pathogens cause infections in the later months (around five months), largely as a result of immunosuppression. The choice of immune suppressants can also affect the timing of infections.[9] In transplant recipients, iatrogenic immunosuppression weakens the immune system leading to progressive impairment in cellular immune function. Thus, transplant recipients become immune compromised and are at increased risk for reactivation of latent infections.[10,11] Tuberculosis is a common bacterial infection in transplant recipients in the developing countries. The impaired immune system increases the risk of tuberculosis in patients with solid organ transplantation.[12] The risk for tuberculosis is higher during initial 6–12 months Post transplantation due to immunosuppression.[13–16] Several Immunosuppressants are reported to enhance the risk of post renal transplantation tuberculosis, such as mycophenolate mofetil (MMF), tacrolimus (TAC), and cyclosporine.[13–16] Thus, the present study was conducted to study the incidence and pattern of tuberculosis, its associated risk factors, and prognosis in renal transplantation recipients in Indian population.

2. Methods

2.1. Study design

This was a retrospective data analysis of post renal transplantation patients, conducted at Ramaiah Hospital, Bangalore, India from 2004 to 2015, following the approval of institutional ethics committee.

2.2. Patient population

The study enrolled a total of 244 patients who underwent renal transplantations between the years 2004–2015. Diagnosis for tuberculosis was made based upon radio imaging, sputum smear, culture, polymerase chain reaction (PCR), and histology.

2.3. Statistical analysis

Discrete variables were expressed as frequencies and percentages. A descriptive univariate analysis was performed to identify the risk factors for association of tuberculosis infection in renal transplantation recipients. Chi square analysis was used to compare categorical data. A 2 tailed $P < 0.05$ value was considered as the threshold of statistical significance. Appropriate statistical analyses were performed using the Statistical Package for the Social Scientists (SPSS), version 18.0 (SPSS Inc., Chicago, USA).

3. Results

A total of 244 patients who underwent renal transplant between the years 2004–2015 were included for the analysis. Of these transplant recipients, 21 (8.6%) patients (mean age ± SD = 44.3 ± 12.9 years) were diagnosed with tuberculosis. Post transplantation tuberculosis was more in male patients (n = 16) compared to females (n = 5), the frequency of tuberculosis infection was highest in the age group of 41–60 years (n = 11). The median (IQR) age and time of tuberculosis diagnosis following transplant was observed to be 50 (30050) years and 2.5 (1.5–4.5) years, respectively. The recipients who underwent live related donor transplant (n = 5; 3.6%) were significantly more ($P < 0.05$) prone to post transplantation tuberculosis as compared to those who underwent unrelated transplant (n = 15, 16.6%). Graft rejections were reported in 7 (33.3%) patients who developed post transplantation tuberculosis. The baseline details are presented in Table 1.

Type II diabetes (14.6%; P = 0.0169) was most common amongst the post transplantation tuberculosis recipients, followed by the autosomal dominant polycystic kidney disease to transplant was found in only one patient (Table 2). The most common clinical symptoms at presentation were fever, weight loss, and cough with expectoration. The tuberculosis infection rate was highest (n = 6/21) within 2–3 years of post transplantation.

3.1. Diagnosis and types of tuberculosis

The diagnosis of tuberculosis was arrived using radio imaging (n = 12), sputum smear (n = 7), culture (n = 3), PCR (n = 5), and histology (n = 2). Pulmonary tuberculosis was the most common type of tuberculosis (57%) (Fig. 1).

Table 1 – Baseline characteristics of Renal Transplant patients.

Characteristics	Tuberculosis Group	Non-Tuberculosis Group
No of patients (%)	21 (8.6)	223 (91.4)
Transplant Donor Relation, n (%)		
Related	5 (3.6)	134 (96.4)
Unrelated	15 (16.6)	75 (83.4)
Deceased	1 (17.1)	13 (92.6)
Rejections, n (%)		
Early	2 (15.4)	11 (84.6)
Late	5 (26.3)	14 (73.7)

*Unrelated: $p < 0.005$.

Table 2 – Conditions associated in renal transplant patients.

Basic Disease N (%)	Tuberculosis Group (n = 21	Non Tuberculosis Group (n = 223)
Type II Diabetes Mellitus	12 (14.6)	70 (85.4)
CGN	4 (4)	96 (96)
CIN	1 (3.3)	30 (96.7)
HIV	1 (12.5)	7 (87.5)
ADPKD	1 (14.3)	6 (85.7)
Alport syndrome	1 (25)	3 (75)
Analgesic nephropathy	1 (8.4)	11 (91.6)

Note: CGN: chronic glomerulonephritis; CIN: Cervical intra-epithelial neoplasia; HIV: human immunodeficiency virus; ADPKD: autosomal dominant polycystic kidney disease.

Table 3 – Infections associated with TB in renal transplant patients.

Infections N (%) = 244	Tuberculosis Group (n = 21)	Non Tuberculosis Group (n = 223)
Hepatitis B	1 (4.3)	6 (85.7)
Hepatitis C	2 (8.6)	5 (71.4)
HIV	1 (12.5)	7 (87.5)
CMV	2 (14.3)	12 (85.7)
Previous History of TB	1 (14.3)	6 (85.7)
Major Infections	6 (24)	19 (76)

*HIV: human immunodeficiency virus; CMV: cytomegalovirus; TB: Tuberculosis.

3.2. *Immunosuppressant therapy*

A total of 21 tuberculosis patients were on triple drug immunosuppressive therapy post transplantation. Majority of these patients received TAC + MMF + prednisolone (n = 18; 10.7%) (Table 3). Two patients showed acute rejection 6 months prior to onset of tuberculosis and 9 patients had concurrent opportunistic infections like hepatitis B, hepatitis C, CMV, candida and mucormycosis (Table 4).

3.3. *Induction treatment*

One third of the patients (n = 8) with post transplantation tuberculosis had received induction with basiliximab, antithymocyte globulin (ATG) and dacluzimab to prevent acute rejections ($\chi 2 = 0.007$; P = 0.934) (Table 5).

3.4. *Anti-tubercular treatment*

Isoniazid (INH), rifampicin, pyrazinamide, and ethambutol were used as first line drugs for the treatment of tuberculosis. Two patients who developed multidrug resistant tuberculosis received second line treatment which includes kanamycin, levofloxacin, cyclosporine, ethionamide, pyrazinamide, and ethambutol. Both the patients succumbed to the illness. The median duration of anti-tubercular therapy was 14 months (range: 9–18 months). Four patients diagnosed with tuberculosis succumbed to the illness and the crude mortality that can be attributed to tuberculosis was 19%. The recurrence of tuberculosis was observed in 2 patients.

4. Discussion

A review by John et al reported the prevalence of several infections following renal transplant in India including deep mycosis (3.8%–6.1%), Nocardiosis, chronic liver disease (30%), hepatitis B virus (40%), hepatitis C virus (15%), cytomegalovirus infection (20%), Plasmodium falciparum (22.5%), persistent urinary tract infections (6.5%), and tuberculosis (12.3%).[17] ESRD patients on hemodialysis have higher incidence of tuberculosis. According to a study done by Cengiz K et al, Tuberculosis was diagnosed in 26 patients (6 females and 20 males) undergoing maintenance hemodialysis, with an incidence of 23.6%.In a study conducted by T Manmadha Rao

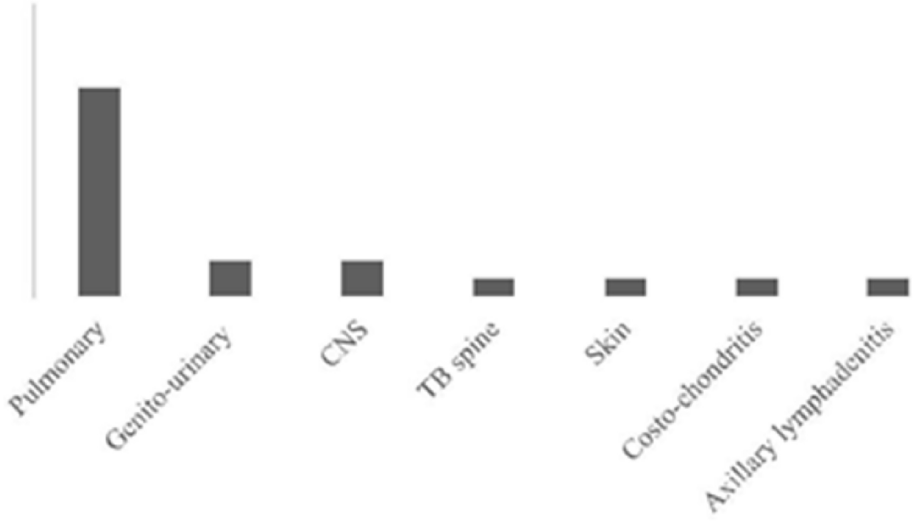

Fig. 1 – Types of Tuberculosis seen in Post Renal Transplant Recipients, *Genito-urinary, CNS, Tuberculosis spine, skin, costo-chondritis and axillary lymphadenitis are extra-pulmonary sites of tuberculosis.

Table 4 – Immunosuppressant therapy given to renal transplant patients.

Immunosuppressants N = 244	Tuberculosis Group (n = 21)	Non Tuberculosis Group (n = 223)
Tacrolimus + MMF + prednisolone	18 (10.7)	151 (89.3)
Cyclosporine + MMF + prednisolone	02 (5.3)	36 (94.7)
mTOR Inhibitors + MMF + prednisolone	01 (6.3)	15 (93.7)
Azathioprine + prednisolone	0 (0.0)	21 (100)

*MMF: Mycophenolate mofetil; mTOR: target of rapamycin.

incidence of Tuberculosis in patients on hemodialysis was found to be 105.9 patients per 1000 patient's years.[18,19]

The current retrospective study showed that tuberculosis is an important opportunistic infection to be considered in the renal transplant patients. Age, type II DM and triple therapy with immunosuppressant (tacrolimus + MMF + prednisolone) were found to be the risk factors associated with susceptibility to tuberculosis infections. Although pulmonary tuberculosis was reported to be prevalent in more than half of the patients with tuberculosis, the occurrence of extrapulmonary tuberculosis with atypical presentation is also alarming.

The incidence of tuberculosis (8.6%) reported in the present study conducted over a period of 12 years is considerably low compared to the previous other studies. Several long term studies from different regions of India reported varying percentages of the incidence (9.5%–13.3%) of tuberculosis in transplantation recipients. This may be attributed to the facts like enrollment of people from tuberculosis endemic areas, age and immunosuppressant therapies being given to these patients.[14,20,21]

In our study, higher age, Diabetes Mellitus, and use of immunosuppressants were considered to increase the risk of tuberculosis in renal transplant patients. Literature review has also shown that elderly age, diabetes (during both pre and post transplantation), co existing infections (cytomegalovirus, systemic mycoses, hepatitis C virus, Nocardia, Pneumocystis jirovecii), and vitamin D deficiency increase the susceptibility for post renal transplant tuberculosis infection.[12,14,17] In a study conducted by Christopoulos AI et al the incidence of TB in diabetics was compared to Non-diabetics and it was common in diabetics (Adj.RR 25.3, 95%CI 17.2–21.1, P < 0.03).[22] In our study 12 out of 21 patients who developed TB had diabetes mellitus.

A recent study reported that recipients of graft from cadaveric donors are also at increased risk for tuberculosis infection following liver and renal transplantation.[14]

Age is determined to be the critical risk factor for the occurrence of tuberculosis in renal transplantation recipients.[14] Our study reported a little higher age (44.3 ± 12.9 years) in patients with tuberculosis as compared to the previous study by John et al, in which the mean age was 34.5 ± 10.3 years and was found to be a significant risk factor associated with tuberculosis infection (OR: 1.01 [CI: 1.0001.03]; P = 0.05).[14]

History of Diabetes Mellitus is a common risk factor for postrenal transplant tuberculosis.[14,20] Our study results are in line with the previous studies reporting Diabetes Mellitus (14.6%) to be the major comorbid condition present among transplantation recipients diagnosed with tuberculosis. A prospective study showed that the risk of tuberculosis increases by 2.2 fold in renal transplantation patients with Diabetes Mellitus.[14] In our study, only one patient had a history of tuberculosis prior to transplantation. History of tuberculosis has not yet been confirmed as a risk factor for post transplantation tuberculosis.

However, some studies have reported the history of tuberculosis in renal transplant patients ranging from 9.5% to 13.5%.[21,23] Fever is the major symptom associated with tuberculosis in transplantation recipients[24] and similar finding was noted in our study. A study by Singh et al also reported fever to be more frequent in transplantation recipients with disseminated tuberculosis (91%) in comparison to localized disease (64%).

Our study showed similar results to the previous studies reporting increased prevalence of tuberculosis in patients on immunotherapy. In the present study, the patients were on triple immunotherapy and majority of those on TAC + MMF + prednisolone were infected with tuberculosis. A study by Atasever et al reported the prevalence of tuberculosis in renal transplantation recipients to be significantly higher in patients receiving MMF and TAC (P > 0.05) in comparison to those receiving conventional immunosuppressive agents (cyclosporine, azathioprine and prednisolone). Further, the study also reported that a significantly higher number of these patients were infected with tuberculosis within 6 months following transplantation (P = 0.042).[14] In a study by John et al the risk of tuberculosis infection in patients receiving cyclosporine was significantly higher i.e.2.5 (P = 0.0311) and 1.9 (P = 0.0430) times at 6 and 12 months, respectively, in comparison to the patients receiving prednisolone + azathioprine therapy.[15]

In our study, considerably high percentages (57.1%) of the patients were diagnosed with radio imaging, and a more sensitive diagnostic method PCR was performed in some patients (23.8%). The longest mean time reported for delay in diagnosis was 41 days from the onset of symptoms.[25]

Clinically involvement of extra pulmonary sites and disseminated tuberculosis is frequent.[26] Urine culture for

Table 5 – Induction therapy in renal transplant patients to prevent acute rejections.

Induction n (%)	Tuberculosis Group (n = 21)	Non Tuberculosis Group (n = 223)
Basiliximab	5 (6.5)	72 (93.5)
Daclizimab	1 (10)	9 (90)
Antithymocyte globulin	2 (25)	6 (75)

*P value = 0.934.

diagnosis of genitourinary tuberculosis could delay the confirmation, thus rapid diagnostic tests such as urine TB PCR should be done for early and rapid diagnosis.[27] Patients with atypical, pyrexia, weight loss and scanty sputum should undergo aggressive investigations. Computed tomography (CT) chest and bronchoalveolar lavage (BAL) should be done in these patients.[28]

In our study, pulmonary (57%) was the most common type of tuberculosis followed by extrapulmonary (43%). The extrapulmonary sites observed in our study include genitourinary, CNS, tuberculosis spine, skin, costochondritis, and axillary lymphadenitis. Literature review also reports pulmonary tuberculosis to be the most frequent type followed by extrapulmonary tuberculosis and disseminated tuberculosis in solid organ transplant recipients.[24,26] Further, the extrapulmonary tuberculosis infection sites reported in literature include lymphadenopathy, gastrointestinal, renal, central nervous system, spine, skin, muscle, osteoarticular, pericardium, spleen and.[24] These extrapulmonary types of tuberculosis present different symptomology in transplant recipients as compared to non-transplant population.[29] For example, radiological presentation of genitourinary tuberculosis in renal transplantation recipients include disseminated tuberculosis, systemic symptoms, multiple parenchymatous renal foci, and lower frequency of lesions of the collecting system.[29] Isoniazid (INH), rifampicin, pyrazinamide, and ethambutol were the first-line drugs used in the present study for the treatment of tuberculosis. The second-line drugs included kanamycin, levofloxacin, cyclosporine, ethionamide, pyrazinamide, and ethambutol.

Literature also reports the use of isoniazid, rifampicin, and pyrazinamide as the first-line essential agents for tuberculosis treatment.[12] INH is associated with increased frequency of hepatotoxicity in renal transplantation recipients.[30] In our study one of our patient developed drug induced hepatitis and he later succumbed to illness.In our study, the duration of anti-tubercular therapy varied from 9 to 18 months. Literature review has shown that the dosage and duration of tuberculosis.

Treatment varies between different centres based on individual preferences and response.[12] In a study by Boubaker et al, four drug therapy including isoniazid, rifampicin, ethambutol and pyrazinamide was given for first 2 months followed by isoniazid and rifampicin. The average duration of the therapy was 1–17 months.[26]

In our study, graft rejections were reported in 33.3% of the renal transplant patients with tuberculosis. Interactions between immunosuppressive agents and anti-tuberculosis drugs cause difficulty in managing tuberculosis in transplantation recipients, and can also result in graft rejection.[31] In our study also, graft rejections might have occurred as a result of interactions between immunosuppressants and anti-tuberculosis drugs. Rifampicin is reported to interact with cyclosporine, TAC and everolimus and decrease their serum concentrations to sub therapeutic levels.

Rifampicin interact by inducing liver enzymes including cytochrome P450, uridine diphosphate-glucuronosyltransferases, glutathione S-transferases and monoamine oxidases which are involved in drug metabolism. A regular monitoring of the levels of immunosuppressive agents in blood is therefore, recommended.[31] On the other hand, fluoroquinolones including ofloxacin and ciprofloxacin are reported to increase the blood levels of cyclosporine.[32] Multi-drug resistance is the other major concern apart from atypical presentation of tuberculosis. In our study, 2 patients showed resistance to first line anti-tuberculosis drugs.

Our study had two major limitations: its retrospective study design and small sample size. However, no previous long-term studies from India have assessed the incidence, risk factors and prognosis of tuberculosis in a single study.

5. Conclusions

The current study suggests that the occurrence of tuberculosis should be considered in patients undergoing renal transplantation owing to their immunocompromised status. The major challenge is the atypical presentation of tuberculosis with a high frequency of extrapulmonary, disseminated forms of tuberculosis in transplant recipients. Higher age, Diabetes Mellitus, and use of immunosuppressive agents increase the risk for post-renal transplantation tuberculosis.

Further, treatment of tuberculosis is being complicated with the development of multi-drug resistance. Interactions of the anti tubercular treatment with immunosuppressive agents should be considered. Drug resistance and atypical mycobacterial infections are major problems in tuberculosis management and should be suspected in non-responding patients.

Patients with chronic kidney disease undergoing renal transplantation should be assessed both pre- and post-transplantation for the risk of tuberculosis.

Conflicts of interest

The authors have none to declare.

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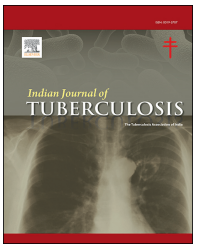

Original article

Predictors of Tuberculosis outcomes amongst drug sensitive patients in Boteti sub-district, Botswana, 2015–2017

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ARTICLE INFO

Article history:
Received 7 March 2019
Accepted 29 April 2019
Available online 7 May 2019

Keywords:
Tuberculosis
Knowledge
Botswana
Cure
Treatment completed

ABSTRACT

Introduction: The. Boteti sub-district in Botswana has a high TB notification rate of 356 per 100 000 population in 2013, a Treatment completion rate of 55%, 13% cure rate, and 4% defaulter rate in 2014. The high TB notification and defaulter rates with lower cure and treatment success rates in this sub-district relative to the country, are indicative of certain determinants that may be hampering TB control. The aim of this study was to determine the factors associated drug sensitive TB treatment outcomes.

Methods: A retrospective cohort study was conducted amongst all the new-smear positive adult pulmonary TB patients who registered and/or completed the treatment period at the six selected health-care centres in Boteti sub-district, between 1 January 2015 and 31 January 2017. An interviewer-administered questionnaire in the patient's language of choice- Setswana or English was utilised for data collection. Adjusted risk ratios (ARR) and their respective 95% confidence intervals (95% CI) were used for expressing associations.

Results: Fifty-eight (56.9%) patients were successfully cured compared to 44 (43.1%) who successfully completed treatment. Patients that attended the clinics by foot (ARR 3.38) ($P < 0.05$), females (ARR: 1.25) and HIV negative patients (ARR: 1.20) were more likely to achieve TB cure. Patients that attended the facility with a vehicle were 2.12 ($P < 0.000$), a primary school and above education (ARR: 1.59), travelled less than 5 km (ARR: 1.05) and less than 38 years of age (ARR:1.02) were more likely to complete TB treatment.

Conclusion: A comprehensive health promotion approach based on the Ottawa charter principles to should be developed and implemented.

List of abbreviations: AIDS, Acquired Immune Deficiency Syndrome; ARR, Adjusted relative risk; CI, confidence intervals; HIV, Human Immune deficiency virus; IQR, Interquartile range; LMIC, Low- and middle-income countries; TB, Tuberculosis; WHO, World Health Organisation.

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https://doi.org/10.1016/j.ijtb.2019.04.014

1. Introduction

In 2017, there were an estimated 10 million (range: 9–11 million) new Tuberculosis (TB) cases equivalent to 133 new per 100 000 population globally. Fifty eight percent of new cases were amongst males, 32% in females and 10% in children.[1] Ninety three percent of the new TB cases were reported in four regions namely; the South East Asia region (44%), African region (24%), the Western Pacific Region (18%) and the Eastern Mediterranean (7%) Region (771 000).[1] India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%) accounted for two thirds of the incident cases of TB in 2017.[1]

Nine percent of all new TB cases globally occurred amongst pople living with HIV,[1] with the proportion of TB cases co-infected with HIV exceeding 50% in parts of Southern Africa.[1] Of the entire incident cases an estimated 558 000 (range, 483 000–639 000) cases were multidrug-resistant TB (MDR-TB). Three countries China, India and the Russian Federation had the highest numbers of MDR-TB.

Botswana has a high burden of TB with the World Health Organisation estimating that the incidence of TB in Botswana was 300 per 100 000 population in 2017,[1] a decline from the 326 per 100 000 population in 2016.[2] The high HIV prevalence in Botswana perpetuates the TB epidemic. Boteti sub-district is no exception, with a TB notification rate of 356 per 100 000 population in 2013, with 50% of all the TB cases were co-infected with HIV. Treatment completion of rate was 55%, cure rate 13%, and 4% default from all types of TB treatment in Boteti sub-district in 2014.[3]

TB control in Botswana is the core mandate of the Botswana National TB and Leprosy Control Program.[3] TB services are decentralized through a network of more than 64 health facilities and 900 mobile stops. Coordination of TB Control activities are by district and hospital TB coordinators and implementation is through TB focal persons and community health workers.

Gene Xpert is the cornerstone method for TB diagnosis, with 52 service points across the country equivalent to one TB microscopy and gene expert service point per 39 678 population. Sputum smears at the end of the intensive and continuation phase are used to monitor treatment response and TB control efforts.

Despite joint efforts by the Botswana government and development partners to intervene in the control of TB, there is still limited awareness and utilization of TB services in general. The high TB notification and defaulter rates with lower cure and treatment success rates in this sub-district relative to the country, are indicative of certain determinants that may be hampering TB control. The aim of this study was to determine the factors associated drug sensitive TB treatment outcomes.

2. Materials and methods

2.1. Study design and participants

A retrospective cohort study was conducted at six health-care centres (Letlhakane clinic, Letlhakane primary hospital, Tawana clinic, Mopipi clinic, Rakops primary hospital and Rakops health post) in Boteti sub-district.

All the new-smear positive pulmonary TB patients 18 years and above who registered and/or completed the treatment period at the six selected health-care centres in Boteti sub-district, between 1 January 2015 and 31 January 2017 were included in the study.

2.2. Data collection

The first step in the data collection process was a review of the facility based TB registers to identify the number of eligible patients for inclusion in the study, as well as the patient's clinical data and treatment outcomes.

An interviewer-administered questionnaire in the patient's language of choice- Setswana or English was utilised for data collection. Trained research assistants administered the questionnaire to the patient's after obtaining consent from them. All the questionnaires were administered anonymously in order to reduce social desirability bias and improve the accuracy and reliability. The questionnaire consisted of two sections. Section one dealt with patient-related factors, socio-demographic characteristics (age, sex, educational background, occupation, smoking and alcohol history), distance and accessibility of facility, knowledge about the disease and treatment (such as name of the disease, causative agent, signs and symptoms, perceived mode of transmission, perceived duration of TB treatment, consequences of interrupted treatment). Section 2 covered attitude and practices regarding stigma and discrimination by relatives, health-care workers and others.

2.3. Data management and analysis

Two independent data capturers entered the data on Microsoft Excel. The principal investigator assessed the data for accuracy, missing information and duplication Data entry was concurrent with data collection in the field. Access to data was password-protected and made accessible to project staff only.

Statistical software package Stata (version 13, Stata Corp) was used for data analysis. Proportions were calculated for categorical values. Unadjusted relative risk ratio were calculated during bivariate analyses. The level considered significant was a probability (*P*) value of less than 0.05. The factors, which had risk ratios (*RR*) > 1, and the biologically plausible ones, despite having a *P* value of >0.1 were included in a multiple linear regression analysis. Adjusted risk ratios (ARR) and their respective 95% confidence intervals (95% CI) were used for expressing associations.

2.4. Analysis of knowledge scores

The questionnaire consisted of seven knowledge questions. The questions required a "yes", "no" or "do not know" answers. One point was allocated for correct answers and incorrect answers given a score of zero (0). The level of knowledge was ranked as above average knowledge and below average knowledge, depending on the number of correct answers each patient gave out of the total questions. A composite variable was then produced and categorized as ≥

50% (above average knowledge) and <50% (below average knowledge). Knowledge and attitude of the participants were evaluated through questions that required a "yes", "no" or "do not know".

2.5. Analysis of attitudes regarding stigma and discrimination

Patients responded to five stigma-related statements, contextualized in the local socio-economic perspective, to assess the level of stigma. Perceptions and experiences towards stigma were assessed through questions that required a "yes", "no" or "do not know". Proportions were calculated for each response based on a positive response.

2.6. Analysis of health service factors

Nine statements with a "yes", "no" answers were used to determine perceptions of clinical care provided by the health service. Proportions based on a positive or negative response were calculated.

2.7. Ethics statement

The protocol for the study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu Natal (BE 308/17) and the Health Research Unit of the Ministry of Health, Botswana (REF NO: HPDME-13/18/1 Vol XI 142). Written consent was sought from each study participant after prospective participants had been fully informed on how the study would be carried out and how the collected data would be handled to ensure confidentiality and privacy. No permanent record of the study patients' names and other information was made to assure confidentiality, and patients were asked to participate in the study voluntarily.

3. Results

3.1. Study population

One hundred sixty-eight pulmonary TB patients receiving TB treatment in the six selected facilities from 1 January 2015 to 31 January 2017 were eligible for inclusion in the study. Sixty-six participants were not reachable; therefore, only 102 participants were included in the analysis (Fig. 1).

3.2. Treatment outcomes

Sixty-five participants (63.7%) converted from sputum positive at the beginning of treatment to negative at 3 months, whilst 61 (59.8%) remain sputum converted at six months (end of continuation phase). Fifty-eight (56.9%) patients were successfully cured at the end of treatment, compared to 44 (43.1%) who successfully completed treatment (Table 1).

3.3. Socio-demographic profile of the participants

There was slightly more male participants in the study with a male to female ratio of 1.04:1. The mean age of the study population was 38 years (SD: 14.3) with a median age of 35 years (IQR: 31–43 years), signifying a positive skewed age distribution (Fig. 2). Patients successfully cured from TB were younger with a mean age of cured TB patients of 36 years (SD: 13.1), whilst those patients that completed TB treatment were older with a mean age of those who completed treatment of 39 years (SD: 15.6) and a median of 35 years.

Overall more than half of the respondents 52 (51%) were males, compared to 50 (49%) females, however fifty-three percent (n = 31/58) of the TB cured patients were and 56.8% (25/44) of successfully completed TB treatment were males. Over 50% of literate participants reporting a secondary education 56 (54.9%), and less than 6% tertiary education 6 (5.9%). More than 50% participants unemployed 57 (55.9%), compared to nine (8.8%) who were employed full-time.

Fifty-one participants (50%) reported to be smoking cigarettes, with a majority among them 34 (66.7%) reporting to be smoking 1–3 cigarettes a day on average; 12 (23.5%) and five (9.8%) reported between four and ten cigarettes a day respectively. Over 60% (n = 70) of the respondents were taking alcohol, with 52 (74.3%) among alcohol consumers reported to be drinking more than twice a week, 16 (22.9%) drinking once a week, and two (2.8%) three times a month. From amongst the TB cured patients more than half of participants 56% (32/58) reported smoking, with 67.4% (n = 39/58) consuming alcohol, with a larger proportion 31 (53.4%) drinking more than twice a week. Fifty percent of the TB cured patients were living with HIV, whilst 43.2% (19/48) of the TB treatment completed patients were living with HIV.

Forty-six (45.1%) participants travelled between 1 and 5 km, one patient (1%) travelled more than 5 km. Ninety-one (89.2%) of these participants accessed the health facility on foot, while a very small proportion of six (5.9%), four (3.9%), and one (1%) used private car, public transport, and lifts, respectively. More than half of the participants were HIV positive 53 (52%). None of the participants had diabetes (Table 2).

3.4. Overall knowledge scores of Tuberculosis

The mean knowledge score for all TB patients across the seven elements tested was 6.51 (SD: 0.38) with a median score of 6.58 (IQR: 6.3–6.73). The knowledge scores for TB cured patients was higher (mean = 6.22 (SD: 0.64); median of 6.02 (IQR: 5.76–6.67)) compared to patients with a status of TB treatment completed (mean = 6.06 (SD: 0.602); median of 5.88 (IQR: 5.67–6.46)).

Almost all respondents 99 (97.1%) had above average knowledge (>50%) of causes of TB, signs and symptoms 97 (95.1%), transmission 96 (94.1%), prevention 95 (93.1%), TB outcome 88 (86.3%), duration of treatment 100 (98%), consequences of stopping/missing treatment 91 (89.2%), and good sputum disposal 96 (94.1%) (Table 5). The proportion of patients responding correctly across the various categories of knowledge questions were lower in the TB treatment completed group versus TB cured patients (Table 3).

3.5. Attitudes towards stigma and discrimination

One quarter 26 (25.5%) of respondents would stay away from their neighbours and friends when infected with TB for the

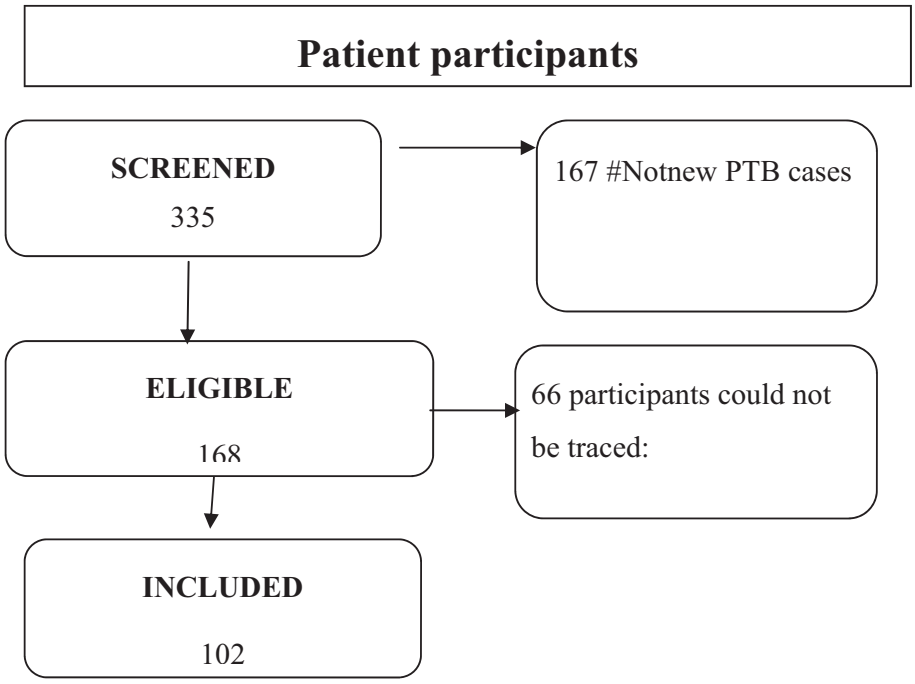

Fig. 1 – Study population.

first time. Approximately 10% (n = 10) held the belief that people would be isolated when they got TB. Twenty-two percent (n = 21) of respondents said that they were not viewed the same within their family or community after getting TB, with 12% (n = 12) of the respondents were of the opinion that they will not be treated as before by the neighbours (Table 4).

Table 1 – Frequency table showing TB treatment outcomes.

Variable	Frequency
Sputum conversion at 2 months	66 (64.7%)
Remained Sputum converted at 6 months	61 (59.8%)
Successfully cured	58 (56.9%)
Successfully completed TB treatment	44 (43.1%)

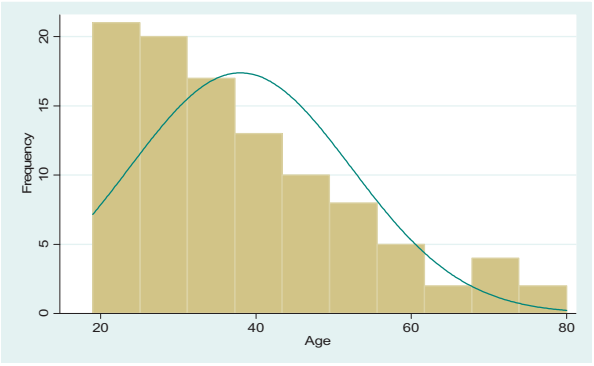

Fig. 2 – Histogram depicting Age distribution of TB patients in Boteti selected clinics.

3.6. *Perceptions towards treatment by healthcare practitioners*

The majority of the patients were treated well 96 (94.1%), given special care 99 (97.1%), felt listened to 89 (87.3%), given a chance to have their say and ask questions 96 (94.1%), treated with respect 91 (89.2%), felt they could trust workforce 94 (92.2%), and were given privacy 88 (86.3%). A very small percentage of patients felt isolated 13 (12.7%), mistreated 6 (5.9%), and discriminated against 2 (2%) (Table 5).

3.7. *Factors associated with TB cure*

Bivariate analysis indicated that patients that attended the clinics by foot were 3.38 ($P < 0.05$), more likely to achieve TB cure. Although the relative risk ratio increased to 3.52 after multivariate analysis for patients that attended the clinics by foot and TB cure the association was not significant. Females (ARR: 1.25) and HIV negative patients (ARR: 1.20) showed a 25% and 20% increased likelihood of TB cure than males and HIV positive patients but this was not statistically significant (Table 6).

3.8. *Factors associated with TB treatment completion*

Patients that attended the facility with a vehicle were 2.12 ($P < 0.000$), more likely to complete.

TB treatment. In addition patients that travelled less than 5 km (ARR:1.05) and patients less than 38 years of age (ARR:1.02) were 5% and 2% more likely than patients that travelled more than 5 km and those that were more than 38 years of age to complete TB treatment. Patients with education (primary school and above) were 59% (ARR: 1.59) more

Table 2 – Frequency table of socio-demographic profile of participants receiving treatment in Boteti selected health facilities.

Factor	Variable	Category	Study population	Treatment cure	Treatment completed
Socio demographic	Age	Mean	38(SD:14.3)	36.75(SD:13.1)	39.9(SD:15.6)
	Sex	Male	52 (51.0%)	27 (46.5%)	25 (56.82%)
		Female	50 (49%)	31 (53.45)	19 (43.18%)
	Level of education	None	23 (22.5%)	17 (29.31%)	6 (13.64%)
		Primary	17 (16.7%)	9 (12.52%)	6 (13.64)
		Secondary	56 (54.9%)	29 (50.0%)	29 (65.91%)
		Tertiary	6 (5.9%)	3 (5.17%)	3 (6.82%)
	Occupational status	Unemployed	57 (55.9%)	36 (62.07%)	21 (47.73%)
		Full-time employment	9 (8.8%)	4 (6.90%)	5 (11.36%)
		Part time employment	19 (18.6%)	8 (13.79%)	11 (25.0%)
		Business	5 (4.9%)	3 (5.17%)	2 (4.55%)
		Farming	12 (11.8%)	7 (12.06%)	5 (11.36%)
	Smoking	Non-smoking	51 (50%)	26 (44.83%)	25 (56.82%)
		1–3 cigarettes daily	34 (66.7%)	24 (41.38%)	10 (22.73%)
		4–10 cigarettes daily	12 (11.7%)	7 (12.07%)	5 (11.36%)
		>11 cigarettes daily	5 (9.8%)	1 (1.72%)	4 (9.09%)
	Alcohol	Not taking alcohol	32 (31.4%)	19 (32.6%)	13 (29.55%)
		Once a week	16 (22.9%)	6 (10.34%)	10 (22.73%)
		More than twice a week	52 (74.3%)	31 (53.45%)	21 (47.73%)
		3 times a month	2 (2.8%)	2 (3.45%)	0 (0%)
	Mode of transport	Foot	91 (89.2%)	56 (96.55%)	35 (79.55%)
		Bus/taxi	4 (3.9%)	0 (0%)	4 (9.09%)
		Private car	6 (5.9%)	2 (3.45%)	4 (9.09%)
		Hiking/lifts	1 (1%)	0 (0%)	1 (2.27%)
Clinical	HIV	Positive	54 (52.9%)	29 (50%)	19 (43.18%)
		Negative	48 (47.1%)	29 (50%)	25 (56.82%)
	Diabetes	Present	0 (0%)	0 (0%)	0 (0%)
Health system	Health facility distance	<2 km	46 (45.1%)	26 (44.83%)	19 (43.18%)
		2–5 km	34 (33.3%)	19 (32.76%)	16 (36.36%)
		>5 km	1 (1.0%)	1 (1.72%)	0 (0%)
		Don't know	21 (20.6%)	12 (20.69%)	9 (20.45%)

Table 3 – Frequency Distribution of TB knowledge scores.

Variables	All TB patients N (%)	TB Cured (N = 58)	TB Treatment Completed (N = 44)
Causes of TB	99 (97.1%)	53 (91.4%)	40 (90%)
Signs and symptoms	97 (95.1%)	48 (82%)	33 (75%)
Transmission	96 (94.1%)	55 (94%)	40 (90%)
Prevention	95 (93.1%)	50 (86%)	37 (84%)
Recovery	88 (86.3%)	48 (82%)	38 (86%)
Duration of new non-drug resistant TB case	100 (98%)	56 (97%)	41 (93%)
Consequences of missing/stopping treatment	91 (89.2%)	46 (80%)	35 (80%)
Sputum disposal after cough	96 (94.1%)	56 (97%)	41 (93%)

likely to complete TB treatment than those without any form of schooling although this was not significant (Table 6).

4. Discussion

Results of the present study indicate that 56.9% (n = 58) and 43.1% (n = 44) of all bacteriologically confirmed drug sensitive PTB new cases had successful treatment outcomes (cure and completion respectively). This result is higher than the results nationally in Botswana for new smear-positive TB treatment outcomes (42% cured and 43% having completed their treatment). However, the TB cure rate in the current study is much lower than the target of 90% set by the World Health Organisation.[4] The TB cure rate in the current study is higher than the pooled estimate of 33.9% (CI: 26.3–41.5) as reported from a systematic review of studies conducted between 2003 and 2016 from all (seven) regions in Ethiopia[5] but much lower than the 80% TB cure rate reported in Brazil.[6]

The treatment completion rates in our current study was lower than 66% (CI: 58.5–73.7%) reported from the pool estimates in the above Ethiopian study[5] and the TB cure rate in the Boeiti sub-district in Botswana is much lower than the 61.6% reported from the seven public TB management units (TB centres) in Mogadishu.[7]

The mean age of cured TB patients was 36 years (SD: 13.1), with a median of 34 years. The predominance of younger age group is consistent with other studies.[7,8] Patients less than 38 years were less likely to be cured, and more likely to complete treatment (ARR: 1.02) although no significant association was

Table 4 – Frequency table showing attitudes towards stigma among TB patients.

Item	Affirmative response (%)		
	All TB patients (N = 102)	TB Cured (N = 58)	TB treatment completed (N = 44)
I preferred to stay away from my neighbours and friends, when I had TB	26 (25.5%)	8 (13.8%)	18 (40.9%)
People would become lonely when they got TB.	10 (9.8%)	9 (15.5)	1 (2.3)
Being a TB patient, you are treated normal in your family as before.	81 (79.4%)	46 (79.3%)	35 (79.6%)
Being a TB patient, you are treated normal from your neighbours, as before.	90 (88.2%)	51 (87.9%)	39 (88.6%)

Table 5 – Frequency table showing perceptions of treatment by healthcare workers.

Variable	All TB patients (N = 102)	TB Cured (N = 58)	TB treatment completed (N = 44)
I was mistreated	6 (5.9%)	1 (1.7%)	5 (11.4%)
I was discriminated against	2 (2%)	0 (0%)	2 (4.5%)
I was isolated	13 (12.7%)	9 (15.5%)	2 (4.5%)
I was given special care	99 (97.1%)	56 (96.6%)	43 (97.7%)
I felt listened to	89 (87.3%)	53 (91.4%)	36 (81.8%)
I was given a chance to state my problems and ask questions	96 (94.1%)	58 (100%)	38 (86.4%)
I was treated with respect	91 (89.2%)	49 (84.5%)	42 (95.5%)
I felt I could trust the health workers	94 (92.2%)	55 (94.8%)	39 (88.6%)
I had privacy during consultation and counselling	88 (86.3%)	51 (87.9%)	37 (84.1%)

Table 6 – Bivariate and multivariate analysis of factors associated with TB cure an TB treatment completion.

	TB cured				TB treatment completed			
	Bivariate	*P* value	Multivariate	*P* value	Bivariate	*P* value	Multivariate	*P* value
Age (<38 years)	0.95 (0.68–1.33)	0.78			1.07 (0.67–1.69)	0.30	1.02 (1.02–1.02)	0.000
Gender (Female)	1.19 (0.85–1.68)	0.30	1.25 (0.9–1.73)	0.181	0.79 (0.50–1.24)	0.30		
Education	0.70 (0.51–0.97)	0.06			1.95 (0.94–4.04)	0.04	1.59 (0.76–3.35)	0.217
Employment (employed)	1.31 (0.62–2.77)	0.43	0.03 (0.45–1.89)	0.84	0.76 (0.40–1.41)	0.43		
Non Smoker	0.81 (0.58–1.14)	0.23			1.32 (0.84–2.06)	0.23	1.41 (0.96–2.07)	0.09
No Alcohol consumption	1.07 (0.75–1.52)	0.73	0.89 (0.62–1.28)		0.92 (0.56–1.50)	0.73		
HIV negative	1.17 (0.84–1.64)	0.36	1.20 (0.86–1.67)	0.30	0.88 (0.56–1.38)	0.57		
Transport (foot)	3.38 (0.96–11.98)	0.006	3.52 (0.96–12.92)	0.06	0.48 (0.32–0.69)	0.006		
Transport (vehicle)	0.30 (0.84–1.05)	0.006			2.13 (1.45–3.11)	0.006	2.12 (1.57–2.88)	0.000
Distance (<5 km)	0.95 (0.64-.0.52)	0.89			1.07 (0.61–1.87)	0.36	1.05 (1.05–1.05)	0.000
Knowledge (>50%)	1.14 (0.43–3.09)	0.78	0.98 (0.47–2.05)	0.95	0.86 (0.31–2.34)	0.78		
Stigma	0.98 (0.69–1.41)	0.92			1.14 (0.69–1.88)	0.60	0.97 (0.097–0.97)	0.000

found. A health facility-based study between November 2012 and May 2013 in Dilla University Referral Hospital, Ethiopia demonstrated similar results, that patients less than 35 years of age were less likely to achieve TB cure when compared to older patients.[9] In contrast to these findings, a retrospective study of TB case records in Imo State, Nigeria, conducted between January 2009 and December 2012, found the highest success rate seen among those in the 31–45 years age category (83.2%).[10] It has been postulated the reduced cure rate in this age group is due to increased alcohol consumption and drug abuse that might result in interruption of their medication, as well as high prevalence of HIV in this age cohort affecting the immune system.[11]

Fifty-three percent (n = 31) of the TB cured patients were females and 56.8% (25/44) of successfully completed TB treatment were males. Numerous studies have reported a lower TB success rate in males.[12,13] In the current study, there was no significant association between gender and treatment outcomes. Although, not statistically significant female patients were 20% more likely than male patients to achieve TB cure. These findings are in keeping with a retrospective cohort analysis of routine data on adult 1668 TB patients treated between 2011 and 2012 in 2 large healthcare facilities in Nigeria. Male gender was associated with a higher failure to smear convert after 2 months (21·8% vs. 17·5%, $P = 0.06$) and 5 months (4.3% vs. 1.5%, $P = 0.02$) of treatment for smear-positive TB patients.[14]

Bivariate analysis indicated a patient with secondary school education and above had an almost two times (RR: 1.95) likelihood of treatment completion compared to patients with less than secondary school education. These findings are comparable with the findings reported from a retrospective cohort study in Kocaeli, north-west Turkey, that demonstrated patients with higher education had significantly higher prevalence of successful treatment outcome ($P < 0.05$ for all).[15] A prospective cohort study conducted in a rural South Africa (Bushbuckridge) reported comparable results-(62%) of the participants who reported secondary education completed treatment versus (18%) of participants with primary education.[16] It can be postulated that patients with higher level of education are more likely to be adherent to TB treatment and thereby completing the TB treatment. The paradoxical finding that a higher level of education is not associated with TB cure could partially be explained by the fact that health education, rather than level of education by itself, may be the factor that drives improved treatment outcomes.[17]

Non-smokers were more likely to complete TB treatment (ARR: 1.42) compared to smokers. These findings are in keeping with a retrospective cohort study conducted in Armenia, that displayed a strong correlation between smoking and unsuccessful TB treatment outcomes (OR: 1.6, 95% CI: 1.07–2.42, $P < 0.02$).[18] The adverse nature of TB outcomes due to smoking is due to the underlying damage in the baseline lung function, as well the disruption of immune cells such as macrophages, monocytes, CD4 lymphocytes.

HIV negative patients were 25% more likely to achieve TB cure than HIV positive patients, whilst HIV and TB co-infected patients were more likely to complete TB treatment. These findings are similar to a retrospective cohort study from Chandrigah in India that showed a TB cure rate (70%) was more among the HIV negative population as compared to the co-infected patients (21.6%). Rate of treatment completion was 63.6% among the HIV positive patients.[19] The emphasis on multidisciplinary care and adherence support to patients within the antiretroviral treatment program may play a role in contributing towards the compliance and treatment success among the HIV/TB co-infected group, particularly among those on ART.[20]

Patients that travelled less than 5 km were 5% more likely to complete treatment when compared to patients travelling more than 5 km. The physical closeness to or distance from a health-care facility is one of the factors that affects the utilization of available health services and treatment outcome. Short distances to the clinic encouraged them to attend regular treatment follow-up thereby improving treatment outcomes.[21] This was further emphasised by a cohort study in Nigeria[22] and Ethiopia[23] that indicated a distance greater than 10 km from a clinic was associated with treatment failure.

Patients that accessed the facility on foot were 3.52 times more likely to achieve TB cure, whilst patients that accessed facilities with a vehicle were 2.12 times more likely to complete treatment compared to patients accessing facility on foot. The increased likelihood of TB cure amongst patients that walked to the facility is an indication of a younger age patient that lives within close vicinity of the clinic. The use of vehicles to reach treatment facilities in our study concurs with a quantitative assessment study of 100 participants in Ribeirão Preto, São Paulo State, between 2006 and 2007, which found that treatment success was associated with use of mobile transport to reach TB control facilities ($P < 0.0072$).[24] This is an indication of the easy access to the clinics. However, transport costs are independent risk factors for non-adherence to TB therapy and outcomes as they both hinder access to health facilities.

4.1. *Study limitations*

Although due diligence was maintained to ensure the integrity of the study, the findings of the study are influenced by a number of limitations. Being a retrospective study, validity of the information obtained by subjects' recall cannot be established with certainty. Our sample size was relatively small, and consequently the ability to detect statistical significance between examined associations was limited. Having used a researcher administered questionnaire, validity of the results may be affected by social desirability bias. Some patients were not reached due to relocation, shifts and long working hours in mines with some reluctant to participate despite being assured of confidentiality.

5. Conclusion and recommendations

The results of this study indicated a substantial proportion of successful TB treatment outcome (cure 56.9% and completion 43.1%) in Boteti sub-district. Female patients, patients that accessed the facility on foot and HIV negative patients were more likely to be cured, whilst patients that used a vehicle to access the facility, travelled a distance of less than 5 km, was HIV negative was more likely to complete TB treatment. A comprehensive health promotion programme using targeted messages through appropriate and accessible magazines, billboards, radio advertisements, and public gatherings should be used to emphasise the importance of early diagnosis and adherence to treatment. Re-orientation of the health services using an integrated clinical model of care for HIV and TB will improve adherence and potential outcomes. The services should be extended through a community-based model for treatment to reduce the barriers to transport and/or geography, thereby enhancing treatment success rates.

Conflicts of interest

The authors have none to declare.

Authors' contributions

AS: Data collection, analysis, first draft of manuscript. OM: Analysis, drafting of second and final versions of manuscript. All authors read and approved the final manuscript.

Acknowledgement

The authors will like to acknowledge the participants of the study for providing access to their homes in order to gather the information.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.04.014.

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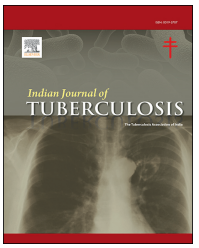

Original article

Treatment outcome of tuberculosis treatment regimens in Kandahar, Afghanistan

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ARTICLE INFO

Article history:
Received 5 September 2018
Accepted 18 October 2018
Available online 7 November 2018

Keywords:
TB
Treatment outcome
Kandahar
Afghanistan
Pulmonary

ABSTRACT

Background: Tuberculosis (TB) is a chronic disease that mostly affects low-income countries. TB is transmitted through droplet aerosolization from a person with active pulmonary TB. Afghanistan is one of the 22 high TB burden countries where 39,445 people develop this disease and 7840 people die each year. Treatment outcome is one of the best measurements that explain how the current regimen works.

Material and methods: This was a retrospective cohort study, conducted in Kandahar Province, to find out the treatment outcome of anti-TB drugs regimens in TB patients. Data of pulmonary and extra-pulmonary TB patients, who fulfilled the eligible criteria of the study and were treated from 2005 to 2015, was retrieved from their medical record forms.

Results: Among 1000 TB patients, 599 (59.9%) were females and 401 (40.1%) males; most of the patients (678/1000 [67.8%]) were from Kandahar city while 322/1000 (32.2%) were from the other districts of Kandahar. Mean age of the patients were 36.1 years with SD of 19.3 years. Main signs and symptoms of fever, cough, and weight loss were present in 949/1000 (94.9%), 880/1000 (88%), and 544/1000 (54.4%) of the patients, respectively. On first visit 459/1000 (45.9%) patients were sputum AFB (acid fast bacilli) positive. Majority (247/459 [53.8%]) of these patients were AFB 2+. After 2 months of intensive anti-TB treatment, 9/459 (1.9%) patients were still AFB positive (1+). Treatment outcome of these 1000 patients showed that 479 (47.9%) completed the treatment, 298 (29.8%) were cured, 35 (3.5%) failed the anti-TB treatment, while 5 (0.5%) patients died.

Conclusion: This clearly shows that TB is still one of the major threats to the people of Kandahar Province. There are cases of TB who do not respond to the first line regimens of anti-TB drugs advised by WHO and Afghan Ministry of Public Health (MoPH).

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https://doi.org/10.1016/j.ijtb.2018.10.008

1. Introduction

Tuberculosis is one of the world's deadliest diseases. During the last five years, TB is the leading cause of death from a single infectious agent, ranking above HIV/AIDS.[1] In 2016, worldwide the incidence of TB was 10.4 million people with the mortality of 1.7 million people. More than 95% of these deaths occurred in low- and middle-income countries.[1] Globally, this fatal disease has an enormous economic impact on many countries.[2] *Mycobacterium tuberculosis*, the causative agent of TB, infects one-fourth of the world's population.[3]

Although the incidence of tuberculosis declined greatly during the twentieth century in the industrially developed nations, these nations are now experiencing an upsurge of this disease. Multi-drug resistant tuberculosis (MDRTB) has become a major problem in several regions throughout the world and in some countries extensively resistant forms of the disease extensively drug-resistant tuberculosis (XDR-TB) have emerged and raise the very serious threat of untreatable disease.[4]

Due to the presence of several decades conflicts in the country, limited or even no studies have been performed in this field. According to 2014 tuberculosis report of World Health Organization (WHO), Afghanistan is included in the category of the world 22 high TB-burden countries. With a population of nearly 31 million, Afghanistan has about 39,445 new cases each year and an overall estimated TB prevalence of nearly 69,000 cases. In 2013, the estimated rate (per 100,000 population) of TB prevalence, incidence, and mortality were 340 (178–554), 189 (167–212), and 42 (27–53), respectively.[5]

Between 2000 and 2014, the estimates of TB incidence in Afghanistan have remained nearly stable as nearly 189 per 100,000 population. On the other hand, case detection rate has gradually increased from 19% (18–21%) in 2000 to 53% (47–60%) in 2014.[6]

WHO targeted treatment success rate was 85% for the year 2015. Some countries have already achieved this target but some are still behind.

There are studies done to identify the treatment outcome of TB treatment regimen and the associated factors that can influence the treatment outcomes in different countries. Among associated factors that were highlighted in the literature were old age,[7–12] male sex,[11–13] co-morbid diseases such as diabetes and HIV,[11,14] advanced chest radiographic findings,[11,13] history of previous TB treatment,[8,15,16] unemployment,[8,15] multi-drug resistance status,[9] alcoholism[15,17] and as well as drug abuse.[15]

WHO has estimated the treatment success rate around 86% in Afghanistan but there are not enough studies in the country to strongly support its reliability.[5]

Afghanistan is one of the 22 high TB burden countries where 39,445 people develop this disease and 7840 people die each year. Treatment outcome is one of the best measurements that explain how the current regimen works. Many studies about treatment outcome of TB in different period of time and several places out of Afghanistan have been carried out but due to the long-lasting conflict in Afghanistan limited studies in this field have been performed and no published study has been done in Kandahar, yet.[18] Through this study, we will be able to find the treatment outcome of TB treatment regimen in Kandahar Province.

2. Materials and methods

2.1. Study design

This was a retrospective cohort study. Data of patients, who fulfilled the eligible criteria of the study and were treated during the 11 years period (2005–2015), was retrieved from their medical record forms.

Medical record forms were screened in a backward order, starting from 2015 to 2005 and relevant information was collected with data collection sheet. Data collection sheets were prepared to pick up all essential data related to our study, including; demographics, symptoms, laboratory investigation plus other essential information.

2.2. Study population

The study population was comprised of all forms of TB patients who were treated in provincial hospital and TB centers of Kandahar Province. We screened medical record forms of tuberculosis patients who were treated during 2005–2015. As per the inclusion and exclusion criteria, 1000 patients were recorded.

2.3. Research question

What is the treatment outcome of current tuberculosis treatment regimen in Kandahar?

2.4. Primary objective

- To achieve the treatment outcome of anti-TB treatment regimen in patients.

2.5. Inclusion criteria

- All age groups
- Pulmonary and extrapulmonary TB patients treated with standard short course regimen (2Isoniazid, Rifampicin, Pyrazinamide, Ethambutol (HRZE)/4HR) or receiving the 8-month retreatment regimen (2HRZES/1HRZE/5Isoniazid, Rifampicin, Ethambutol (HRE))

2.6. Exclusion criteria

- Pregnant women
- Patients who changed regimens from 2HRZE/4HR or 2HRZES/1HRZE/5HRE due to any problems such as adverse events or drug resistance.

2.7. Sample size calculations

Sample size was determined using the formula: $n = Z2pq/d^2$. Our sample size was 1000 patients.

2.8. Ethical considerations

Ethical approval was taken from Kandahar University Ethics Committee.

2.9. Data analysis

Data was analyzed with SPSS (version 22).

2.10. Operational definitions

1. **Sputum Smear Positive:** Patients were considered smear positive, if at least two sputum specimens were positive for AFB (acid fast bacilli) by microscopy, one sputum specimen positive for AFB with the presence of chest radiographic abnormalities suggestive of pulmonary tuberculosis (PTB) or at least one sputum smear positive with a culture positive conformity.[17]
2. **Sputum Smear Negative:** A case of pulmonary TB is considered to be smear-negative if at least two sputum specimens at the start of treatment are negative but culture positive for AFB. Or meet the following diagnostic criteria:
   - Decision by a clinician to treat with a full course of anti-TB therapy
   - Radiographic abnormalities consistent with active pulmonary TB
3. New and previously treated patients with their treatment regimens:
   - **New patients:** Who have never had treatment for TB, or have taken anti-TB drugs for less than 1 month. A total of six-month treatment (category-1) is given in two phases; intensive phase of two months with regimen consisting of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) {2HRZE} and the continuation phase of four months comprising isoniazid and rifampicin (4HR).[17]
   - **Previously treated patients:** Default, failure or relapse cases with current TB disease are defined previously treated patients. They are taking the eight-month standard treatment regimen (category-2) containing HRZE for two months; HRZE for the third month and HRE for the continuous 5-month phase {2HRZES/1HRZE/5HRE}.[17]
4. Treatment outcome:
   - **Cure:** A patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
   - **Treatment completed:** A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion.
   - **Treatment failure:** A patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbor a multidrug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or -positive.
   - **Died:** A patient who dies for any reason during the course of treatment.
   - **Default:** A patient whose treatment was interrupted for 2 consecutive months or more.
   - **Transfer out:** A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.
   - **Treatment success:** The sum of cured and completed treatment.[17]

3. Results

This was a retrospective study conducted in Kandahar. Data were collected from the health clinics and district hospitals of all the 17 districts of Kandahar Province. For this study, medical records of 1000 TB patients were observed according to the inclusion and exclusion criteria.

3.1. Baseline characteristics

Among 1000 TB patients, 599 (59.9%) were females while 401 (40.1%) were males. The mean age was 36.1 years, with SD of 19.3 years (range 1–100 years). Majority of the patients (678 [67.8%]) were from Kandahar city, while 322 (32.2%) were from other districts of Kandahar province as well as surrounding provinces (Table 1).

3.2. Signs and symptoms

Percentage of each symptom based on available data was recorded. Among these patients, 880/1000 (88%) of the patients were complaining from cough while 103/1000 (10.3%) patients were not coughing. Fever was present in 949/1000 (94.9%) patients, weight loss in 544/1000 (54.4%), chest pain in 101/1000 (10.1%), 37/1000 (3.7%), while dyspnea in 108/1000 (10.8%) of the TB patients (Table 2).

3.3. Diagnostic findings

Among the TB patients, 984/1000 (98.4%) were new cases while 16/1000 (1.6%) were retreatment cases. Majority (670/1000

Table 1 – Distribution of the patients.

Address	Frequency, n	Percent, %
Kandahar City	678	67.8
Arghistan District	3	0.3
Daman District	8	0.8
Dand District	36	3.6
Ghorak District	1	0.1
Khak Rez District	23	2.3
Maiwand District	6	0.6
Mianashin District	4	0.4
Nesh District	4	0.4
Panjwai District	93	9.3
Shah Wali Kot District	47	4.7
Shorawak District	1	0.1
Spin Boldak District	4	0.4
Takhta Pul District	1	0.1
Zarai District	14	1.4
Surrounding Provinces	33	3.3
Total	1000	100

Table 2 – Main signs and symptoms present in TB patients.

Symptom/sign	Number (/1000)	Percentage, %
Fever	949	94.9
Cough	880	88.0
Weight loss	544	54.4
Chest pain	101	10.1
Dyspnea	108	10.8

[67%]) of the patients were having pulmonary tuberculosis while 330/1000 (33%) of the patients were diagnosed as extrapulmonary tuberculosis. Contact with a TB patient was present in only 117/1000 (11.7%) patients, with 332/1000 (33.2%) patients not having any previous history of contact with TB patients.

On first visit, 459/1000 (45.9%) of the patients were sputum AFB (acid fast bacilli) positive. Majority (247/459 [53.8%]) of these patients were AFB 2+. After 2 months of intensive anti-TB treatment, 9/459 (1.9%) patients were still AFB positive (1+) (Table 3).

3.4. *Treatment regimens*

For all the patients, 6 months anti-TB drug regimens were used. For the first 2 months, 4 drugs were used, i.e., Isoniazid (INH), rifampicin, ethambutol, and pyrazinamide. For the last 4 months, 2 anti-TB drugs were used, i.e., INH and rifampicin.

3.5. *Treatment outcome*

Treatment outcome of all the TB patients are shown in Table 4. Eighty-seven patients in the study defaulted. Their main age was 36.1 years, with SD of 18.7 years (range 7–87) (Table 5).

In this study, 670/1000 (67%) patients were diagnosed as having pulmonary TB while 330/1000 (33%) were having extrapulmonary TB. The mean age of the pulmonary TB patients was 37 years, with SD of 19.3 (range 1–100) (Table 6).

4. Discussion

Worldwide, TB is more common among men than women.[19–21] But in our study, 599/1000 (59.9%) of the TB patients were females while 401/1000 (40.1%) were males. Among our neighbor countries, exceptions to the global pattern of male preponderance of TB are found in Iran and Pakistan. In Iran, the rate is slightly higher in females than in males.[22,23] In Pakistan, the relation between sex and TB rates varies between provinces. In Punjab and Sindh provinces, females account for less than half of the reported TB cases, but in Khyber-Pashtunkhwa and Balochistan provinces the percentage of females is about 60%.[23,24] The two later provinces have common border with Afghanistan as well as have the people of similar ethnicity. The main causes of preponderance of TB case in female in Afghanistan have not been established. However cultural and religious issues may play a role. Due to cultural restrictions in most of the areas in the country, female cannot work outside home. Prolong TB contacts have been reported increasing the spread of the TB bacilli. It has been reported that TB bacilli are indoor infections and the chance of transmission in closed areas is quite common.[24,4]

Treatment outcomes were assessed based on WHO guidelines.[17] In this study, treatment success rate was 77.7% (cured were 29.80% while treatment completed were 47.9%). Our findings are under the figure of WHO report for

Table 3 – Status of sputum AFB at first visit.

AFB status at 1st visit	Frequency, n	Percent, %
AFB 1+	98	21.4
AFB 2+	247	53.8
AFB 3+	114	24.8
TOTAL	459	100

Table 4 – Treatment outcomes of the 1000 TB patients.

Treatment outcome	Frequency, n	Percent, %
Treatment completed	479	47.9
Cured	298	29.8
Transferred	96	9.6
Failed	35	3.5
Defaulted	87	8.7
Dead	5	0.5
Total	1000	100

Table 5 – Data of only defaulted cases of TB.

Variable	Frequency, n	Percent, %
Age (n = 87)		
<50 years	67	77.0
≥50years	20	23.0
Gender (n = 87)		
Male	39	44.8
Female	48	55.2
Site of disease (n = 87)		
Pulmonary	52	59.8
Extra-pulmonary	35	40.2
History of contact (n = 54)		
Yes	19	35.2
No	35	64.8
Fever (n = 76)		
Present	73	96.1
Absent	3	3.9
Cough (n = 76)		
Present	64	84.2
Absent	12	15.8
Weight loss (n = 87)		
Present	48	55.2
Absent	39	44.8
AFB status at first visit (n = 34)		
1+	12	35.3
2+	17	50.0
3+	5	14.7
Sputum smear at first visit (n = 72)		
Positive	34	47.2
Negative	38	52.8
Sputum smear after 2 months of intensive treatment (n = 23)		
Positive	0	0
Negative	23	100

Table 6 – Data of only pulmonary TB patients.

Variable	Frequency, n	Percent, %
Age (n = 670)		
<50 years	456	68.1
≥50 years	214	31.9
Gender (n = 670)		
Male	281	41.9
Female	389	58.1
History of contact (n = 269)		
Yes	86	32.0
No	183	68.0
Fever (n = 666)		
Present	656	98.5
Absent	10	1.5
Cough (n = 667)		
Present	653	97.9
Absent	14	2.1
Weight loss (n = 670)		
Present	388	57.9
Absent	282	42.1
AFB status at first visit (n = 448)		
1+	97	21.7
2+	237	52.9
3+	114	25.4
Sputum smear at first visit (n = 640)		
Positive	448	70.0
Negative	192	30.0
Sputum smear after 2 months of intensive anti-TB treatment (n = 372)		
Positive	10	2.7
Negative	362	97.3
Treatment outcome (n = 559)		
Success	522	93.4
Failure	37	6.6

Afghanistan indicating the success rate of TB treatment regimen around 86%[5] and also less than the figures reported from neighboring countries.[5] The main cause could be the persistent insecurity, lack of health information, illiteracy, and economic problems in this region. To find out the main reasons behind the low cure rate and treatment success, further studies should be conducted in different parts of Afghanistan.

Table 7 explains the outcome of tuberculosis treatment regimens in different countries with different settings.

Prevalence of pulmonary TB in the setting of lower HIV prevalence is around 60–70% while the prevalence of extra-pulmonary TB is high in HIV high prevalence countries (40–45%).[27] As the prevalence of HIV is lower in Afghanistan particularly in Kandahar Province, hence we found that majority (670/1000 [67%]) of the patients were having pulmonary tuberculosis while 330/1000 (33%) of the patients were diagnosed as extra-pulmonary tuberculosis. A recent study which was conducted in Bahawalpur, Pakistan by Atif Muhammad et al. is quite similar to our study found that 71.2% of the study populations were having pulmonary tuberculosis.[28] This figure is in correspondence to our study.

In this study around 10% of the patients were transferred out to other health facilities. Transferring of the patients from one health center to other in the same or different districts or even provinces is not a favorable outcome. As the literacy and education level of the people in our country is not sufficient, they may not attend a newly introduced health facility for follow up. The achieved figure from our study is quite similar to other studies conducted in People's Democratic Republic of Laos,[29] Malawi[30] and Morocco[31] with reported rates of 16.4%, 13%, and 8.4%, respectively.

In conclusion, the treatment success rate among PTB patients in this study were lower than the expected success target of 85%. Similarly, treatment success rates in new smear positive PTB cases were also less than targets set by the WHO.[5] A large proportion of patients were lost to follow-up (defaulted) during treatment, which causes serious concern and warrants urgent action.

Table 7 – Outcome of TB treatment regimens in different countries with different settings.

Study	Population	Outcome	
		Success	Not success
Berhe et al., 2012[25,8] (Northern Ethiopia)	• 407 • Sputum smear positive PTB patients • Rx. Regimen: 2HRZE/4HR	89.2% • Cure 85.5% • Rx. complete 4.4%	10.8% • Failure 3.7% • Death 3.9% • Default 3.2% Transfer out 1.5%
Ige and Oladokun, 2011[26] (Ibadan, Nigeria)	• 857 • New sputum smear positive PTB patients • Rx. Regimen: 2HRZE/4HR	74.4% • Cure 60.4% • Rx. complete 14%	• Failure 2.6% • Death 5.6% • Default 2.1% • Transfer out 15.3%
Joseph et al., 2011[19] (South India)	• 286 • Sputum smear positive PTB • Rx. Regimen: 2HRZE/4HR and 2HRZES/ 1HRZE/5HRE	• New PTB 77.4% • Retreatment PTB 47.3%	• New smear positive PTB • Failure 15.1% • Default 7.5% • Retreatment smear positive PTB • Failure 32.4% • Default 20.3%
This study, (Kandahar, Afghanistan)	• 1000 • All types of tuberculosis patients • Rx. regimen 2HRZE/4HR and 2HRZES/1HRZE/5HRE	78% • Cure 30% • Rx. Complete 48%	• Failure 4% • Death 1% • Default 9% • Transfer out 10%

Rx. = treatment, PTB = pulmonary tuberculosis.

5. Conclusion and recommendations

TB is prevalent in Kandahar Province. This devastating disease is still one of the major threats to these people and a major economic burden for Afghan MoPH. Effective tracing methods for patients lost to follow-up should be developed and implemented to minimize treatment interruptions. Moreover, patients with an increased risk of having unsuccessful treatment outcomes should be provided with enhanced supervision and treatment monitoring to improve outcomes. There were the cases of TB who did not respond to the first line regimens of anti-TB drugs advised by WHO and Afghan MoPH. Further studies are needed to find out the main reasons behind the low cure rate and treatment success.

Conflicts of interest

All authors have none to declare.

Acknowledgments

We present our highest and sincere thanks to the authorities of Ministry of Higher Education of Afghanistan and Kandahar University for their kind support. We are thankful of World Bank for providing the fund for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2018.10.008.

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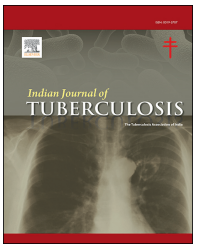

Original Article

Quantitative estimation of isoniazid content in the commercially available and government-supplied formulations

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ARTICLE INFO

Article history:
Received 25 June 2018
Accepted 18 October 2018
Available online 2 November 2018

Keywords:
Bioequivalence
Isoniazid
Tuberculosis
Spectrophotometer

ABSTRACT

Background: Multi-drug resistant tuberculosis is on the rise, resulting in treatment failure. One potential reason for drug resistance is the substandard quality of manufactured antituberculous drugs. This study aims at finding out the difference in the quantity of isoniazid between government-supplied tablets and commercially available tablets.

Method: Tablets from the single most commonly used brand of isoniazid manufactured by a pharmaceutical company and from RNTCP DOTS providing centre were obtained for the estimation of concentration using a spectrophotometer. The results were analysed using Un-paired Student's t-test.

Results: Of the 98 isoniazid tablets from each arm studied, none had the strength that deviated from the WHO limit of 90–110%, i.e. 270–330 mg. The mean strength ±SD of the commercial preparation of isoniazid tablets was found to be 295.16 ± 12.14. The mean strength ± SD of DOTS isoniazid tablets was found to be 298.69 ± 9.55. The difference observed in the strengths of isoniazid tablets between DOTS and commercial preparation was statistically insignificant ($p = 0.1704$).

Conclusion: This method to estimate the strength of isoniazid tablets is inexpensive, relatively easy, and considerably accurate to perform, and hence can be employed in primary or secondary care centres to ensure the standard strengths of tablets dispensed from such centres.

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https://doi.org/10.1016/j.ijtb.2018.10.002

1. Introduction

Isoniazid has always been the backbone of anti-tubercular drug regimens.[1] INH drug is activated by the bacterial enzyme catalase-peroxidase, and binds to InhA, an enoyl-acyl carrier protein reductase thereby blocking fatty (mycolic) acid synthesis in the TB bacterial cell wall.[2] Development of resistance against isoniazid is linked with poorer treatment outcomes, increased relapse and death.[3] Poor quality of the commercially available medicines is a common problem in the developing world.[4] Substandard medication can contain the wrong quantity of the stated drug as per the label, contaminants, or degradation products which can be harmful or can yield poor clinical outcomes.[5] Substandard treatment of an individual suffering from TB predisposes towards the development of multi-drug resistant strains.[6] In turn, substandard treatment of MDR-TB predisposes toward the development of XDR-TB.

2. Materials

Permission to carry out the study as per protocol was obtained from the Institution Review Board and Ethics Committee of Christian Medical College, Vellore, India (IRB minute number 10,577 dated 08.03.2017), and also from State (Tamil Nadu, India) and District (Vellore) Tuberculosis Officers. 49 units of DOTS (Direct observed treatment short-course) isoniazid 300 mg tablets were obtained from the District Tuberculosis office, Vellore. Another 49 Tablets of isoniazid 300 mg manufactured by a pharmaceutical company (blinded) for commercial purposes (masking the brand), were purchased from a private pharmacy.

The brand of commercial preparation of isoniazid chosen for the study was one that had a maximum frequency of prescription by private practitioners in the district. Chemical reagents like Vanillin (99% pure – HPLC grade), ethanol (absolute) and hydrochloric acid were obtained from Thermofisher and Qualigens, India. Colorimetric concentration estimation was done using T60UV–Visble spectrophotometer, PG Instruments, India. Pure form of isoniazid chemical was obtained from Sigma Aldrich Inc., India as pure powder ≥99% (TLC grade) to prepare the stock and working standards. The tablets were stored at room temperature, away from sunlight and moisture.

3. Methods

Only tablets containing isoniazid (300 mg – as per the label) were included in the study. Isoniazid tablets in combination with vitamin supplements like pyridoxine were not used in the analysis due to the structural similarity between these compounds leading to interference with the assay. Similarly, tablets containing other anti-tubercular drugs (Fixed dose combinations) were also excluded.

3.1. Assay

The method of spectrophotometric analysis was adopted from Enoche Florence Oga et al[7] Isoniazid reacts with the aldehyde group Vanillin (4-hydroxy-3-methoxy - benzaldehyde), resulting in the formation of a coloured compound called hydrazone. This reaction is catalysed by the presence of 0.5 M ethanolic hydrochloric acid. This coloured compound is estimated against standards, using a spectrophotometer read at wavelength 405 nm. The range of detection was 1–12 μg/mL, with 12 μg/mL as the upper limit of detection.[7] The assay is specific to isoniazid as it measures the intensity of the colour that is proportional to the formation of hydrazone ring from isoniazid. It is highly sensitive as the study conducted by Oga showed a % recovery ranging between 99.21 and 100.84%. The mean of the quantification error (in %) estimated at the time of validation of this assay was found to be 2.47%.[7]

4. Preparation of standards

Isoniazid is readily soluble in distilled water and hence it was used as the solvent medium to quantitate the drug. Stock standard of isoniazid was prepared using pure powder of isoniazid obtained from Sigma Aldrich Inc. at a concentration of 1 μg/μl. From this stock standard, 2.5 ml of 3 working standards were prepared fresh on the day of experimentation at concentrations within the working limit [100,200, and 600 or 100, 400, and 600 μg/ml].

4 1. Preparation of quality control

A separate aliquot of known concentration of isoniazid was freshly prepared from a different stock standard on the day of experimentation (200 μg/ml or 400 μg/ml).

5. Preparation of sample aliquots

Tablets were coded with random numbers and the nature of the tablets (DOTS or the commercial preparation) was hidden from the principle investigator until the completion of the whole experiment. The tablets were carefully crushed and dissolved in 100 ml of water using a magnetic stirrer. The supernatant was collected from which 250 μl were pipetted out into 2.25 ml of distilled water.

5.1. Reaction

To 2.5 ml of aliquots of standard (100 μg/ml, 200 μg/ml and 600 μg/ml), quality control and tablets solution, 2 ml of freshly prepared 3% vanillin was added followed by a thorough vortex of the mixture. To these, 8 ml of freshly prepared 0.5 M ethanolic hydrochloric acid was added and subjected to vortex. This mixture developed a bright yellow colour due to the formation of hydrazones. The formed colour was allowed to stabilise for 10 minutes.

6. Preparation of standard curve

All the standards, QC and Tablet aliquots were finally diluted in the ratio 1:4 using distilled water. 1 ml from each aliquot was individually added to the quartz cuvette and subjected for

spectrophotometric reading at 405 nm. Coefficient of correlation was calculated for the standard curve.

7. Validation of standard curve

The validity of calibration curve was confirmed using a quality control prepared as mentioned earlier. In this experiment, the quality control used was a pure aliquot of isoniazid prepared from another stock standard. Any calibration curve with quality control value deviating >10% from its actual concentration, was considered invalid. The mean ± SD of QC at the end of the experiment (in %) was 98.6 +/− 4.46.

8. Estimation of concentration of tablet aliquots

The concentration of tablets was estimated using the standard curve obtained for the day. The obtained concentration (in terms of μg/ml) was multiplied by 1000 (the dilution factor) to get the total amount of isoniazid in each tablet (in mg). Each tablet aliquot was measured in duplicate and was averaged for better accuracy.

9. Statistical analysis

The study was done with the primary objective to compare the actual strengths of isoniazid in the DOTS preparation and other commercial preparation. The strength of the tablet was considered using the given formula.

$$Strength\ of\ the\ tablet = \frac{Observed\ Quantity}{Label\ Quantity} \times 100$$

The acceptable range of strength is between 90% and 110% of label values as per WHO Report 2011.

For the sample size calculation, the statistical input of percentage of tablets within the acceptable range of strength (90–110%) for the government-supplied isoniazid arm was considered to be above 90%[8] and for the commercially available isoniazid arm it was considered to be 83%.[9] The sample size was calculated using the nMaster version 2.0 software. With the power of 80%, considering an α error of 5%, the study required a total sample size of 98 tablets, with 49 tablets in each arm (DOTS and commercial preparations) to compare the strength of Isoniazid between DOTS and commercial preparation.

Blinding of principle investigators and co-investigators towards the sources of tablets was achieved using code numbers which was decoded after analysis. Samples were segregated into groups A and B (depending on whether they were from DOTS or Commercial sources), but were not revealed to the statistician until analysis. Quality control for the day of experiment was prepared separately without revealing its concentration.

Unpaired student's t-test was applied to the data to compare the strength of tablets between DOTS and commercial preparations.

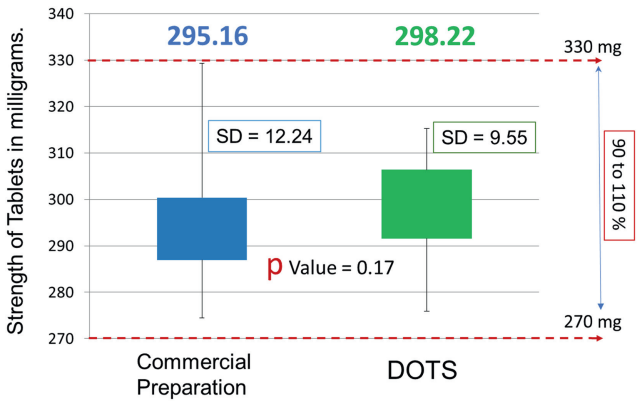

Fig. 1 – Boxplot showing the comparison between the commercial and DOTS preparations of isoniazid.

10. Methods to minimize risk of bias

The strength of tablets was classified as "below <90%, within (90–110%) and above >110% for the group of DOTS and Non-DOTS. P Value < 0.05 was considered to be statistically significant. All analysis was done using Microsoft Excel Version 2016.

11. Results

A total of 98 tablets were estimated in the study of which 49 belonged to the DOTS arm and 49 belonged to the commercial arm. The mean strength ± SD of tablets in the DOTS arm was 298.69 mg ± 9.55 mg. The mean strength ± SD of tablets from the commercial source was 295.16 mg ± 12.24 mg. 25th percentile, median and 75th percentile of strengths of DOTS tablets were 291.27, 299.03, and 306.87 mg, respectively. Similarly, in the commercial arm, it was 286.92, 293.46, and 300.49 mg respectively as shown in Figs. 1 and 2. On performing unpaired student's t-test to compare the strengths of isoniazid under DOTS versus commercial arm, the p-value obtained was 0.17, indicating that there is no statistically significant difference between the two arms.

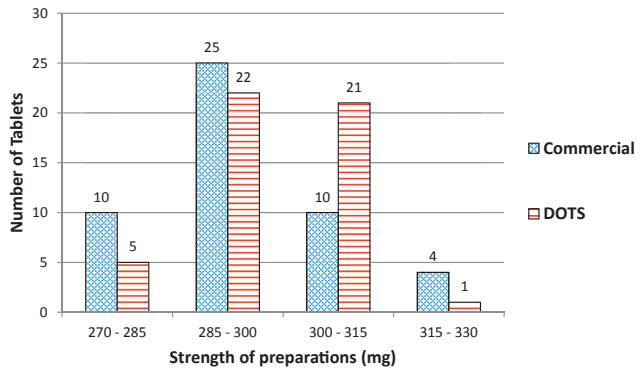

Fig. 2 – Distribution of commercial and DOTS preparations of isoniazid as per strength.

12. Discussion

Two studies on anti-TB drugs from India similar to the current study, showed about 12% of isoniazid tablets being substandard in quality.[9] In the year 2013, Anti-TB Drugs collected from various Revised National Tuberculosis Control Program (RNTCP) centres from the state of Tamil Nadu, were subjected for estimation, showing 9–10% of isoniazid tablets being quantitatively substandard.[8] Therefore, this study aimed at comparing the strengths of isoniazid tablets from government supply against the most commonly used brand of isoniazid commercially available. In India, the number of TB patients treated by private sectors is twice as high as tuberculosis patients receiving treatment from government sectors. On an average each patient would be spending approximately $20 to get himself or herself treated for a full 6 month course of anti-tubercular therapy.[10] India's RNTCP is committed to provide the anti-tubercular drugs free of cost even in private hospitals/ medical colleges in order to encourage the participation of private practitioners in the treatment of TB.[11] The overall economic burden on India due to private pharmacies dispensing anti-tubercular drugs grosses over 59 million USD.[10] There is always a general stigma among the public against government supplied medications, in that they are substandard.

From these results, we can conclude that the isoniazid tablets obtained from government supply under RNTCP programme, were quantitatively at par with commercial preparations and tablets from both the groups were within the normal WHO assigned limits of 90–110%. This method of quantifying the tablet strength using the spectrophotometer is definitely a cheaper alternative to more expensive, time consuming and skill-demanding procedures like HPLC or LCMS. Therefore this simple method can be used in Health Care Centres, whenever and wherever possible in order to quality check the tablets obtained as consignments before dispensing them to patients. In case of treatment failure or relapse, the drugs provided to the patient can be subjected for quantification using this simple method to rule in or rule out substandard quantity of therapy as a reason for their treatment failure. It is very essential to ensure the standard quality of drugs that each and every patient consumes in order to prevent sub-therapeutic responses which pave way for failure of treatment and drug resistance. Appropriate quality of drug is also mandatory to deliver best quality of health care to the public.

This study has some limitations in that isoniazid tablets in combination with pyridoxine were not evaluated due to interference in the assay caused by pyridoxine which is similar in structure to isoniazid. Tablet isoniazid available as fixed dose combination with other first-line anti-tubercular drugs was not evaluated. Moreover, studies should have been done to compare and evaluate the strengths of other first-line and second-line anti-tubercular drugs under RNTCP against commercial preparations. The effect of higher storage temperatures on the stability of the drug was also not analysed in this study.

Acknowledgements

The authors acknowledge Dr Jacob Peedicayil for his comments on the manuscript and Ms. Reka K for statistical inputs. The authors acknowledge the Institutional Review Board, Christian Medical College, Vellore for financial support and RNTCP for providing isoniazid tablets.

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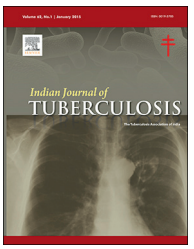

Original article

The comparison of pleural fluid TNF-α levels in tuberculous and nontuberculous pleural effusion

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ARTICLE INFO

Article history:
Received 22 February 2018
Accepted 28 May 2018
Available online 8 June 2018

Keywords:
TB pleural fluid
Non-TB pleural fluid
TNF-α pleural fluid level
Mycobacterium tuberculosis

ABSTRACT

Background: Tuberculous pleural effusion is the manifestation of Mycobacterium tuberculosis infection in pleura. With existing means, it is difficult to establish the diagnosis of tuberculosis (TB) and non-TB pleural effusions; thus, establishing the diagnosis of TB pleural effusion and non-TB pleural effusion is still a clinical problem. Tumour necrosis factor alpha (TNFα) is a potent inflammatory cytokine that plays an important role in immunity to Mycobacterium tuberculosis infections, this level of cytokine increases in pleural effusion due to tuberculosis.
Objective: To compare the TNF-α level of pleural fluid in TB and non-TB pleural effusion.
Methods: The samples in this study that fulfilled the inclusion criteria were patients with non-TB pleural tuberculosis effusion in the inpatient ward in Pulmonology Unit Dr. Soetomo General Hospital Surabaya, male and female, aged between 15 and 60 years. The data is divided into two: primary data and secondary data of patients who fulfilled inclusion and exclusion criteria. The data with normal distribution was analyzed using independent *t*2 test and if the data distribution is abnormal, it was analyzed using Fisher's exact test.
Results: There were 22 subjects divided into 2 groups that were 11 patients with TB pleural effusion and 11 patients with non-TB pleural effusion. The TNF-α level of pleural fluid in TB pleural effusion was 25.43 ± 13.55 pg/mL. The TNF-α level of pleural fluid in non-TB was 5.98 ± 1.89 pg/mL. The serum TNF-α level in TB pleural effusion was 83.22 ± 88.15 pg/mL. The serum TNF-α level in non-TB was 68.54 ± 57.88 pg/mL. There was higher level of TNF-α pleural fluid in TB pleural effusion than in non-TB pleural effusion (25.43 ± 13.55 pg/mL vs 5.98 ± 1.89 pg/mL, p value <0.05). The serum TNF-α level in patients with TB pleural effusion was higher than TNF-α serum level of non-TB pleural effusion. There was no significant difference between TNF-α level of pleural fluid and serum TNF-α levels in the TB pleural effusion group (p value >0.05).
Conclusion: The TNF-α level of pleural fluid in TB pleural effusion was higher than non-TB pleural effusions and there was no significant difference between serum TNF-α levels in the TB pleural effusion group and in the non-TB pleural effusion group.

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https://doi.org/10.1016/j.ijtb.2018.05.017

1. Introduction

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis and is a major cause of morbidity and mortality in developing countries. Indonesia is on the fourth rank after India, Africa and China. Pleural effusion in TB is a manifestation of Mycobacterium tuberculosis infection in the pleura with an incidence rate of approximately ±31%.[1,2] Medical record data in Pulmonary Ward of dr. Soetomo General Hospital Surabaya in 2012 found 37 patients with TB pleural effusion per year while there were 39 patients in 2013. The golden standard of TB pleural effusion is a conventional test in discovering Mycobacterium tuberculosis. Conventional methods such as acid fast bacilli smear and Mycobacterium tuberculosis culture from pleural fluid are often found to be negative due to the small number of germs. On the other hand, the right and effective diagnosis is important in controlling the disease. Given the process of hypersensitivity reactions in TB, there are some biomarkers for diagnostic testing of TB pleural effusion, such as examining IFN gamma levels in pleural fluid.[3]

Tumor necrosis factor alpha (TNFα) is a cytokine derived from Th1 cells that play an important role in immunity against Mycobacterium tuberculosis infection. This cytokine contribute to granuloma formation, which controls the disease progression. The mycobacteria antigen in the pleura interacts with T cells which is previously sensitized by mycobacteria. This will trigger a delayed type hypersensitivity and cause a caseous necrosis of granuloma which will subsequently affect the pleural capillary permeability towards the protein resulting in pleural effusion.[4]

TB pleura effusion is an exudative pleural effusion mostly caused by Mycobacterium tuberculosis. With existing means, it is difficult to establish the diagnosis of TB and non-TB pleural effusions; thus, establishing the diagnosis of TB pleural effusion and non-TB pleural effusion is still a clinical problem. Previous study on differential diagnostic markers for both TB and non-TB pleural effusions had significantly higher levels of TNF-α pleural fluid in the TB pleural effusion group compared with the non-TB pleural effusion group.[5]

In Indonesia, research on the level of TNF-α pleural fluid in TB pleural effusions has not been done; therefore, the researchers are intended in conducting the comparison the TNF-α levels of pleural fluid in TB and non-TB pleural effusion.

2. Methods

This research was cross sectional analytic observational study. The samples in this study that fulfilled the inclusion criteria were patients with TB and non-TB pleural tuberculosis effusion in the inpatient ward in Pulmonology Unit Dr. Soetomo General Hospital Surabaya, male and female, aged between 15 and 60 years, and signed the informed consent.

The variables were divided into independent and dependent variable in which the independent variable was TNF-α level of pleural fluid while the dependent variable was the pleural effusion of TB and non-TB. The TNF-α level of pleural fluid and TNF-α were examined with human TNF alpha ELISA kit.

The samples were undergone pleural fluid aspiration and collected their venous blood. It was examined the TNF-α of pleural fluid and peripheral blood serum. The examination began with collecting 3 cc of pleural fluid began, then put in a tube and stored in a refrigerator with a temperature of −70 °C. The measurement of TNF-α level was performed using ELISA kit by centrifuging the pleural fluid sample for 20 min. The supernatant obtained was added to TNF-α reagent. In examining the serum, venous blood was taken as much as 3 cc; then, it was centrifuged for several minutes. It was put in a tube and stored in a refrigerator with a temperature of −70 °C. Afterwards, the examination of TNF-α level was measured by ELISA kit by adding TNF-α reagent in patients' serum.

The data is divided into two: primary data and secondary data of patients who fulfilled inclusion and exclusion criteria. The data with normal distribution was analyzed using independent *t*2 test and if the data distribution is abnormal, it was analyzed using Fisher's exact test.[6,7]

3. Results

In the TB pleural effusion group, there were 7 (63.6%) male and 4 (36.4%) female patients. In the non-TB pleural effusion group, there were 5 (45.5%) male and 6 (54.5%) female patients. The mean age in the TB pleural treatment group was 27 years old, with the youngest age of 16 and the oldest age of 40 years old. The most age group was 16–25 years old that were 5 (45.5%) patients. The mean age in the non-TB pleural treatment group was 61.3 years old, with the youngest age of 47 years old and the oldest age of 78 years old. The most age group was 46–55 years old that were 4 (36.4%) patients (Figs. 1 and 2). The independent *t*-test results showed that there was a significant difference between the age group in TB pleural effusion and the age group in non-TB pleural effusion with p value <0.05. The TB pleural effusion group had a younger age than the non-TB pleural effusion group.

The normality included the age data, TNF-α pleural fluid level and serum TNF-α level were examined by using Kolmogorov Smirnov test. It was obtained that the age data, TNF-α level of pleural fluid and serum TNF-α level were normally distributed with $p > 0.05$. The result of Chi-square test between gender and TNF-α level of pleural fluid in the TB and non-TB pleural effusion group concluded that there was no significant association between gender and TNF-α level of pleural fluid with $p > 0.05$. The result of Pearson correlation test between age and TNF-α level of pleural fluid in TB and non-TB pleural effusion group showed that there was no significant association between age and TNF-α fluid level with $p > 0.05$.

The mean TNF-α level of pleural fluid in the TB pleural group was 25.43 pg/mL, with the lowest levels of 11.17 pg/mL and the highest level of 55.12 pg/mL. On the other hand, the mean TNF-α level of pleural fluid in the non-TB pleural effusion group was 5.98 pg/mL, with the lowest level of 3.35 pg/mL and the highest level of 10.20 pg/mL. The independent t test results showed that there was a significant difference between TNF-α level of pleural fluid in TB and non-TB pleural effusion group with p value <0.05 (Fig. 3). The mean TNF-α serum level in TB pleural effusion group was 83.22 pg/mL, with the lowest level of 12.62 pg/mL and the highest level

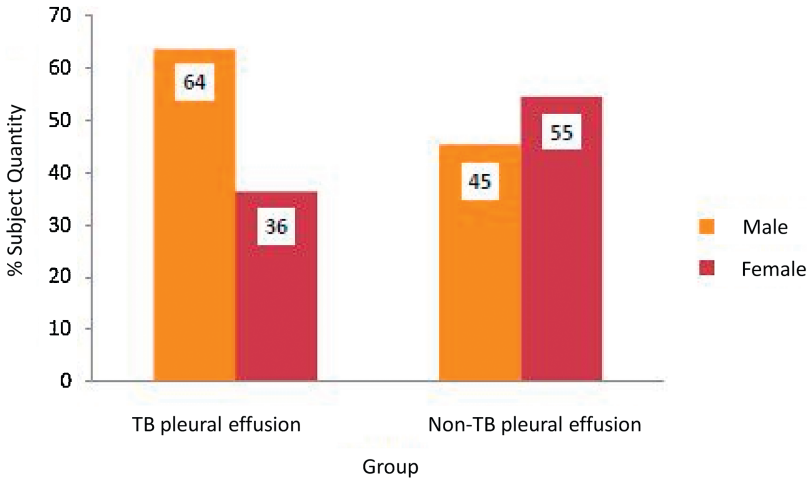

Fig. 1 – The characteristics of research subjects based on gender.

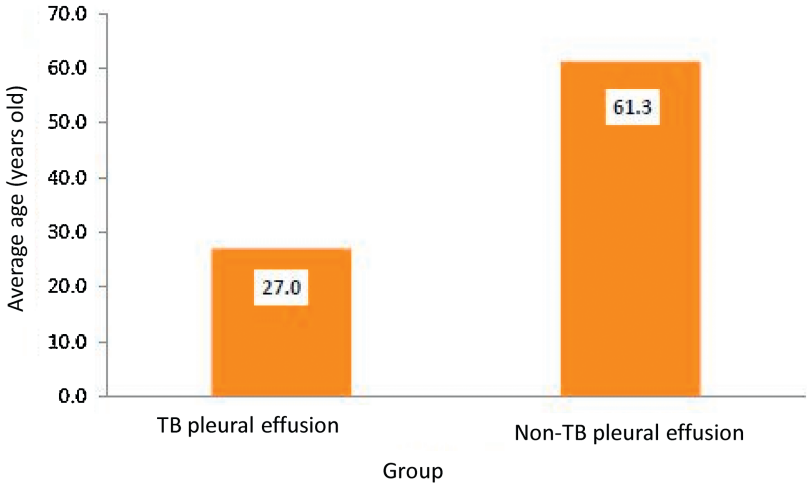

Fig. 2 – The characteristics of research subjects based on age.

of 259.69 pg/mL. On the other hand, the mean TNF-α serum level in the non-TB pleural effusion group was 68.54 pg/mL, with the lowest level of 13.08 pg/mL and the highest level of 203.80 pg/mL. The independent *t* test results showed that there was no significant difference between TNF-α serum level in TB and non-TB pleural effusion group with *p* value >0.05 (Fig. 4). The result of paired t test showed that there was no significant difference between TNF-α level of pleural fluid and TNF-α serum level in the TB pleural effusion group with *p* value >0.05 (Fig. 5).

In the non-TB pleural effusion group, the average TNF-α pleural fluid level was 5.98 pg/mL, with the lowest level of 3.35 pg/mL and the highest level of 10.20 pg/mL. On the other hand, the mean TNF-α serum level was 68.54 pg/mL, with the lowest level of 13.08 pg/mL and the highest level of 203.80 pg/mL. The result of paired *t* test showed that there was a significant difference between TNF-α level of pleural fluid and TNF-α serum level in the non-TB pleural effusion group with *p* value <0.05 (Fig. 6).

4. Discussion

There were 22 subjects divided into 2 groups that were 11 patients with TB pleural effusion and 11 patients with non-TB pleural effusion. In the TB pleural effusion group, there were 7 (63.6%) male and 4 (36.4%) female patients. In the non-TB pleural effusion group, there were 5 (45.5%) male and 6 (54.5%) female patients. This is in accordance with WHO Global Tuberculosis Report in 2013 which is male to female ratio of 1.5:1.[1] The Chi-square test results concluded that there was no significant association between gender and TNF-α level of pleural fluid with $p > 0.05$. This means gender is not associated with high levels of TNF-α pleural fluid.

The age characteristic in the TB pleural effusion group was 27.0 years old, with the youngest age of 16 years old and the oldest age of 40 years old. The most age group is 16–25 years old that is 5 (45.5%) patients. The mean age in the non-TB pleural treatment group was 61.3 years old, with the youngest

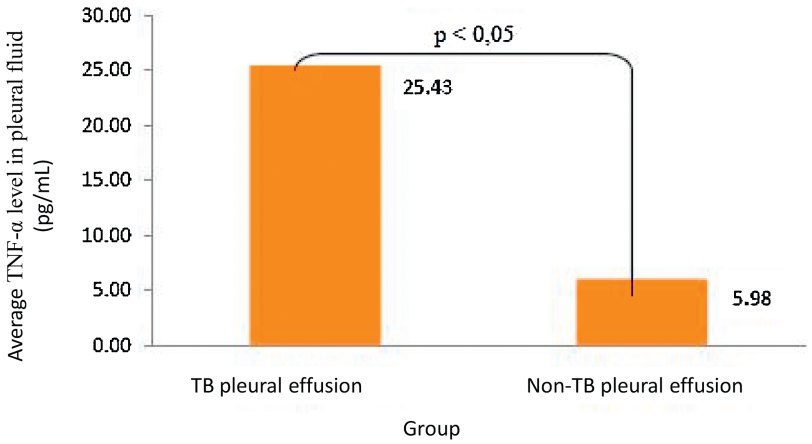

Fig. 3 – The comparison of TNF-α pleural fluid level between TB and non-TB pleural effusion group.

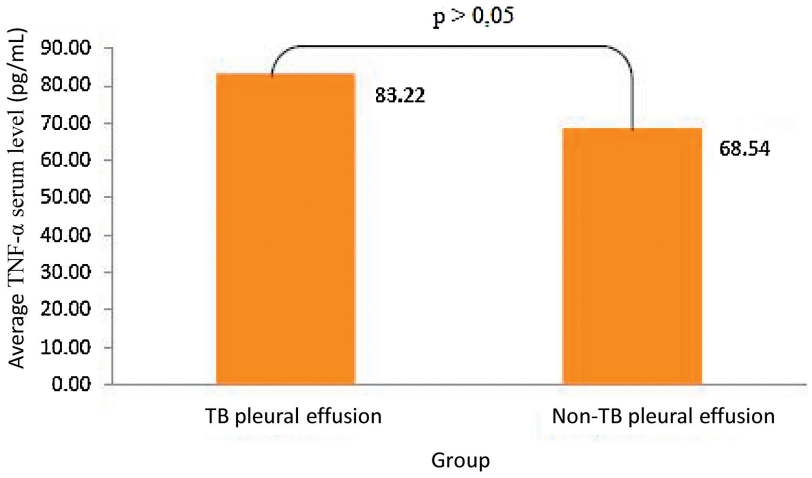

Fig. 4 – The comparison of TNF-α serum level between TB and non-TB pleural effusion group.

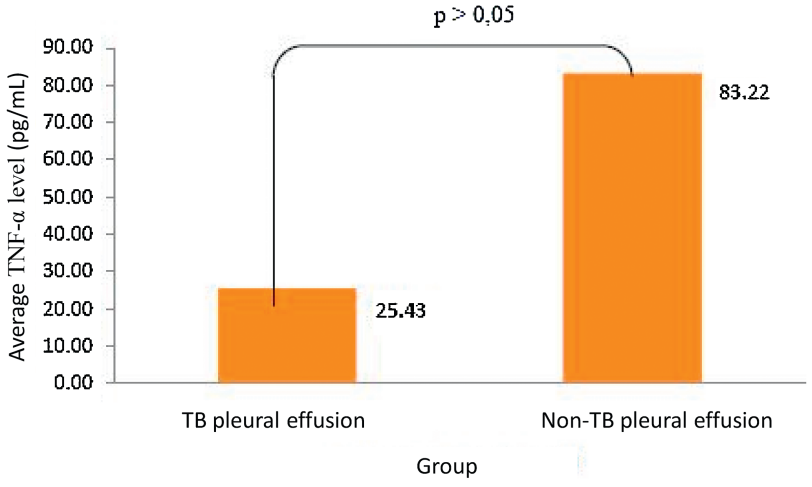

Fig. 5 – The comparison of TNF-α pleural fluid level and TNF-α serum level between TB pleural effusion group.

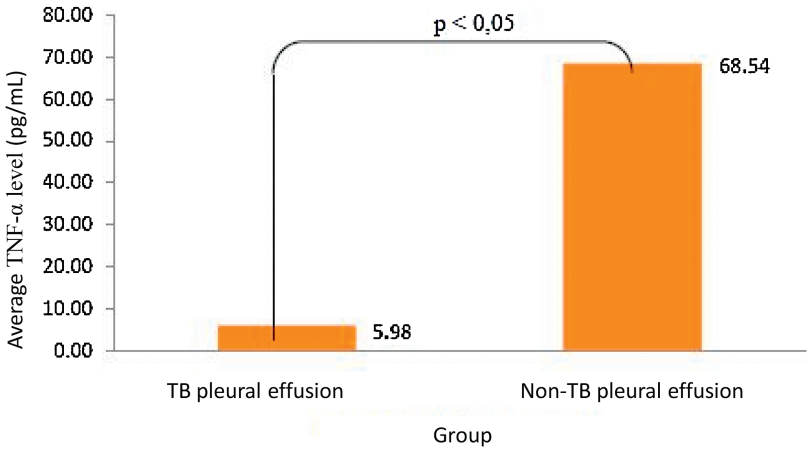

Fig. 6 – The comparison of TNF-α pleural fluid level and TNF-α serum level between non-TB pleural effusion group.

age of 47 years old and the oldest age of 78 years old. The most age group was 46–55 years old that were 4 (36.4%) patients. The independent t test results showed that there was a significant difference between the age group in TB pleural effusion and the age group in non-TB pleural effusion with p value <0.05. Pearson correlation results concluded that there was no significant association between age and TNF-α level of pleural fluid with $p > 0.05$. It can be concluded that age is not associated with high levels of TNF-α fluid pleural. The TB pleural effusion group had a younger age than the non-TB pleural effusion group, according to a study conducted in Korea in 2012 that reported TB disease occurred in the productive age group between 15 and 49 years old.[8] It indicates that the susceptible age group to TB is the productive age group and males are more susceptible than females.[1,8] The result of the normality test by using Kolmogorov Smirnov test showed that the data was normally distributed.

In this study, the mean TNF-α fluid effusion in the TB pleural effusion group of 25.43 pg/mL, with the lowest levels of 11.17 pg/mL and the highest levels of 55.12 pg/mL. Yamada et al. obtained TNF-α levels in pleural fluid of 37.8 ± 11.7 pg/mL. Tahhan et al. obtained TNF-α level of pleural fluid at 65.4 ± 136.9 pg/mL whereas Ambade et al., on TB and non-TB pleural effusion obtained TNF-α level of 195.5 ± 292.1 pg/mL.[5,9,10] The mean TNF-α pleural fluid in the non-TB pleural effusion group was 5.98 pg/mL, with the lowest level of 3.35 pg/mL and the highest level of 10.20 pg/mL. It shows a major protective immune response mediated by local CMI by macrophages that work with Th1 lymphocytes. The Th1 lymphocyte complex with specific antigen of Mycobacterium tuberculosis presented in the pleural cavity through IL-12 will trigger the secretion of cytokines from Th1 cells including TNF-α.[11] The assessment of TNF-α level of TB pleural fluid effusion indicates its role in the body's defense mechanisms especially the process of granuloma formation, elimination of intramacrophage bacillary antigens, and the formation of fibrosis that inhibits disease progression.[12,13] The study examined experimental rats, in which rats with deficiency of this receptor would be more susceptible to the occurrence of Mycobacterium tuberculosis infection. This is due to the inability of macrophages to produce TNF-α.[14]

The mean TNF-α serum level in the TB pleural effusion group was 83.22 pg/mL, with the lowest level of 12.62 pg/mL and the highest level of 259.69 pg/mL. On the other hand, the mean TNF-α serum level in the non-TB pleural effusion group was 68.54 pg/mL, with the lowest level of 13.08 pg/mL and the highest level of 203.80 pg/mL. The independent t test results showed that there was no significant difference between TNF-α serum level in TB and non-TB pleural effusion group with p value >0.05.

Tahhan et al. obtained TNF-α serum level of 2.55 ± 5.23 pg/mL which is lower than the result of this study.[10] However, it is similar to the study conducted by Andrate et al. that obtained higher TNF-α serum level than the level of TNF-α pleural fluid. TNF-α serum levels were 9055.6 pg/mL, 1519.9 pg/mL and 2848.0 pg/mL affected by the clinical severity of Mycobacterium tuberculosis.[15]

The mean TNF-α level of pleural fluid in the TB pleural group was 25.43 pg/mL, with the lowest levels of 11.17 pg/mL and the highest level of 55.12 pg/mL. On the other hand, the mean TNF-α level of pleural fluid in the non-TB pleural effusion group was 5.98 pg/mL, with the lowest levels of 3.35 pg/mL and the highest levels of 10.20 pg/mL. The independent t test results showed that there was a significant difference between TNF-α level of pleural fluid in TB and non-TB pleural effusion group with p value <0.05 (25.43 ± 13.55 pg/mL vs 5.98 ± 1.89 pg/mL). It is in accordance with a research conducted by Tahhan et al. that higher TNF-α level of pleural fluid than the serum level (65.4 ± 136.9 pg/mL vs 54.5 ± 144.2 pg/mL; $p < 0.001$) while Ambade et al., obtained higher TNF-α level in TB group than non-TB group (195.5 ± 292.1 pg/mL vs 59.7 ± 128.9 pg/mL; $p < 0.01$).[5,10] It can be concluded that TNF-α level of pleural fluid is higher in TB pleural effusion than in non-TB pleural effusion group.

In this study, four patients with pleural effusion in pneumonia had TNF-α level of 6.74 pg/mL, 4 pg/mL, 5.87 pg/mL and 5.45 pg/mL. It is considered lower compared to TNF-α level of pleural effusion in TB pleural effusion. The previous study conducted by Yamada et al. found that the level of TNF-α in TB pleural effusion was higher than TNF-α in pleural effusion caused by inflammation (9.2 ± 2.3 pg/mL vs 37.8 ± 11.7 pg/mL).[9] They also attained lower TNF-α level in

malignant pleural effusion of 6.3 ± 0.7 pg/mL than in TB pleural effusion (37.8 ± 11.7 pg/mL).[9] Among 11 patients with non-TB pleural effusion in this study, seventeen of whom were patients with malignant pleural effusion. TNF-α level of pleural fluid was also found to be lower than the mean level of TNF-α pleural fluid in TB. Lie et al. obtained higher TNF-α level of pleural fluid (45.55 ± 15.58 pg/m/L) than TNF-α level in malignant pleural effusion (17.18 ± 4.84 pg/mL).[16] Ambade et al. also obtained the mean TNF-α level in TB pleural effusion of 195.5 pg/mL, TNF-α level of pleural effusion because by pneumonia of 55 pg/mL and TNF-α level in malignant pleural effusion of 61 pg/mL.[5]

In the TB pleural effusion group, the mean TNF-α pleural fluid level was 25.43 pg/mL, with the lowest levels of 11.17 pg/mL and the highest level of 55.12 pg/mL. On the other hand, the mean TNF-α serum level was 83.22 pg/mL, with the lowest level of 12.62 pg/mL and the highest level of 259.69 pg/mL. The result of paired *t* test showed that there was no significant difference between TNF-α level of pleural fluid and TNF-α serum level in the TB pleural effusion group with *p* value >0.05 (25.4 ± 13.55 pg/mL vs 83.22 ± 88.15 pg/mL).

In the non-TB pleural effusion group, the average TNF-α pleural fluid level of 5.98 pg/mL, with the lowest level of 3.35 pg/mL and the highest level of 10.20 pg/mL. On the other hand, the mean TNF-α serum level was 68.54 pg/mL, with the lowest level of 13.08 pg/mL and the highest level of 203.80 pg/mL. The result of paired *t* test showed that there was a significant difference between TNF-α level of pleural fluid and TNF-α serum level in the non-TB pleural effusion group with *p* value <0.05 (5.98 ± 1.89 pg/mL vs 68.54 ± 57.88 pg/mL). The TNF-α serum level was higher than TNF-α level of pleural fluid.

The high concentration of cytokines in pleural fluid reflects local immune stimulation. It occurs because of the migration of T cells from the periphery to the site of the disease. Thus, TNF-α cytokines are secreted at the site of the disease to increase the level of TNF-α cytokine in pleural effusion than TNF-α level in plasma.[17,18] This study obtained different results with Prabha et al.'s research on 46 patients with TB pleural effusion encountered increased level of TNF-α significantly than the level in plasma.[19] The role of TNF-α as proinflammatory cytokines that have immunoprotective role to control the growth of Mycobacterium tuberculosis as well as the detrimental role in immunopathology of TB. In patients with weight loss, TNF-α serum levels are elevated; thus, this mediator is presumed to play an important role in cortex.

Table 2 – The normality data of age, TNF-α level of pleural fluid and TNF-α serum level.

Data	*p* value	
	TB pleural effusion	Non-TB pleural effusion
Age (years old)	0.995	0.996
TNF-α level of pleural fluid (pg/mL)	0.884	0.932
TNF-α serum level (pg/mL)	0.601	0.912

Table 3 – The association of gender and age with TNF-α level of pleural fluid.

TNF-α level of pleural fluid (pg/mL)		TB pleural effusion	Non-TB pleural effusion
Chi-square test	Gender	0.545	1.000
Pearson correlation	Age	0.967	0.393

Table 4 – The association of gender and age with TNF-α serum level.

TNF-α serum level (pg/mL)		TB pleural effusion	Non-TB pleural effusion
Chi-square test	Gender	0.576	1.000
Pearson correlation	Age	0.910	0.243

Table 5 – The Comparison of TNF-α level of pleural fluid between TB and non-TB pleural effusion group.

Group	TNF-α level of pleural fluid (pg/mL)	
	mean ± SD	*p* value
TB pleural effusion	25.43 ± 13.55	0.001
Non-TB pleural effusion	5.98 ± 1.89	

Table 1 – The characteristics of research subjects.

Characteristics	Group		*p*
	TB pleural effusion	Non-TB pleural effusion	
Gender			
Male	7 (63.6%)	5 (45.5%)	0.392
Female	4 (36.4%)	6 (54.5%)	
Age (mean ± SD)	27.0 ± 7.6	61.3 ± 9.7	0.000
16–25 years old	5 (45.5%)	0 (0.0%)	
26–35 years old	4 (36.4%)	0 (0.0%)	
36–45 years old	2 (18.2%)	0 (0.0%)	
46–55 years old	0 (0.0%)	4 (36.4%)	
56–65 years old	0 (0.0%)	3 (27.3%)	
66–75 years old	0 (0.0%)	3 (27.3%)	
76–85 years old	0 (0.0%)	1 (9.1%)	

Table 6 – The comparison of TNF-α serum level between TB and non-TB pleural effusion group.

Group	TNF-α serum level (pg/mL)	
	mean ± SD	*p* value
TB pleural effusion	83.22 ± 88.15	0.649
Non-TB pleural effusion	68.54 ± 57.88	

Table 7 – The comparison of TNF-α level of pleural fluid and TNF-α serum level in TB pleural effusion group.

Variable	TB pleural effusion group	
	mean ± SD	*p* value
TNF-α level of pleural fluid	25.43 ± 13.55	0.073
TNF-α serum level	83.22 ± 88.15	

Table 8 – The comparison of TNF-α level of pleural fluid and TNF-α serum level in non-TB pleural effusion group.

Variable	Non-TB pleural effusion group	
	mean ± SD	*p* value
TNF-α level of pleural fluid	5.98 ± 1.89	0.005
TNF-α serum level	68.54 ± 57.88	

Andrate et al. in his study regarding the association between TNF-α level and clinical TB severity was found that patients with lower body weight had higher serum TNF-α level (15,468.54 ± 4580.54 pg/mL) than patients without weight loss (2904.98 ± 1367.89 pg/mL) with p value <0.05. This suggests that, besides being caused by virulence levels, it is also caused by the effect of TB pathogenesis that is affected by clinical severity marked by weight loss conditions.[2,4] Andrate et al.'s research obtained the association between BB with high TNF-α serum level. Patients with a low weight obtained higher TNF-α serum level than patients without decreased weight (Tables 1–8).

5. Conclusion

The level of TNF-α pleural fluid in TB pleural effusions were higher than in non-TB pleural effusions and there was no significant difference between TNF-α serum levels in TB and non-TB pleural effusion group.

Conflicts of interest

The authors have none to declare.

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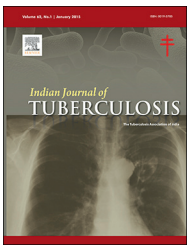

Original Article

Treatment outcomes with daily self-administered treatment and thrice-weekly directly-observed treatment in two cohorts of newly-diagnosed, sputum-positive adults with pulmonary tuberculosis

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ARTICLE INFO

Article history:
Received 10 January 2017
Accepted 11 May 2017
Available online 24 June 2017

Keywords:
Default
DOTS
Pulmonary tuberculosis
RNTCP
Sputum smear examination

ABSTRACT

Background: The Revised National Tuberculosis Control Program (RNTCP) envisages shifting from thrice-weekly to a daily anti-tuberculosis treatment (ATT) regimen. The potential merits and demerits of both regimens continue to be debated.

Methods: This retrospective study compared treatment outcomes in 191 HIV-negative, newly diagnosed, sputum-positive adults with pulmonary tuberculosis from Vellore district of Tamil Nadu who were treated at a private medical college during 2009 to 2012 with intermittent Directly Observed Treatment Short Course (intermittent DOTS cohort, $n = 132$) or who opted for daily Self-Administered Treatment (daily SAT cohort, $n = 59$). Treatment outcomes obtained from medical records were supplemented by interviews with consenting, traceable patients.

Results: The rates for the RNTCP-recommended sputum smear examinations were suboptimal (42% for daily SAT and 72% for intermittent DOTS). However, treatment success with daily SAT and intermittent DOTS (76.2% *vs.* 70.4%); default (11.9% *vs.* 18.2%); death (6.8% *vs.* 5.3%); treatment failure (5.1% *vs.* 4.6%); and relapse (0% *vs.* 1.5%) did not significantly differ.

Conclusions: While evaluable treatment outcomes were not significantly different with daily SAT and intermittent DOTS, rates for timely smear examinations and for treatment success

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http://dx.doi.org/10.1016/j.ijtb.2017.05.012

were lower, and for default higher, in both cohorts than comparable RNTCP data from Vellore district. Further strengthening of RNTCP facilities within private medical colleges and regular, real-time audits of performance and outcomes are needed if daily ATT regimen under the RNTCP is to succeed.

1. Introduction

The World Health Organization (WHO) recommends that new patients with pulmonary tuberculosis (TB) should ideally be treated with six months of a daily regimen of four drugs (isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E)) in the first two months of intensive phase, and two drugs (isoniazid and rifampicin) in the four month continuation phase (2HRZE/4RH) of short course Anti-Tuberculosis Therapy (ATT).[1] The ''Standards for TB care in India'' proposed by the WHO permits, for logistic reasons, intermittent thrice-weekly ATT regimens in adults with pulmonary TB who are not infected with the Human Immunodeficiency Virus (HIV), if all doses are directly observed (DOTS).[2] The Revised National Tuberculosis Control Program (RNTCP) is criticized for providing a partially observed treatment short course (POTS) thrice-weekly regimen as only one-third of the doses of the continuation phase are directly observed.[3] The RNTCP envisages changing to a daily ATT regimen due to increasing concerns of higher relapse and drug resistance with intermittent regimens under program conditions.[2] A pilot study of daily ATT regimen under the RNTCP is underway in 100 districts in India.[4] The burdens of costs and supervision are reasons cited for the delay in introducing the WHO recommended daily ATT regimen in India.[5]

Randomized control trials (RCTs) have demonstrated the comparable efficacy of intermittent (thrice-weekly) regimens of short course (6 months) ATT (containing rifampicin throughout) and daily short course ATT regimens.[6] Some systematic reviews have supported this conclusion,[7] while others have been inconclusive,[8] or have contested this conclusion and reported higher relapse rates with intermittent-ATT, particularly with cavitary TB.[9] A recent systematic review of RCTs and cohort studies that used improved methods for meta-analysis reported a trade-off between lower default rates but higher relapse with intermittent regimens *versus* lower relapse but higher default rates with daily short course ATT regimens.[10]

A related debate is about the usefulness of direct observation of treatment. The recently updated Cochrane Review did not find directly observed treatment short course (DOTS) to improve rates for cure or treatment completion compared to self-administered short course ATT (SAT).[11] Another meta-analysis did not find direct observation to reduce microbiological failure, relapse or acquired drug resistance compared to SAT.[12] However, a molecular epidemiologic analysis found molecular evidence to suggest a decrease in the acquisition and transmission of resistant TB with universal DOT for TB.[13] Thus, while intermittent regimens offer practical and convenient solutions to high pill burdens and adverse drug reactions associated with daily TB therapies,[10] these have to be offset by the possibility of higher relapse rates with intermittent regimens.

In India, though the RNTCP provides thrice-weekly DOTS free of cost through government and non-government health facilities, an estimated 46% (95% CI 34–57%)[14] or more seek treatment from providers outside the RNTCP. In many private medical colleges affiliated with the RNTCP, adults with TB who are not HIV-infected have the option of thrice-weekly DOTS under the RNTCP, or a short course of the same ATT (2HRZE/4RH) regimens self-administered daily (SAT) that the patient pays for. There are also other special situations, such as in conflict areas, or geographically remote tribal areas that are hard to reach, where the only option may be to provide daily SAT; operational research in such areas indicate that daily SAT may be an acceptable alternative to the standard DOTS.[15,16]

Given the uncertainties inherent in translating evidence from experimental studies to managing TB under program conditions, this study aimed to evaluate treatment outcomes in two retrospective cohorts of adults with pulmonary TB who sought treatment from a non-government institution with thrice-weekly intermittent DOTS *via* the RNTCP, or who opted to pay for daily SAT through general or specialist medical services.

2. Methods

This non-concurrent cohort study was conducted in 2013 (June–November) at the Christian Medical College, a private, not-for-profit, medical college in Vellore, South India. Residents of Vellore district with newly diagnosed, HIV-negative, sputum positive pulmonary TB treated during 2009–2012 with intermittent DOTS through the RNTCP-affiliated DOTS clinic at the Community Health department, or daily SAT prescribed by the Internal Medicine and Pulmonary Medicine departments of the institution, were identified from medical records, yielding the two cohorts. Data were extracted from their medical records using semi-structured, pilot-tested extraction forms. Those in both cohorts who were traceable and consented were interviewed for data on socioeconomic status, alcohol and substance misuse, and family involvement in supervision of ATT.

The TB outcomes recorded were cure, treatment completion, treatment success (cure + treatment completion), default, death, treatment failure, and relapse using WHO/IUATLD definitions.[17] Severity of alcohol consumption was graded using definitions provided by the Centre for Disease Control and Prevention (CDC), Atlanta.[18] Tobacco smoking was measured in terms of pack years. Socioeconomic class was determined by Modified Kuppuswamy Scale 2012.[19]

Table 1 – Demographic profile of the daily self-administered treatment (SAT) and intermittent directly observed treatment (DOTS) cohorts (*n* = 191).

Demographic characteristics		SAT (*n* = 59)		DOTS (*n* = 132)		*P* value
		n	%	*n*	%	
Age (years)	18–30	14	23.7	27	20.5	0.517
	31–60	34	57.6	87	65.9	
	Above 60	11	18.7	18	13.6	
Gender	Male	31	52.5	90	68.2	0.038
	Female	28	47.5	42	31.8	
Residence	Rural	20	33.9	41	31.1	0.697
	Urban	39	66.1	91	68.9	

Data entered into Epidata software version 3.1 were analyzed by R software version 3.1.1. Differences in the sample characteristics and treatment outcomes were compared using chi square tests or Fisher exact tests, as appropriate. Odds Ratios (OR) with their 95% Confidence Intervals (CI) were also estimated. The study was approved by the Institutional Review Board.

3. Results

3.1. *Characteristics of the cohorts*

Of 191 HIV-negative adults from Vellore district with sputum-positive pulmonary TB treated during the study period, 132 (69%) were treated with thrice-weekly DOTS and 59 (31%) opted for daily SAT. The majority were aged 31–60 years, were male and urban residents. While the cohorts were comparable in terms of age, and locality of residence, the DOTS cohort had significantly more men than women (68.2% *vs.* 52.2%, $P = 0.038$) compared to the daily SAT cohort (Table 1).

Of the 191 patients, data on socio-economic status, alcohol and tobacco use, and family involvement in supervision could be ascertained for only 155 (81%) patients. Of these, 38 (25%) had received daily SAT and 117 (75%) intermittent DOTS (Table 2). The type of family unit and the level of family involvement in supervision of ATT were comparable in both cohorts (Table 2). However, patients in the daily SAT cohort were more affluent, with only nine (24%) patients in the lower socioeconomic class compared to 93 (80%) in the DOTS cohort (OR 0.03; 95% CI 0.08–0.19; $P < 0.001$; Table 2). Patients on DOTS were also significantly more likely to use or misuse alcohol (47% *vs.* 24%; OR 2.86; 95% CI 1.25–6.56; $P = 0.004$); and smoke tobacco than those in the daily SAT cohort (44% *vs.* 16%; OR 4.12; 95% CI 1.60–10.61; $P = 0.005$; Table 2).

In the191 patients treated, co-morbid conditions were more frequent in the daily SAT cohort than the intermittent DOTS cohort (61% *versus* 42%; Table 3). The co-morbid conditions included diabetes mellitus, systemic hypertension, chronic obstructive pulmonary disease, cardio vascular diseases, nephropathy, chronic liver disease, psychotic disorders and epilepsy.

3.2. *Treatment outcomes*

Treatment outcomes were available for all the 191 patients treated.

Table 2 – Socioeconomic details, substance use and family involvement in treatment of those in the two cohorts who were interviewed (*n* = 155).

Characteristics		SAT (*n* = 38)		DOTS (*n* = 117)		*P* value	OR (95% CI)
		n	%	*n*	%		
Type of family	Nuclear	23	60.5	80	68.4	0.634[a]	Nuclear *vs.* non-nuclear
	Extended	12	31.6	31	26.5		0.71 (0.33–1.51)
	Joint	3	7.9	6	5.1		
Socio-economic class	Lower	0	0.0	7	6.0	<0.001[b]	Lower *vs.* middle or upper
	Upper lower	9	23.7	86	73.5		0.03 (0.08–0.19)
	Lower middle	13	34.2	17	14.5		
	Upper middle	14	36.8	7	6.0		
	Upper	2	5.3	0	0.0		
Alcohol use	Nil	29	76.3	62	53.0	0.004[a]	No alcohol use *vs.* mild to heavy use
	Mild	8	21.1	23	19.7		2.86 (1.25–6.56)
	Moderate/heavy	1	2.6	32	27.3		
Tobacco smoking	Non smoker	32	84.2	66	56.4	0.005[b]	Non-smoker *vs.* smoker
	≤20 pack years	2	5.3	29	24.8		4.12 (1.60–10.61)
	>20 pack years	4	10.5	22	18.8		
Treatment supervision in family	Direct observation (informal)	18	47.4	55	47.0	0.269	No involvement *vs.* some involvement
	Prompting	9	23.7	16	13.7		0.63 (0.29–1.39)
	No involvement	11	28.9	46	39.3		

[a] Chi square with Yates correction.
[b] Fischer's exact test; OR = odds ratio; CI = confidence interval.

Table 3 – Co-morbidity profile of the daily self-administered treatment (SAT) and intermittent directly observed treatment (DOTS) cohorts (*n* = 191).

Number of co-morbidities	SAT (*n* = 59)		DOTS (*n* = 132)		*P* value	OR (95% CI)
	n	%	*n*	%		
≥4	3	5.1	0	0.0	<0.001[b]	Two or more *vs.* one or no co-morbidity
3	5	8.5	4	3.0		4.35 (1.97–9.59)
2	11	18.6	9	6.8		
1	17	28.8	42	31.8		
0	23	39.0	77	58.3		

[b] Fischer's exact test; OR = odds ratio; CI = confidence interval.

3.2.1. *Sputum smear conversion*

At the end of the two month intensive phase, only 31 (52.5%) patients in the daily SAT cohort and 104 (78.8%) patients in the intermittent DOTS cohort had sputum smear examinations. The third month sputum smear conversion rate in the patients who had sputum examination done was significantly lower with daily SAT than with intermittent DOTS (14/31, 45.2% *vs.*76/104, 73.1%; OR 0.30; 95% CI 0.13–0.70; $P = 0.005$).

3.2.2. *Bacteriologically confirmed cure*

Follow-up sputum smear examinations as required in the RNTCP guidelines (two sputum smear examinations out of which one should be in the last month of treatment) were done for 25 (42.3%) patients in the daily SAT cohort and for 95 (72.5%) in the intermittent DOTS cohort. The bacteriologically confirmed cure rate from available data (Table 4) was significantly lower in the daily SAT cohort than in the intermittent DOTS cohort (22% *versus* 60.6%; OR 0.18; 95% CI 0.09–0.37; $P < 0.001$). If the bacteriological cure rate was compared only in those patients in both cohorts in whom data for two sputum smear examinations were available, this difference was still significantly lower with daily SAT (13/25, 52%*vs*. 80/95, 84.2%; OR 0.20; 95% CI 0.08–0.53; $P = 0.002$).

3.2.3. *Treatment completion*

In those without sputum smear examination, treatment outcome is usually established by chest X-ray or clinically. Treatment completion rate was 54.2% with daily SAT and 9.8% with intermittent DOTS (Table 4). Among those who completed treatment and whose first follow up sputum smear positive for acid fast bacilli, the recommended second follow-up sputum smear examinations were done only for 11 of 32(34%) on daily SAT and 10 of 13 (76%) on intermittent DOTS.

3.2.4. *Treatment success*

Treatment success in the program setting is a composite outcome of microbiologically-demonstrated cure, 'clinical cure' and 'treatment completion.' Treatment success with daily SAT was 76.2% (95% CI 64.0–85.0%) and with intermittent DOTS was 70.4% (95% CI 62.2–77.6%); these proportions were not significantly different (Table 4).

3.2.5. *Default*

Default with daily SAT (11.9%; 95% CI 3.5–20.3%) and with intermittent DOTS (18.2%; 95% CI 11.5–24.9%) were not significantly different (Table 4).

3.2.6. *Death*

Deaths in the daily SAT cohort (4/59; 7%) and intermittent DOTS cohort (7/132; 5%) were also not significantly different (Table 4).

3.2.7. *Treatment failure*

Roughly similar proportions (5%) were treatment failures in both cohorts (Table 4).

Table 4 – Treatment outcomes in the daily self-administered treatment (SAT) and intermittent directly observed treatment (DOTS) cohorts (*n* = 191).

Outcome	SAT (*n* = 59)		DOTS (*n* = 132)		*P* value	OR (95% CI)
	n	%	*n*	%		
Cure	13	22.0	80	60.6	<0.001	0.18 (0.09–0.37)
Treatment completed	32	54.2	13	9.8	<0.05	10.85 (5.03–23.39)
Treatment success[c]	45	76.2	93	70.4	0.41	1.35 (0.66–2.73)
Default	7	11.9	24	18.2	0.38	0.61 (0.25–1.50)
Died	4	6.8	7	5.3	1.0[a]	1.30 (0.37–4.62)
Treatment failure	3	5.1	6	4.6	1.0[a]	1.13 (0.27–4.66)
Relapse	0	0.0	2	1.5	1.0[b]	Not estimable
Total[d]	59	100	132	100		

[a] Chi square with Yates correction.
[b] Fischer's exact test.
[c] Sum of cure and treatment completed.
[d] Sum of treatment success, default, died, treatment failure and relapse; OR = odds ratio; CI = confidence interval.

3.2.8. Relapse

There were no relapses with daily SAT over a median follow up of 24.7 months and two (1.5%) relapses with intermittent DOTS over a median follow up of 26.8 months (Table 4). Both these relapses occurred in the first six months after treatment completion.

4. Discussion

In this retrospective cohort study we compared treatment outcomes with daily self-administered ATT and thrice-weekly intermittent directly observed treatment. The cure rate in this study with intermittent DOTS (61%; 95% CI 52–69%) was lower than the cure rates in RNTCP Tamil Nadu reports (84% to 86.1%) for the years of this study (2009–2012).[15–18] Cure rate was even lower in the daily SAT cohort (22%; 95% CI 13–34%). This is because only 72% in the intermittent DOTS cohorts and 42% in the daily SAT cohort had the two recommended sputum examinations done to qualify for being considered cured.[12] However, bacteriological cure in those in the cohorts who did qualify to being considered cured by these criteria were similar to RNTCP data for the intermittent DOTS cohort (84.2%), though lower with daily SAT (52%).

Conversely, those who completed treatment but did not have two negative sputum smear examinations were classified as treatment completers[12]; and the treatment completion rates (54% with daily SAT and 10% with DOTS) were correspondingly higher than the RNTCP rates from Tamil Nadu for the same period for DOTS (0.8–1.5%).[15–18] While treatment success (those cured and those who completed treatment) did not differ significantly between daily SAT (76.2%; 95% CI 65.4–87.2%) and intermittent DOTS cohorts (70.4%; 95% CI 62.2–77.6%), only the daily SAT cohort had treatment success rates approaching the RNTCP treatment success rates reported with DOTS for Tamil Nadu during the same period(85–86.9%).[15–18] Treatment success was also lower in both cohorts than that reported for Vellore district during the same period (89–91%).[15–18]

Default was higher in the DOTS cohort (18.2%) than the daily SAT cohort (11.9%), though this difference was not statistically significant. However, the fact that both cohorts had higher default rates than comparable data from RNTCP reports for Tamil Nadu (5.9–7%) is worrying.[15–18] The default rates in this study did not follow the meta-analysis prediction[10] that daily ATT regimens would have higher default than intermittent regimens. The higher default in the thrice-weekly DOTS cohort could be due to the greater proportion of poorer people who were smokers and consumed alcohol compared to the daily SAT cohort. These characteristics also increased the risk for default in studies done in Tamil Nadu (that reported a default rate of 17%)[20] and in other parts of India.[21,22] Using these risk factors to create individualized risk profiles to predict defaulters could help in initiating targeted interventions to prevent default.[21] However, health system related factors (such as poor patient-provider interaction, poor support from health staff, poor service satisfaction, and sub-optimal follow up of potential defaulters), and patient-related risk factors (such as poor knowledge of TB, and practical considerations), should also be considered in future endeavors aimed at reducing default rates in medical colleges affiliated with the RNTCP.[20]

Other TB treatment outcomes did not differ significantly in the cohorts. While those in the DOTS cohort were poorer, and had a higher prevalence of alcohol and tobacco use compared to those in the daily SAT cohort, they also had access to free drugs, formal direct observation, and had fewer co-morbid conditions. Though more people in the daily SAT cohort had one or more co-morbid conditions, they were relatively more affluent, and perhaps better motivated by virtue of self-payment for treatment. The lack of formal direct observation of treatment could also have been mitigated to an extent by the informal supervision of family members.

The sputum smear examination at the end of the two months of intensive phase treatment is important for predicting relapse (85% specificity) and treatment failure (81% specificity).[23] Fewer sputum smear examinations after two months were done in the daily SAT cohort in this study (53%) and even in the DOTS cohort, smear examination rates were sub-optimal (79%). Rates for follow-up sputum smear examination required to determine cure were also suboptimal in the daily SAT cohort (42.3%) and in the intermittent DOTS cohort (71.9%). The reasons for this were unclear from patient records, but could include oversight by clinicians, or because patients were not producing sputum. The daily SAT cohort had fewer smokers and may have had fewer people with productive cough due to smoking to provide sputum to examine. Those in the daily SAT cohort who had responded to ATT by two months would also add to the number with insufficient sputum for testing. The lower smear conversion rates in the daily SAT cohort with productive cough could be attributed to the larger number of co-morbidities, particularly diabetes. Extension of the RNTCP implemented case-based online software 'Nikshay'[18] to monitor TB treatment and follow up in medical colleges and other non-government TB treatment facilities could ensure timely sputum examination, enable recording the reasons for non-examination, and help to identify those at high risk of relapse.

The limitations of this study include its retrospective nature, the relatively small numbers in both cohorts, imbalance in prognostic variables in the two cohorts, the limited amount of information available from medical records and interviews for detailed evaluations of the risk factors associated with treatment outcomes, and the lack of systematic monitoring of adverse drug reactions. Not all patients could be interviewed for supplementary data. However, treatment outcomes ascertained under the RNTCP were available for all in both cohorts.

The relevance of this study lies in the fact that increasing the involvement of medical colleges in India, including those in the private sector, to improve TB case detection and management has been an important part of the RNTCPs initiatives for over a decade.[24] In 2010–2011, 291of 321 medical colleges in India were involved with the RNTCP.[18] The National Task Force set up to facilitate this involvement by the RNTCP had also proposed that the Medical Council of India should include the RNTCP in the medical curriculum and MCI recognition norms.[18] The suboptimal treatment outcomes in the daily SAT and intermittent DOTS cohorts in this study from a large, well-resourced, private, not-for profit medical

college compared to relevant official data from the RNTCP indicates that much needs to be done to increase the value that medical colleges can play in partnering the RNTCP,[25] and may also call into question the veracity of data reporting in the RNTCP.[3]

Future collaborative action between the RNTCP and medical colleges should include the following: implementing real-time, effective, web-based, referral, notification, and monitoring mechanisms; improving recording and reporting systems in medical colleges through better involvement of their medical records departments[26]; supporting TB treatment facilities in medical colleges; facilitating good-quality operational research to help inform the program; and conducting ongoing real-time audits of practices and outcomes from medical colleges and other treatment facilities, in order to ensure better compliance with the RNTCPs objectives and guidelines, and to ensure more reliable outcome data.[24]

These measures would be particularly important if India were to completely switch over to daily treatment for TB control, as ensuring treatment completion with the greater pill burden of daily treatment (that can be partially mitigated by using fixed drug combinations) and monitoring for adverse drug reactions (particularly liver injury in those with pre-existing vulnerabilities such as alcohol abuse, and viral infections) would be additional operational burdens that require effective systems and mechanisms in place before a wider roll out.

Authors' contribution

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Conflicts of interest

The authors have none to declare.

Acknowledgements

This study was supported by an intramural grant from the FLUID Research fund, Christian Medical College, Vellore. We acknowledge the support of the Medical Records and Microbiology Departments and CHAD Tuberculosis Unit in conducting the study.

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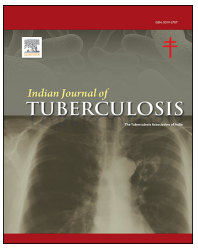

Review article

Female genital tuberculosis in light of newer laboratory tests: A narrative review

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ARTICLE INFO

Article history:
Received 17 June 2019
Received in revised form
10 October 2019
Accepted 3 January 2020
Available online 18 January 2020

Keywords:
Female genital tuberculosis
Infertility
Laboratory diagnosis

ABSTRACT

Female genital tract tuberculosis (FGTB) is a chronic disease with varied presentation. The diagnosis of FGTB for early institution of treatment remains a clinical challenge. Its laboratory diagnosis is difficult because of paucibacillary nature of the condition and limitation of available diagnostic tests. In view of the intricate problems in diagnosis of FGTB, physicians tend to over treat with empirical anti-tuberculosis drugs. Apart from concerns of drug toxicity, this may be a contributing factor in the increasing incidence of multidrug-resistant TB reported in India. The main goal for advances in TB diagnostics is to reduce delay in diagnosis and treatment. In addition, there should be reduced complexity, improving robustness, and improving accuracy of the laboratory test for diagnosis of Female genital tuberculosis.

Objective: This narrative review is written with the following objectives.

1) To get a comprehensive overview as well as recent advances in diagnostic test used in the detection of FGTB.

2) To understand the limitations as well as advantages of these laboratory diagnostic test.

3) To provide clinical guidance regarding the detection in susceptible women.

Method: The literature search was performed using electronic database of Pubmed, Medline, Embase and Google Scholar. Grey literature search was also done. Studies published in English were included. Following keywords were used for search – Tuberculosis, extra pulmonary tuberculosis, female genital tuberculosis, diagnosis of female genital tract tuberculosis. The personal knowledge and experience of authors in the field, helped in archiving the relevant articles.

Result: Studies suggest that though culture is an invaluable contributor in the diagnosis of FGTB, molecular tests like PCR, LAMP, Xpert MTB/RIF and line probe assays have shown potential and are now being explored to strengthen the diagnostic algorithm of FGTB.

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https://doi.org/10.1016/j.ijtb.2020.01.002

Conclusion: The use of algorithm approach with combination of both rapid culture and newer molecular techniques will facilitate the accurate and timely diagnosis of FGTB.

1. Introduction

Female genital tract TB (FGTB) is a chronic infectious disease which causes significant morbidity in the reproductive health of women. It predominantly presents with wide spectrum of signs and symptoms. Though it is the second most common form of extra pulmonary TB, isolated genital TB with no other organ involvement is seen in 5–30% of cases.[1] The global prevalence of genital TB is estimated to be approximately 8–10 million cases.[2] The recent prevalence of female genital tuberculosis reported from India varies from 45.1 cases per 1,00,000 women in a community based study at Andaman Islands, 48.5% from infertile women in north India and 26% from infertile women in Varanasi.[3–5] This wide heterogeneity in reporting is attributed not only to the variation in sample size and population but also to the diagnostic method used in detection of the disease. Clinically, FGTB can presents with common gynecological complaints such as menstrual irregularities or chronic pelvic pain. But majority of times it is asymptomatic and presents as infertility that too once the reproductive damage is already done.[6] Most frequently affected genital organs are fallopian tubes followed by endometrium, ovaries and cervix.[7,8] Anti-tuberculosis drug used in the management need to be given very cautiously because of the emerging issue of antimicrobial resistance verses potential for damage to the reproductive health of women if not given. Thereby there is need to understand the advances in FGTB diagnostics test which will not only enhance the clinician's perspective but also result in improved accuracy of diagnosis and prevent treatment delays.

2. Material and methods

This review is undertaken with the following objectives-

l) To get an overview of the advances in diagnostic test used in the detection of FGTB
2) To understand the limitations as well as advantages of these newer diagnostic tests
3) To provide clinical guidance regarding the detection of FGTB in women with suspected infection

An English language literature search was performed using electronic database of PubMed, Medline, Embase and Google. Following keywords were used for search – genital tuberculosis OR tuberculosis in India OR female genital tuberculosis OR Infertility OR extrapulmonary TB. The personal knowledge and experience of authors in the field, helped in archiving the relevant articles. The articles which met the following criteria are included in the current review:

1. Studies published in English
2. Studies published in recent ten years from 2009 to 2019 are included
3. Studies focusing only on FGTB are included

3. Results

3.1. *Test used for diagnosis of female genital tuberculosis*

The exact diagnosis of FGTB has always been challenging for the clinician primarily because of the multifarious clinical presentation, observer bias on imaging and laparoscopy, paucibacillary yield of microorganisms in specimens and availability of battery of bacteriological test and histopathological examination which are often required for diagnosis of FGTB. Table 1 enumerates the various recent studies done on the Indian and global platforms to determine the prevalence of FGTB using various microbiological test.[9–26] Majority of studies are from Indian subcontinent highlighting that the magnitude of problem is in developing countries like India. As enumerated in Table 2, various samples like endometrial biopsy/curettage, pelvic aspirated fluids, ovarian tissue biopsies, fluid samples from the pouch of Douglas and menstrual blood have been used by clinicians for the diagnosis of FGTB.[25,27–30] Predominant number of studies have been done on infertile women and endometrial biopsy is the most common specimen used for diagnosis. Menstrual blood has been reported to have lowest sensitivity as compared to conventionally used endometrial biopsy/curettage.[28] Apart from conventionally used hysterosalpingography and hysterolaproscopy, conventional microbiological test such as Ziehl–Neelsen (ZN) staining, culture on Lowenstein Jenson (LJ) medium, histopathological detection of epithelioid granuloma and polymerase chain reaction [PCR] all complement each other for diagnosis of FGTB. Different diagnostic tests currently available have been elaborated in Fig. 1. However, there are certain advances in the diagnostic methods used which are discussed under various subheadings.

3.2. *Acid-fast bacilli (AFB) staining*

Ziehl–Neelsen (ZN) staining is a rapid and cost-effective way of detecting tubercular bacilli but it lacks sensitivity. The alternate use of fluorescent dyes (auramine, rhodamine) over conventional staining enables easier reading at lower magnification, and fluorescent microscopy (FM) is about 10% more sensitive than light microscopy. Traditional Fluorescent microscopes require dark rooms and have high costs. These challenges have been addressed by light emitting diode (LED)

Table 1 – Global and Indian studies on prevalence and diagnostic tests used for FGTB.

Sr No	Author (s), (Year)	Place	Study design	No. of women	Population characteristic	Sample	Test used	Prevalence of Genital TB (%)
1	Garg et al, 2018[9]	Uttar Pradesh India	Prospective	81	Infertile	Endometrial biopsy	HPE, GeneXpert	1.23
2	Farhana et al, 2018[10]	Brazil	prospective	87	Women suspected of tuberculosis	Endometrial biopsies. Fluid from the pouch of Douglas	ZN Stain, culture. Xpert MTB/RIF Assay	8.05
3	Saxena R et al,2017[11]	Varanasi India	Prospective	62	Tubal factor infertility	Endometrial biopsy	ZN Stain, culture, BACTEC, GeneXpert	11.62
4	Tal et al, 2017[12]	North east of US	Prospective	326	Infertility	Blood. Endometrial biopsy	QTB gold ZN stain PCR and culture	7.7
5	Shende et al, 2017[13]	Mumbai India	Prospective	120	Infertile	Endometrial biopsy	HPE, PCR	27
6	Guru et al, 2017[14]	Mumbai India	Prospective	30	Infertile	Endometrial biopsy	HPE	22.85
7	Rajaram et al 2016[15]	Delhi India	Prospective	50	Chronic pelvic pain	Endometrial biopsy	PCR, Culture, BACTEC	34
8	Ohri et al, 2016[16]	Karad India	Prospective	50	Infertile	Endometrial biopsy	ZN Stain, HPE,PCR	18
9	Sethi et al 2016[17]	Chandigarh India	Prospective	300	Infertile	Endometrial biopsy	ZN Stain, Culture, HPE, PCR, LAMP	21.70
10	Gautam et al, 2016[18]	Jaipur India	Prospective	50	Infertile	Endometrial biopsy	PCR	10
11	Al eryania et al 2015[19]	Yemen	prospective	151	Tubal factor infertility	Biopsy during laparotomy Endometrial curettage	Culture HPE PCR	31.10
12	Rao et al, 2013[20]	Hyderabad India	Retrospective & Prospective	1102	Infertile	Endometrial curettage	ZN Stain, LJ culture, Liquid culture, Line probe assay	2.08
13	Sankar et al 2012[21]	New Delhi India	Prospective	620	Infertile	Endometrial curettage sample	ZN Stain, HPE, Culture, Multiplex, PCR	25.48
14	Shahazad et al, 2012[22]	Pakistan	Retrospective	150	Infertile	Endometrial biopsy	HPE, HSG	15.30
15	Kohli et al, 2011[23]	New Delhi India	Prospective	100	Infertile	Endometrial curettage	ZN Stain, Culture, HPE, PCR	13
16	Nadgouda et al, 2010[24]	Karnataka India	Prospective	170	Infertile	Endometrial biopsy	Culture, PCR, HPE, HSG, USG	10
17	Kulshrestha et al, 2011[25]	New Delhi India	Prospective	196	Infertile	Endometrial aspiration Peritoneal washing	ZN Stain, culture, HPE, PCR	60.20
18	Jindal et al, 2010[26]	Chandigarh India	Prospective	162	Infertile	Endometrial biopsy	PCR	32.09

Table 2 – Samples used for diagnosis of FGTB by Molecular methods.

Author (s), (Year)	Place	Study design	No. of women	Population characteristic	Sample	Prevalence of Genital TB (%)
Bhanothu et al,2014[27]	Hyderabad	Prospective Case control	302	Infertile	Endometrial tissue biopsies (ETBs)	49.5
					Ovarian tissue biopsies (OTBs)	33.17
					Pelvic aspirated fluids (PAFs)	5.44
Patil AD et al, 2015[28]	Mumbai	Cross sectional	123	Infertile	Menstrual blood	0.8
Kulshrestha et al 2011[25]	New Delhi	Prospective	196	Infertile	Endometrial aspiration (EA)	41.3
					Peritoneal washings	8
Thangappah et al, 2018[29]	Chennai	Prospective	173	Infertile	POD aspirate	19.8
					Urine	7.7
Rana T et al, 2011[30]	New Delhi	Prospective	143	Infertile	Endometrial aspirate (EA)	42.65
					Peritoneal fluid/peritoneal washing (PF/PW)	9.57
					Cornual biopsy (CB)	33.33

microscopes. Apart from ZN staining, Kashyap et al in 2013 has compared various other staining techniques such as Gabbett staining, fluorescent staining and haemotoxylin and eosin[HE] staining for bacteriological diagnosis of FGTB. In this study Gabbet cold staining method was more cost effective and time saving as compared to Ziehl Neelsen staining. Fluorescent and HE staining also had higher sensitivity and comparable specificity as compared to ZN staining.[31] Cold staining methods such as Gabbett staining and modified cold staining have also been found to be more technically easier, faster and accurate for diagnosis of pulmonary tuberculosis by Abdelaziz et al but their utility in diagnosis of FGTB is unexplored.[32] Even with the newer staining techniques, the disadvantages of sensitivity persists and therefore technique of staining can never be forerunners in the diagnosis of FGTB.

3.3. *Culture methods*

Isolation of Mycobacteria from clinical specimen by culture still remains gold standard for diagnosis of tuberculosis as well as its utility for drug sensitivity testing is known. Culture for mycobacteria can be performed on conventional egg based solid media such as Lowenstein Jenson (LJ) medium and agar based 7H10 or 7H11 broth and liquid media like Krischner or Middlebrook 7H9 broth. Culture using conventional media can take 6 weeks or more due to the slow growth of *Mycobacterium tuberculosis*.

Various rapid methods are now available which can detect mycobacterial growth in as early as 2 weeks.

3.3.1. *BACTEC 460 radiometric culture system*

In this broth-based method for mycobacteria detection, the organism metabolize the C-labeled substrates and release radioactively labeled CO_2 in the atmosphere which is detected by the instrument. BACTEC 460 showed a sensitivity of 40% with a specificity of 90% for detection of FGTB and combination of BACTEC 460 with PCR increases the sensitivity upto 52%.[33] Despite better sensitivity than staining and reduced time for detection, this method has certain disadvantages which include cost, cross contamination, risk of needle stick injury and use of radioactive material which can be hazardous.[34]

3.3.2. *BACTEC MGIT 960 system*

It is a non-radioactive, non-invasive liquid culture system for culture of *M. tuberculosis* complex. Culture tube contains Middlebrook 7H9 broth and a fluorescent compound embedded in a silicone sensor. O_2 consumption by organism present in the medium are detected as an increase in fluorescence. A recent study by Jindal N et al in 2018 reported that the detection rates of FGTB using MGIT culture was 46.7% but this study suggested that a combination of MGIT and conventional LJ cultures do not provide any additional advantage for diagnosis of FGTB.[35]

3.3.3. *MB/Bact system*

This recent system is based on the colorimetric detection of CO_2. It had slightly longer time for detection of growth as compared to BACTEC 460 system. Reported sensitivity values for the MB/BacT ALERT 3D System is 78% which is less

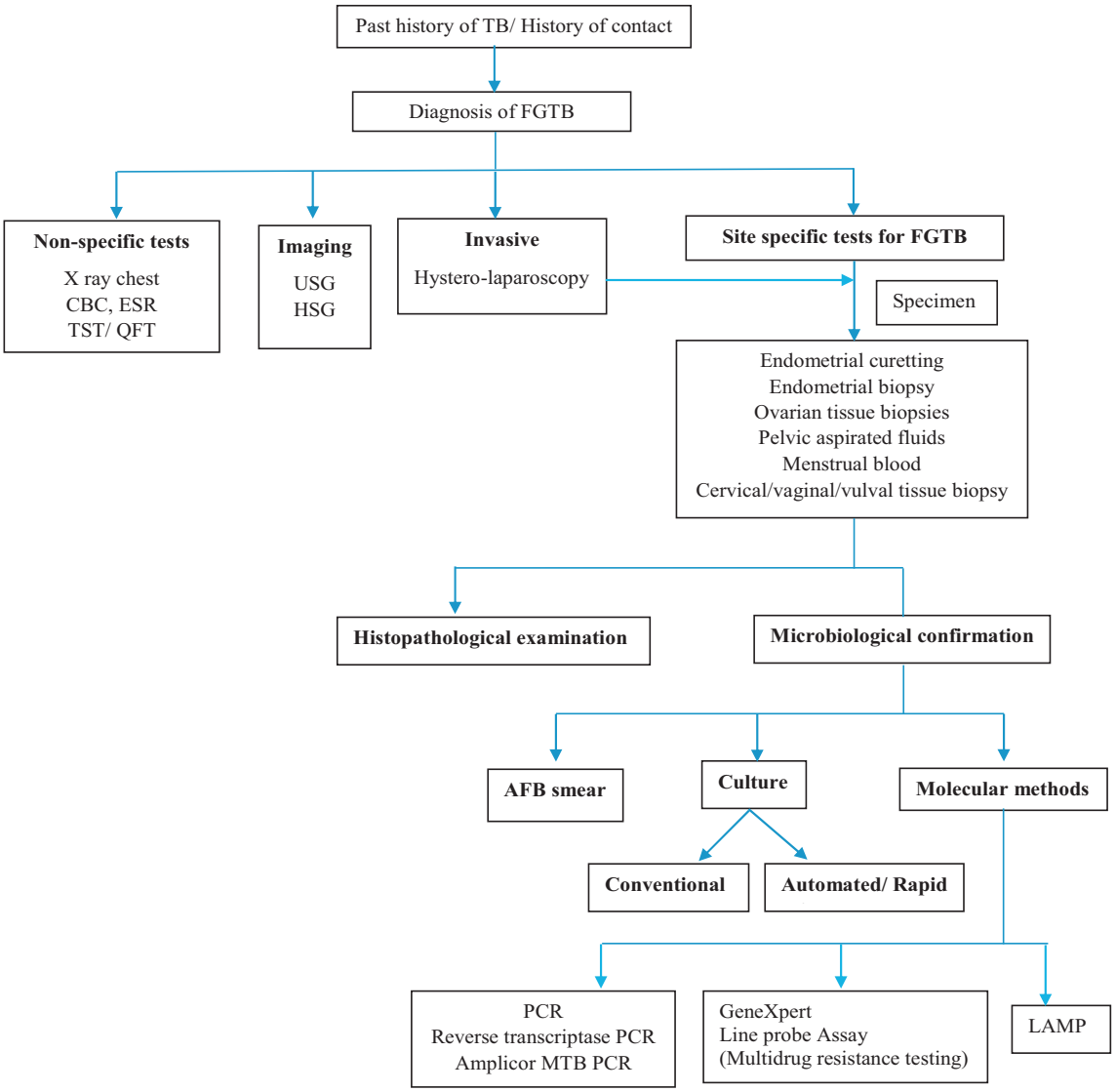

Fig. 1 – Diagnostic flowchart of FGTB.

sensitive than BACTEC MGIT 960 as described by Sorlozano A et al in their study comparing 3 different culture media for isolation of tubercular mycobacteria.[36]

3.3.4. *Liquid based culture for TB using Versa TREK*

Versa TREK is the FDA approved machine used for liquid based culture for Tuberculosis. Special bottles called Myco bottles are used for the culture. In a study by Patil A et al 2015, *Mycobacterium tuberculosis* was detected in 0.8 per cent and Mycobacterium other than Tuberculosis (MOTT) was detected in 2.43 per cent menstrual blood culture from infertile women using Versa TREK.[28]

There are certain advantages of liquid culture media over solid media. These include better sensitivity, ability to test drug susceptibility patterns and identification of Mycobacterium species.[6] Though cultures are cornerstone in definitive diagnosis of genital tuberculosis it has limitations in terms of time required in weeks to label them as positive or negative which leads to treatment delays.

Other rapid culture methods are also available like microcolony detection on solid media (MODS), septi-check AFB method, ESP II culture system, microscopic observation of broth culture. Their sensitivity and specificity in diagnosis of FGTB has not been studied in literature.

3.4. *Identification of mycobacteria from culture*

As there is difference in treatment of Non tuberculous mycobacterial (NTM) infections and *Mycobacterium tuberculosis* complex infection, species identification of mycobacterial clinical isolates is necessary. Various techniques available for species identification like conventional methods based on biochemical tests, antibody-based assays like HPLC, matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) and Lateral Flow Immunochromatography (Rapid strip test). Molecular assays like AccuProbe test, PCR restriction enzyme analysis DNA chips (DNA-microarrays) are promising.

For phenotypic drug susceptibility testing (DST), mycobacteria are often initially grown in a variety of solid or liquid culture media. DST using commercial liquid culture systems like **BACTEC MGIT** requires less time around 9–10 days as compared to 4–8 weeks required for DST using solid media. Thus, drug susceptibility testing using rapid culture method can improve patient management.[8]

3.5. *Non culture based methods*

3.5.1. *Lipoarabinomannan assay*

The commercially available TB LAM test detects the lipoarabinomannan (LAM) antigen from *Mycobacterium tuberculosis* in urine of patients with pulmonary and extra-pulmonary TB. The detection of mycobacterial lipoarabinomannan (LAM) antigen in urine have emerged as potential point-of-care tests for tuberculosis (TB). But its utility in genital tuberculosis is highly limited as appears to be present only in people with active TB disease.[37]

3.5.2. *Serology*

Due to inconsistent nature of commercially available serological test and wide variation in sensitivity and specificity, WHO has banned the usage of serological tests in individuals suspected of any form of active TB, regardless of their HIV status.[38]

3.6. *Molecular diagnostic tests*

3.6.1. *Polymerase chain reaction (PCR) test*

PCR is a more rapid, sensitive and specific method as compared to culture and histopathology for diagnosis of genital tuberculosis.[6] One of the major disadvantages of PCR is the inability to detect a difference between viable and nonviable organisms. Therefore, the test can remain positive for longer periods in patients who are taking anti-TB medications or who have completed TB treatment. False-negative results may occur because of the inefficient extraction of the DNA due to low mycobacterial numbers or the presence of PCR inhibitors. As the uniplex PCR detects single target gene, Sankar et al did a study in 2012 to understand the usefulness of multiplex PCR in the diagnosis of genital tuberculosis.[21] The major advantage of multiplex PCR was the ability differentiate between *M. tuberculosis*, *M. kansasii*, *M. avium* complex, and other nontuberculous mycobacteria (NTM) in a single tube and in a single gel electrophoresis run.[21] In a study by Bhanothu V et al, 2014, multi-gene/multi-primer PCR method was found to have a much higher sensitivity of 99.01% with 19 kDa antigen (131bp) gene and a specificity of 100%, resulting in a positive predictive value of 100% and a negative predictive value of 98.03%.[27] There is need to undertake more studies using multiplex PCR or multigene PCR for diagnosis of genital tuberculosis before any conclusions are drawn.

3.6.2. *Amplicor MTB Polymerase chain reaction*

It amplifies a portion of the 16S ribosomal RNA gene that contains a sequence that hybridizes with an oligonucleotide probe specific for MTB complex bacteria. The sensitivity, specificity, positive predictive value, and negative predictive value for the AMPLICOR MTB PCR test when compared with the confirmed clinical diagnosis of TB were 58.3%, 99.5%, 87.5%, and 97.4% respectively.[39] However, this assay is validated only for respiratory samples and has limited use in non-respiratory samples.

3.6.3. *Reverse transcriptase PCR*

Rana et al used reverse transcriptase for diagnosis of genital tuberculosis in 200 infertile patients at All India Institute of Medical Sciences (AIIMS), New Delhi. This test was positive in 2.8% of samples. The main highlight of this test was its ability to detect active infection as it was hundred per cent in concordant to culture in LJ medium. Therefore, it can be used in cases where active infection is suspected and culture is unavailable.[30]

3.6.4. *Gene-Xpert (Xpert MTB/RIF assay)*

The Xpert is a cartridge-based assay that uses heminested real-time PCR to amplify a *Mycobacterium tuberculosis* (MTB)-specific sequence of the rpoB gene with molecular beacons. Using culture as gold standard, it has a high specificity though low sensitivity.[40] This is among the recent test used by Garg et al, Farhana et al and Saxena et al for the diagnosis of genital tuberculosis.[9–11] Gene-Xpert has the advantage of detecting tuberculosis and rifampicin resistance within two hours with minimal hand on technical time.[10] However, the disadvantages of cost, contamination of endometrial samples by blood which could be inhibitory for Xpert MTB, as well as not detecting resistance to other antimicrobial drugs exist. Despite these, the molecular test certainly holds great potential by early detection of genital tuberculosis.

3.6.5. *LAMP*

LAMP stands for loop-mediated isothermal amplification. It is faster (about 40 minutes) and less expensive than Xpert TB. LAMP is more sensitive than smear microscopy, with a sensitivity of 40.3%–42.2% in smear-negative samples. However, this test cannot detect drug resistance and requires several manual steps. A meta-analysis done by Yu G et al, 2019 to observe the diagnostic efficacy of LAMP for extrapulmonary tuberculosis determined that sensitivity and specificity of LAMP for the detection of EPTB was 99% and 77%, respectively, which further varies with the type of specimen used.[41] Sethi et al did the first study in India to evaluate loop-mediated isothermal amplification (LAMP) technique for diagnosis of FGTB. Results of LAMP and PCR have shown good concordance, and thus, in developing countries with limited resources LAMP can act as an alternative to expensive PCR.[17]

3.6.6. *MTD-2*. The Gen-Probe Amplified *Mycobacterium Tuberculosis* Direct Test (MTD) has been widely used as a rapid test for the identification of *Mycobacterium tuberculosis*. This amplified nucleic acid probe test has been used in very few studies for diagnosis of genital tuberculosis. A study done by Patil A in 2015 used MDT test for diagnosis of genital tuberculosis using 123 menstrual blood samples of infertile women. In this study none of them were positive by MTD test.[28] False negative results are concern due to presence of inhibitors of the AMTD amplification reaction in clinical specimens.[42] The studies using MTD-2 are inadequate to draw meaningful conclusion from them.

3.6.7. *Molecular line probe assays*

The line probe assays (LPA) have been endorsed by the World Health Organization for the rapid detection of multidrug resistant TB. Adoption of line probe assays does not eliminate the need for conventional culture and drug sensitivity testing. Rao MS et al used line Probe Assay for drug sensitivity testing of confirmed isolates from patients with female genital tuberculosis.[20]

3.7. *Immunological tests*

Diagnostic role of immunological test is controversial in Female genital tuberculosis. The tuberculosis skin test (TST) has limited utility in diagnosis of genital tuberculosis because of its poor sensitivity.[8,42]

The Interferon gamma release assays (IGRAs) have an excellent specificity (99.4%) that is unaffected by BCG vaccination. They detect the presence of cellular immune responses toward MTB-specific antigens.[43] T-SPOT.TB is an enzyme-linked immunospot (Elispot) assay, a type of IGRA. Liu Xet al, 2016, suggested that T-SPOT.TB could be considered as a potential triage test for FGTB, which is rapid, practical and appears to have high sensitivity of 94% and 76% specificity.[44] QuantiFERON-TB test is based on detection in serum of the release of IFN-gamma on stimulation of sensitized T cells by antigens of *M. tuberculosis*. QuantiFERON-TB Gold (QFN Gold) test is a more definitive form of QFT. It uses antigens that are highly precise to MTB. A newer version of QFT, the QuantiFERON-TB Gold Plus (QFT-Plus), was approved by the United States FDA in June 2017. The QFT-Plus differs from QFT by the addition of a fourth tube designed to measure interferon gamma released from CD8 cytotoxic lymphocytes. There is low correlation between IGRA and DNA-PCR for evaluation of sub-clinical GTB in patients with Unexplained Infertility.[43]

3.8. *Comparison of various test used for diagnosis of female genital tuberculosis*

Studies done with the aim to compare the sensitivity and specificity of different methods i.e histopathological examination (HPE), acid-fast bacilli (AFB) smear, Lowenstein-Jensen (LJ) culture, rapid culture and polymerase chain reaction (PCR) in diagnosing genital tuberculosis are enumerated in Table 3.[29,15,17,27,45] This literature suggests that conventional methods ZN stain, culture HPE culture have low sensitivity in diagnosing FGTB as compared to molecular tests. Sensitivities of all the tests in a study by Bhanothu V et al are higher than other studies, as the study population were infertile women suspected of having FGTB on laparoscopic examination.[27] Overall, PCR has better sensitivity but newer methods like LAMP and Gene expert are under evaluation and look promising.

3.9. *Combination of tests/algorithm*

Though various tests are available for diagnosis of FGTB, diagnostic dilemma still exists. Thus, high degree of clinical suspicion, suggestive findings from laparoscopy or imaging and microbiological or histopathological correlation is needed for correct diagnosis and management of FGTB. The results of PCR should be interpreted cautiously as there is an issue of false positivity and false negativity in PCR. False positive results can occur due to contamination or presence of dead *Mycobacterium tuberculosis* bacilli in the clinical specimen.[45] While reasons for false negativity are paucibacillary nature of the specimen, improper extraction of sample or presence of PCR inhibitors.[45] Development of multiple diagnostic algorithms for diagnosis of FGTB has been initiated.[8] Index TB guidelines on extrapulmonary tuberculosis, an initiative of Central TB Division Ministry of Health and Family Welfare, Government of India and the WHO elaborates a series of investigations for the diagnosis of FGTB. The guidelines mention that the diagnosis of FGTB should be made if there is laparoscopic appearance typical for FGTB or microbiological confirmation of gynecological specimen in the form of microscopy (AFB) or culture positive for MTB, or histopathological findings consistent with FGTB.[48,49]

Despite that, the diagnostic algorithms to detect FGTB is still not well defined. There is need to do elaborate work to develop and strengthen these algorithms which are reproducible and viable across all health systems of developing countries, depending on the infrastructures and manpower.

4. Discussion

Despite availability of molecular methods since decades, the diagnostic dilemma related to FGTB still exists. Any diagnostic method used to detect genital TB should be sensitive enough to diagnose the disease in early stages, so as to initiate appropriate treatment. Using laparoscopy, hysteroscopy, hysterosalpingography as adjuvants, multiple studies have been done in developing countries to diagnose FGTB using various microbiological tests. Arpitha et al[2] and Mala et al[46] have tried to assess the comparative utility of laparoscopy with routinely used microbiological tests. These studies suggest that though culture and molecular tests are invaluable contributors in the diagnosis of FGTB, but laparoscopy definitely improves the potential to diagnose the disease in

Table 3 – Sensitivity and specificity of tests used for diagnosis of FGTB.

Author, Year	Sensitivity (%)				Specificity (%)			
	ZN stain	culture	HPE	PCR	ZN stain	culture	HPE	PCR
Thangappah RBP et al, 2018[29]	6.7	6.6	8.2	44.3	98.9	100	100	80.4
Rajaram S et al, 2016[15]	5.88	23.53	17.65	76.97	100	100	100	96.97
Sethi S et al, 2016[17]	2.94	10.29	8.82	95.59	100	100	100	100
Bhanothu V et al, 2014[27]	21.78	42.08	51.48	99.01	100	99	99	100
Thangappah RBP et al, 2011[45]	–	7.14	10.7	57.1	–	100	100	90.5

suspected women. Nucleic acid amplification tests like LAMP and Xpert MTB/RIF are now being explored for early diagnosis of FGTB as reported by Sethi et al,[17] Sharma et al[40] and Garg et al[9] but cost and availability of infrastructure are the major limitations in resource poor settings.

Due to its diverse gynecological presenting symptoms, a strong clinical suspicion still makes the backbone for diagnosis of FGTB. But, the clinical screening for FGTB should not only be limited to women suffering from infertility but also should include women with other reproductive morbidities.[15] All levels of health care providers addressing women concerns should be aware of these varied clinical presentations and recent advances in diagnostic tests for FGTB which will help in early detection and treatment. Due to increased burden of MDR TB in developing countries, molecular testing of multidrug resistance should be done in FGTB cases with various clinical presentations like tubo-ovarian abscess not responding to anti-tubercular treatment.[47]

Though newer methods like whole genome sequencing, specimen transport mediated technology, mycobacterium load detection assay and molecular diagnosis of multidrug resistance tuberculosis are among the recent approaches for molecular detection of pulmonary tuberculosis but their potential to detect genital tuberculosis is yet to be addressed.

High index of clinical suspicion and combination of available tests which complement each other should define these algorithms for early diagnosis of FGTB, which can prevent long term reproductive morbidity.

5. Limitation

This review has few limitations. We are restricting the review to published articles between January 2009 and January 2019. The data reviewed is obtained from studies with different setting and different methods are used for diagnosis of female genital tuberculosis in them. Most of the studies rely on PCR for diagnosis, but higher incidence of false positivity mentioned by few studies raise the question of true prevalence.

Declaration of Competing Interest

There are no conflicts of interest.

Acknowledgement

We acknowledge the encouragement and mentorship of Dr Smita D Mahale, Director ICMR-NIRRH.

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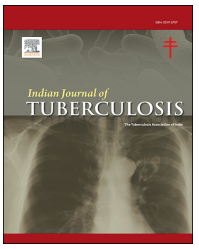

Review article

Risk factors of tuberculosis infection among health care workers: A meta-analysis

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ARTICLE INFO

Article history:
Received 23 July 2019
Accepted 11 October 2019
Available online 18 October 2019

Keywords:
Tuberculosis
Health care workers
Risk factor
Meta-analysis

ABSTRACT

Backgrounds: Health care workers (HCWs) are globally known to have high risk of tuberculosis (TB) infection while risk factors of TB infections among HCWs are still inconclusive.
Objectives: To perform a meta-analysis in effort to identify risk factors of TB infection among HCWs.
Methods: A meta-analysis was conducted between February and July 2019. Papers were searched in Pubmed, Embase, Cochrane, and Web of science and information of interest were extracted. The correlation and effect estimation were analyzed using random or fixed effect model.
Results: A total of 12 studies consisting of 2871 cases and 15,673 controls were included and six risk factors were available for meta-analysis. Cumulative calculation found that age, working duration, and types of job were significant risk factor of TB infection while gender, active TB contact, and types of workplace were not associated significantly with TB infection among HCWs. Our pooled data revealed that decreased risk of TB infection was observed in age less than 30 years (age < 30 years *vs*. age ≥ 30 years) and working duration less than five years (working duration < 5 years *vs*. ≥5 years). Being more than 40 years, working more than 10 years, and being physicians increased the risk of TB infection significantly compared to age ≤40 years, working duration ≤10 years, and other job types, respectively.
Conclusions: Our meta-analysis has identified the significant risk factors of TB infection among HCWs. Our results may be useful for establishing future TB prevention program among HCWs.

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https://doi.org/10.1016/j.ijtb.2019.10.003
0019-5707/

1. Introduction

Tuberculosis (TB), an ancient disease affecting human population for more than 4000 years, is a leading cause of morbidity and mortality in developing countries and remains the main health problem worldwide.[1,2] The global TB incidence is 140 per 100,000 population, ranges between 27 per 100,000 population in United State and 554 per 100,000 population in the Philippines.[3] The management of TB has been well established by World Health Organization (WHO) and it consists of six points: (1) expanding and enhancing high-quality directly observed treatment short-course (DOTS); (2) resolving some challenges such as TB/human immunodeficiency virus (TB/HIV), multidrug-resistant TB (MDR-TB), and other challenges; (3) contributing to the strengthening of health care systems; (4) involving all care providers; (5) strengthening or empowering patients with TB; and (6) supporting and promoting research.[4] The management of TB is complex, requires a long time follow up with high cost expenditure. The average costs incurred by a patient for treatment and diagnosis of TB ranged between $55 and $8198 in low- and middle-income countries.[5] One of the main problem in TB management is disease transmission in which TB is transmitted by airborne transmission making transmission of this disease facilely affects wide population.[6]

One of specific populations having high risk of TB infection is health care workers (HCWs). This because their job requires frequent contacts with TB patients during TB treatment and prevention.[7] A study found that HCWs had 3.1-fold higher risk of TB infection compared to working in non-health care facility.[8] A previous meta-analysis confirmed that compared to general population, HCWs had higher risk for TB infection.[9] The incidence of TB infection among HCWs ranged from 25 to 5361 per 100,000 HCWs.[10,11] Because of this condition, the prevention of disease transmission among HCWs is required to be a priority, including identification of specific risk factors for TB transmission. Studies have reported the potential risk factors among HCWs, such as age, gender, duration of work, education, types of job, job location, income, and frequent TB contact.[12–23] However, conflicting results were observed across the studies.

The objective of this meta-analysis was to assess the risk factor of TB infection among HCWs in order to provide solid evidence that it might be useful to establish specific TB prevention program among HCWs.

2. Methods

2.1. Study design

A meta-analysis was conducted between 05 February and 12 July 2019 to assess the risk factors of TB infection among HCWs. Papers published in Pubmed, Embase, Cochrane, and Web of Science were collected to determine odd ratio (OR) and 95% confidence interval (95% CI) either using fixed or random effect model. A Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) checklist was used to guide the study.[24] Moreover, the design of our present study was also adapted from our previous meta-analyses.[25–35]

2.2. Search strategy

A comprehensive searching up to 12 July 2019 in Pubmed, Embase, Cochrane, and Web of science was undertaken. Combination of the keywords adapted from Medical Subjective Heading (MeSH) terms and text words was used: ["risk factors" OR "predictors"] AND ["tuberculosis infection" or "TB infection" or "TBC infection"] AND ["health care workers" or "HCWs"]. No language restriction was applied. If articles were written neither in English or Indonesian, a consultation with Language Center of Universitas Syiah Kuala was performed. If case two studies used the same data set, only the study with larger sample size and more up-to-date was included. Furthermore, a manual reference search of relevant studies was also conducted to find additional papers.

2.3. Eligibility criteria

The eligibility criteria for inclusion were: (1) all studies that employed design of retrospective, prospective, cross-sectional, and randomized-controlled trials (RCTs); (2) investigating the risk factors of TB infection among HCWs; and (3) providing data that required for calculation of OR and 95% CI. Papers with irrelevance title and or abstract, family-based study, review and or commentary, incomplete and or ungeneralized data, and having poor quality were excluded.

2.4. Data extraction

The following information was extracted from each study: (1) name of first author; (2) year of publication; (3) country of study population; (5) sample size of case and control groups; and (6) risk factors frequency of case and control groups. Data extraction was carried out by two independent authors (JKF and SP) using a piloted data extraction form. If there was disagreement between two authors, a consensus was performed.

2.5. Assessment of the methodology quality

A Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of papers. Quality evaluation was conducted by two independent authors (JKF and SP). NOS consisted of three factors: patients selection (4 points), the comparability of the groups (2 points), and the ascertainment of the exposure (3 points). The total score ranged from 0 (the worst) to 9 (the best). The quality was interpreted as good (score $\geq$7), moderate (score $\geq$5 to <7), and poor (score $\leq$4).[36] The discrepancy between the two authors was accomplished by consensus.

2.6. Measure outcome

The main outcome measure was TB infection among HCWs. The predictor covariates consisted of age, gender, active TB contact, duration of work, type of job, and type of workplace. Age was classified into <30 years, 30–40 years, and >40 years while duration of work was divided into <5 years, 5–10 years, and >10 years. Type of job was classified into physician, nurse, and other job types (such as pharmacist, laboratory technicians, housekeeper, radiology technicians, administrative,

and other support staff). Type of workplace was categorized as high risk (TB clinic, medical ward, internal medicine, emergency room, radiology, and laboratory department) and low risk (pharmacies, fee charging rooms, and other administrative section).[12] These covariates classifications were established in accordance with initial evaluation of available data presented from included studies.

2.7. Statistical analysis

The significant risk factors of TB infection among HCWs were determined by the calculation of pooled OR and 95% CI. The significance of pooled ORs was determined using Z test ($p < 0.05$ was considered statistically significant). Prior to determine the significant risk factors, data were evaluated for heterogeneity and potential publication bias. For evaluating the heterogeneity, a Q test was performed. If heterogeneity existed ($p < 0.10$), a random effect model was used, otherwise, a fixed effect model was employed. An Egger's test was used to assess publication bias ($p < 0.05$ was considered statistically significant). All data were analyzed using Comprehensive Meta-Analysis (CMA, New Jersey, USA) version 2.1 and Review Manager (Revman Cochrane, London, UK) version 5.3. To prevent analysis errors, statistical analysis was performed by two authors (JKF and SP).

3. Results

3.1. Eligible studies

Initial searching in Pubmed, Embase, Cochrane, and Web of Science found 23,183 papers, of which 23,146 papers were excluded because of irrelevant title and or abstract. A total of 37 papers were included for further review in full text. The additional 25 studies were excluded because of review ($n = 7$), not providing data for calculation of OR and 95% CI ($n = 16$), and having poor quality ($n = 2$). A total of 12 papers was included in our meta-analysis.[12–23] The flowchart of the result of literature search is provided in Fig. 1. While, Baseline characteristics of studies included in our analysis are described in Table 1.

3.2. Risk factors of TB infection

Six risk factors; age, gender, active TB contact, duration of work, type of job, and type of workplace, were compatible for meta-analysis. Five studies assessed age as risk factor for TB infection.[15,18,19,21,23] Of those, three studies were identified having correlation,[15,21,23] while two other studies failed to confirm the correlation.[18,19] Our pooled calculation found that HCWs with age <30 years were associated with decreased risk of TB infection (Fig. 2A) compared to age ≥30 years (OR: 0.56; 95% CI: 0.40–0.80, $p = 0.002$). While, increased risk of TB infection (Fig. 2B) was observed in HCWs with age >40 years compared to age ≤40 years (OR95% CI = 2.09 [1.44–3.03], $p < 0.001$). Moreover, for working duration, we confirmed seven studies available for meta-analysis. Six of them showed significant correlation,[12,15,19,21–23] while another study failed to show the association.[18] Cumulative data identified that decreased risk of TB infection was observed in HCWs with duration of work less than five years (Fig. 3A)compared to ≥5 years (OR95% CI = 0.58 [0.41–0.82], $p = 0.002$). HCWs who working more than >10 years increased the risk for TB infection (Fig. 3B) compared to those working ≤10 years (OR: 1.61; 95% CI: 1.12–2.34, $p = 0.011$). Concerning job type, of eight studies identified, the correlation was found in five studies,[14–16,19,23] while three others showed otherwise.[12,17,22] Our data indicated that only physician was associated with 1.65-fold increased risk of TB infection (Fig. 4). Our data indicated that gender, active contact with TB patients, and type of workplace were not associated with TB infection. Summary of the potential risk factors of TB infection among HCWs is provided in Table 2.

3.3. Source of heterogeneity and publication bias

Heterogeneity was found within groups of gender, contact with TB patients, type of job and type of workplace, and therefore, data were analyzed using random effect model. Heterogeneity was found for <30 years and >40 years group, while no evidence of heterogeneity among HCWs within 30–40 years group. Evidence for heterogeneity was found HCWs with duration of work <5 years and >10 years, and therefore random effect model was employed while for those who had duration of work 5–10 years, the data were assessed using fixed effect model. Type of job were analyzed using fixed effect model due to no heterogeneity of data.

To evaluate publication bias, an Egger test was used and data suggested that there was potential publication bias within age 30–40 years group and miscellaneous type of job.

4. Discussion

Our entire analyses found that age and working duration remained the potential risk factors for TB infection among HCWs. We disclosed that, compared to age ≤40 years and working duration ≤10 years, age more than 40 years and working duration more than 10 years; 2.09-fold and 1.61-fold, respectively; were associated with increased risk of TB infection among HCWs. While, decreased risk of TB infection, approximately 0.56-fold and 0.58-fold, was observed in HCWs with age less than 30 years and working duration less than five years compared to HCWs with age ≥30 years and working duration ≥five years, respectively.

Until now, no meta-analysis reporting the risk factors of TB infection among HCWs makes we could not compare our results. The explication of our results was a matter of debate and had a very broad scope. However, some possible reasons might be proposed. First, TB infection among HCWs may be governed by duration of exposure to TB patients.[37] In the context of duration of exposure to TB patients, younger and shorter working duration HCWs may have short duration of exposure. While, longer duration of exposure to TB patients may be found in older and longer working duration HCWs. A study found that longer duration of contact with evidence of TB infection was at high risk of the development of active disease in five years.[38] Theoretically, the ability of organism to infect human is impressed by the triangle of infection

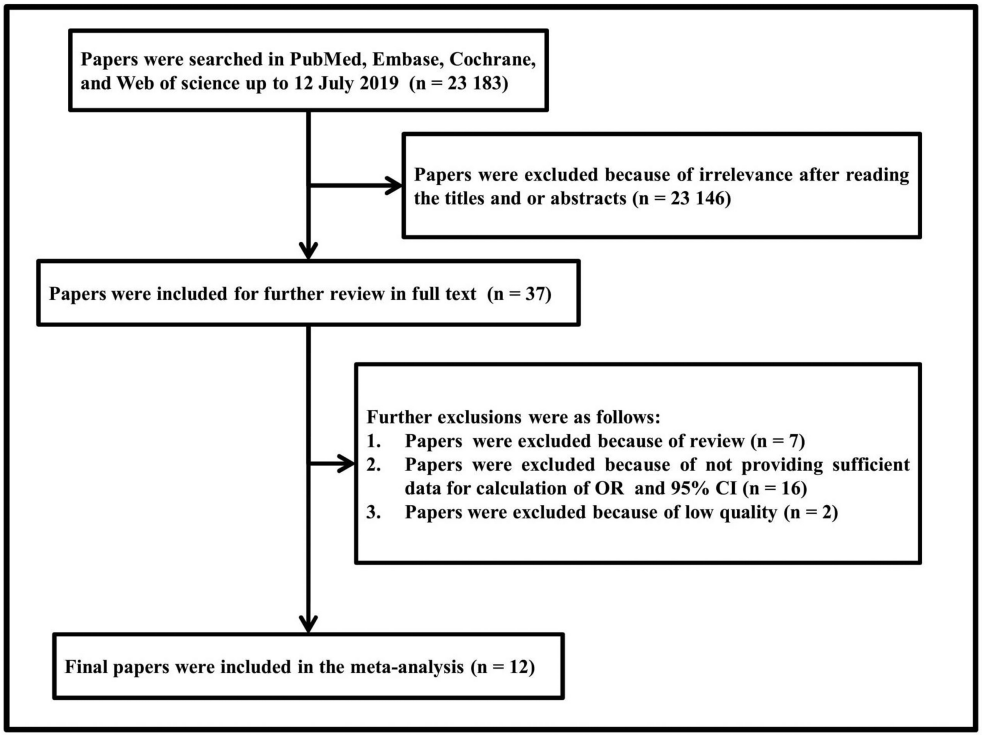

Fig. 1 – A flowchart of eligibility pathway in our study.

Table 1 – Baseline characteristics of studies included in our analysis.

Author & year	Country	Design	Quality	Main results
Agaya et al 2015	Kenya	Cross-sectional	Moderate	Frequent TB contact is associated with increased risk of TB infection.
Aksornchindarat et al 2019	Thailand	Cross-sectional	Moderate	Increased risk of TB infection is found in advanced age, longer working duration, and frequent TB contact.
Bukhary et al 2018	Saudi Arabia	Cross-sectional	Moderate	Increased risk of TB infection is related to longer employment.
Chen et al 2019	China	Cross-sectional	Moderate	Increased risk of TB infection is associated with longer working duration and frequent TB contact.
Chu et al 2014	China	Cohort	Good	Nurse is significantly at high risk of TB infection.
Garcell et al 2014	Qatar	Cross-sectional	Moderate	Active contact with TB patients is associated with increased risk of TB infection.
He et al 2010	China	Cross-sectional	Moderate	Advanced age, longer working duration, and frequent TB contact are correlated with increased risk of TB infection.
He et al 2012	China	Cross-sectional	Moderate	Greater age and longer career are associated with increased risk of TB infection.
Ito et al 2015	Japan	Case-control	Moderate	Active contact with TB patients is the risk of TB infection.
Janagond et al 2017	India	Cohort	Good	Advanced age, duration of employment, and working in medical wards or Intensive Care Unit are associated with TB infection.
Mathew et al 2013	India	Case-control	Moderate	Frequent contact with TB patients is the risk of TB infection.
Rafiza et al 2011	Malaysia	Cross-sectional	Moderate	Male, nurse, older age, and frequent contact with TB patients are related to increased risk of TB infection.

Note, TB, tuberculosis.

including the environment, the host, and an infectious agent.[39] Longer duration of exposure means that a large amount of microorganisms was existed to infect the human. In this circumstance, although the host has a good defense, the human may remain having the high risk for infection. Second, poor awareness to TB infection may also have the role for TB infection among HCWs. In HCWs, it had been reported that older HCWs had poorer awareness regarding TB infection than younger.[40] While, awareness concerning TB infection has been proven to be associated with attitude toward the protection of TB infection.[41] A study reported that poor knowledge regarding TB prevention was observed higher in older people,[42] and therefore, the morbidity and mortality of TB was reported higher in this specific population.[43] Third, immunity may play a crucial role for TB infection among HCWs.[44] In the theory of immunity evolution, it is proposed

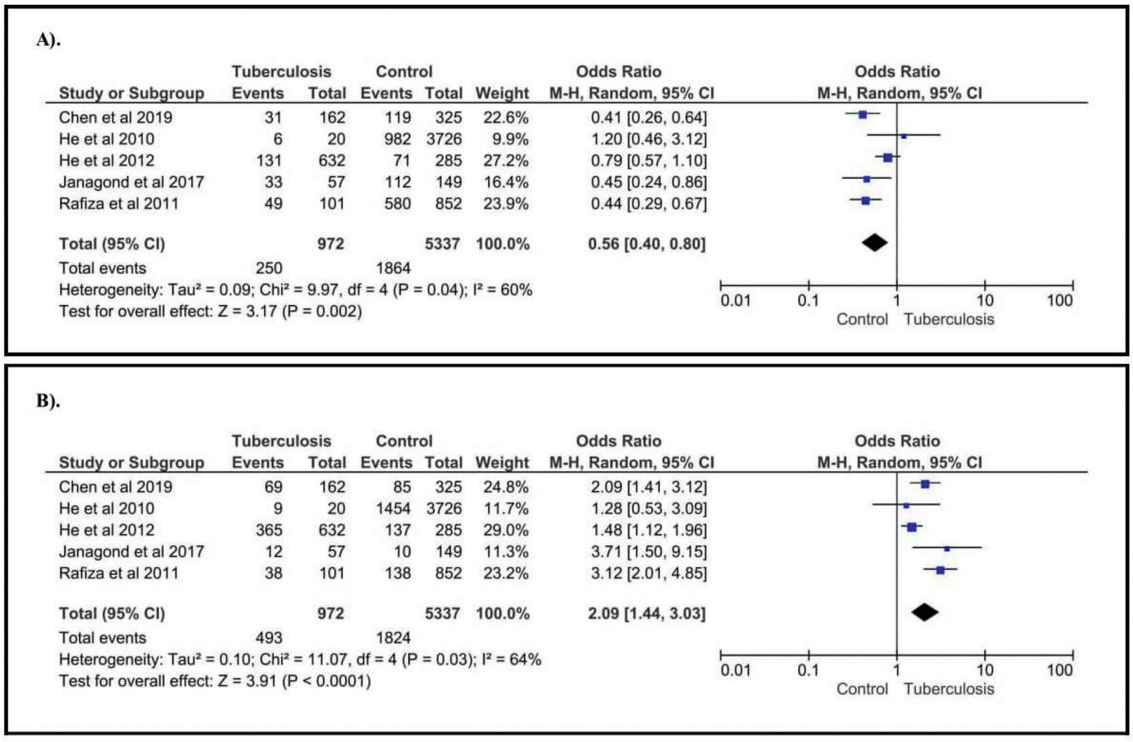

Fig. 2 – Forest plot of the association between age and the risk of TB infection among HCWs. A). Age <30 years *vs.* ≥30 years. B). Age ≥40 years *vs.* <40 years.

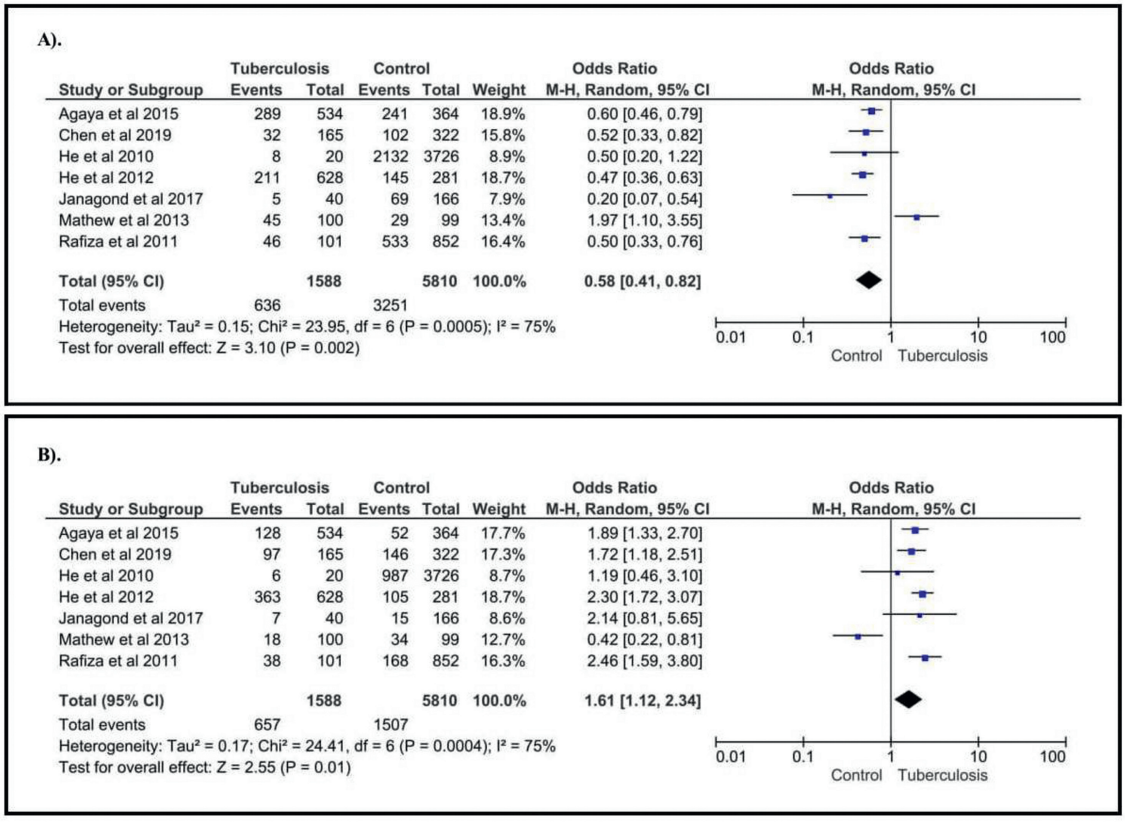

Fig. 3 – Forest plot of the association between duration of work and the risk of TB infection among HCWs. A). Duration of work <5 years *vs.* ≥5 years. B). Duration of work >10 years *vs.* ≤10 years.

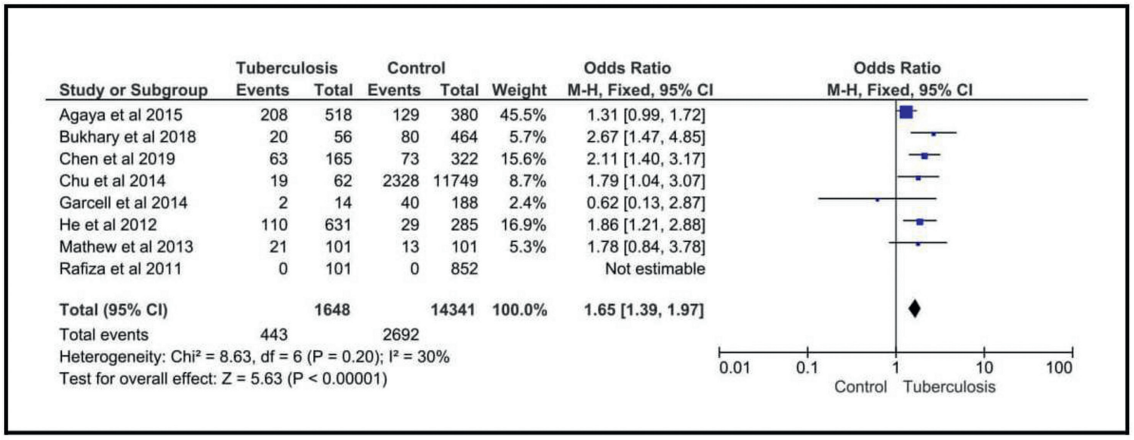

Fig. 4 – Forest plot of the association between job type (physician) and the risk of TB infection.

that the immune response develops with age and it ends with the decline in old age.[45] In this context, HCWs with younger age might have better immunity, and therefore it was related to decreased risk of TB infection. While, older age has been known as one of classical risk factors for TB infection.[37] Subjects with older age might have less immunological protection and therefore they were susceptible for infectious diseases especially TB infection.[46] Moreover, due to less immunological protection, older people with TB were shown to have a higher frequency of atypical features, more adverse drug reactions, and greater TB-related mortality.[47] These explanations may be a benchmark for our results showing that age and working duration were the significant risk factors of TB infection among HCWs.

Additionally, our findings also confirmed that job type was the significant risk factor of TB infection among HCWs. Our combination data revealed that the significant association was only observed in physicians. Our findings found that physicians had 1.67-fold increased risk of TB infection compared to other job types (Fig. 4). Our results were dilemma for health care system. It was a surprising that the physicians, the leader in health care system, obviously were proven to have significant association with increased risk of TB infection. Our results are required to be further investigated. However, some possible reasons may represent our results. First, previous studies had shown that physicians were found correlating with poor awareness regarding infection control especially TB infection.[48,49] In another report, although physicians were reported having good knowledge regarding infection control; however, they had poor practice.[50] Therefore, it was not a surprise if our findings confirmed that physicians were significantly at risk for TB infection. Second, low compliance to use personal protective equipment was also reported in physicians by previous study.[51] Personal protective equipment is the most crucial method for protecting HCWs from potentially fatal infectious disease.[52] Therefore, no adequate protection of physicians and the frequent contact with TB patients may be a fundamental factor governing TB infection among physicians. Third, there is an assumption that, due to their habits, physicians require no protection when they contact with TB patients.[53] This factor may also contribute to the high risk of TB infection among physicians. However, further studies are required to clarify the exact factors contributing for the high incidence of TB infection among physicians.

Interestingly, our findings failed to emphasize active TB contact and job location as the risk factors of TB infection among HCWs (Table 2). Theoretically, these factors should be related to the risk of TB infection, because active TB contact and working in high risk area have put the HCWs in relatively at risk for TB transmission. Active TB contact has been globally known as the classical risk factor of TB infection. Therefore, in the management of TB, one of the crucial recommendations is to perform contact screening for TB among people with close TB contact.[54] In non-HCWs setting, it was reported that close contact with TB patients, ranging from three to six months, had higher rate for TB infection.[55–57] While, in HCWs setting, it had been proposed that, although not supported by data transparency, the high incidence of TB active disease was highly related to HCWs with active TB contact and working in high risk area.[58,59] However, disease transmission is governed by multifactorial. In this context, HCWs with active TB contact and working in high risk area may have high awareness for potentially disease transmission and therefore they may have prepared for the use of personal protective equipment. Furthermore, infection control committee in the hospital may have targeted and emphasized the HCWs in high risk of disease transmission to actively use personal protective equipment. This result might be described by a proverb: "monkeys will not fall because of strong winds, but breeze". These explications may be the cornerstone of our results reporting that active TB contact and working in high risk area were not associated with the risk of TB infection among HCWs.

To the best of our knowledge, our study was the first meta-analysis evaluating the risk of TB infection among HCWs. Identification of HCWs at high risk of TB infection may provide us direct TB-control program to arrange the prevention strategy. Our current study identified age, working duration, and physicians as the significant risk factors of TB infection among HCWs. It has been globally known that active disease of TB infection among HCWs may lead to loss of skilled

Table 2 – Summary of risk factors of TB infection among HCWs.

Risk factors		NS	Model	TB infection		Non-TB infection		OR	95% CI	pH	pE	*p*
				SS	Value	SS	Value					
Age	<30 years	5	Random	972	250 (25.72)	5337	1864 (34.93)	0.56	0.40–0.80	0.0410	0.3020	0.0020
	30–40 years	5	Fixed	972	229 (23.56)	5337	1649 (30.90)	0.87	0.70–1.07	0.5740	<0.0001	0.1880
	>40 years	5	Random	972	493 (50.72)	5337	1824 (34.18)	2.09	1.44–3.03	0.0260	0.3190	<0.0001
Gender	Male	12	Random	2871	1092 (38.04)	15,673	4245 (27.08)	1.24	0.98–1.58	0.0030	0.2860	0.0790
	Female	12	Random	2871	1779 (61.96)	15,673	11,428 (72.92)	0.81	0.64–1.03	0.0030	0.2860	0.0790
Active TB contact	Active contact	5	Random	1408	921 (65.41)	2061	632 (30.66)	1.60	0.81–3.17	<0.0001	0.7180	0.1780
	Non-active contact	5	Random	1408	487 (34.59)	2061	1429 (69.34)	0.63	0.32–1.24	<0.0001	0.7180	0.1780
Duration of work	<5 years	7	Random	1588	636 (40.06)	5810	3251 (55.96)	0.58	0.41–0.82	0.0005	0.3840	0.0020
	5–10 years	7	Fixed	1588	295 (18.58)	5810	1052 (18.11)	1.08	0.89–1.30	0.1440	0.2040	0.4450
	>10 years	7	Random	1588	657 (41.37)	5810	1507 (25.94)	1.61	1.12–2.34	0.0004	0.4090	0.0110
Job type	Physician	7	Fixed	1648	443 (26.88)	14,341	2692 (18.77)	1.65	1.39–1.97	0.1970	0.1650	<0.0001
	Nurse	8	Random	1648	594 (36.04)	14,341	8188 (57.10)	0.98	0.78–1.23	0.0590	0.2220	0.8540
	Others	8	Fixed	1648	611 (37.08)	14,341	3461 (24.13)	0.73	0.62–0.85	0.5060	<0.0001	<0.0001
Job location	High risk	6	Random	953	355 (37.25)	5494	2794 (50.86)	1.49	0.96–2.30	0.0120	0.4280	0.0730
	Low risk	6	Random	953	598 (62.75)	5494	2700 (49.14)	0.67	0.44–1.04	0.0120	0.4280	0.0730

Note, value was presented in *n* (%); NS, number of studies; SS, sample size; TB, tuberculosis; OR, odd ratio; 95% CI, 95% confidence interval; pH, p heterogeneity; pE, p Egger; HCWs, health care workers.

workers. This effect may have the serious impact on the hospital service system, and in a long time, this is very detrimental to the hospital. Therefore, it was clear that, for the near future, the prevention policy including administrative, personal, and engineering controls should target and be implemented to special population including age more than 40 years, working duration more than 10 years, and physicians. The alleviation of the risk of TB infection among HCWs should be a priority.

Several important limitations were identified in our present study. First, some classical TB risk factors including HIV, diabetes mellitus, the use of steroid, and family history of TB were not included and controlled for. Second, since the design of included studies in our analysis was non-RCT, it may yield low-evidence. Therefore, further meta-analysis including only RCT is required. Third, the diagnosis method of studies included in our analysis is not same. Therefore, this may govern study bias. Moreover, fourth, due to small sample size, sub-group analysis was not possible to perform.

5. Conclusions

Our present meta-analysis reveals that decreased risk of TB infection among HCWs are found in age less than 30 years and working duration less than five years compared to age $\geq$30 years and working duration $\geq$5 years. While, some specific populations including age more than 40 years, working duration more than 10 years, and physicians are shown as the susceptible factors of TB infection among HCWs compared to age $\leq$40 years, working duration $\leq$10 years, and other job types. Our results may clarify preliminary data regarding the risk factors of TB infection among HCWs.

Ethical approval and consent to participate

Ethic approval and informed consent were not required in our study.

Consent for publication

Not applicable.

Availability of data and materials

Data used in our study were available on request.

Authors contributions

Idea/concept: SP, JKF. Design: JKF. Control/supervision: TS. Data collection/processing: SP, JKF, FT, AIM, CYR, ORA. Extraction/Analysis/interpretation: SP, JKF, FT, AIM, CYR, ORA. Literature review: SP, JKF. Writing the article: JKF. Critical review: TS. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Conflicts of interest

The authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.10.003.

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INDIAN JOURNAL OF TUBERCULOSIS 67 (2020) 130–132

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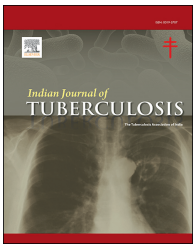

Correspondence

Pulmonary nocardiosis in patient with pulmonary tuberculosis in an immunocompetent male: A rare case report

Pulmonary tuberculosis can occur with other pulmonary diseases caused by opportunistic organisms such as *Nocardia* spp. particularly in immunocompromised patients. Pulmonary Nocardiosis can manifest as acute, subacute, chronic illness. Very few cases from India have reported mixed infection with Tuberculosis. Untreated pulmonary nocardiosis is similar to tuberculosis and *N. asteroids* is the most frequent cause of pulmonary infection in humans (85%).[1] Diagnosis of co-infection at the early stage of the disease could be life -saving.

Here we present a rare case of pulmonary tuberculosis with nocardial co infection in an immunocompetent male. He was admitted for generalized weakness. Later on microbiology lab reported it a case with mixed infection of *Nocardia* and *Mycobacterium tuberculosis*.

A 67 year old male was admitted to our hospital in Feb 2017 with complain of generalized weakness and off and on low grade fever since 1 year. He was a k/c/o DM for 17yrs and was on oral hypoglycemic agents with a good glycemic control. He had an unremarkable family and social history. On Examination he had pallor, low grade fever (99 °F) with mild increase in pulse rate (100b/mt). There was no respiratory distress and his cardiac examination was normal. His complete blood counts showed moderate anemia and leucopenia. Liver function test revealed raised SGOT and alkaline phosphatase.

He was managed conservatively. Pleural fluid was obtained and sent for ADA and routine examination. X ray chest and CECT was performed (Fig. 1a and b, showing features before treatment and Fig. 1c and d after six months of treatment) Sputum examination revealed branching filamentous structures which were confirmed as *Nocardia* spp. after Grams stain and modified AFB stain (Fig. 2a,b and c). He developed high grade fever for which paracetamol and Inj. meropenem was added. On day 6 culture grew *Nocardia* sp. shown in Fig. 2d, which was identified as *N farcinica*. Sputum was found to be negative for AFB on day 1. Repeat sputum was sent which revealed both *Nocardia* and AFB in same smear. Based on high ADA and positive sputum examination for AFB, patient was started on ATT. Septran was added based on culture report showing *Nocardia* spp. growth. Patient started improving and was discharged. A follow up with repeat sputum smear examination for AFB and Nocardia spp after two months was found negative.

In countries like India where tuberculosis is very common, anti-tuberculosis drugs are started on basis of radiology and clinical symptoms. A classic radiographic picture of tuberculosis that is unresponsive to medication should raise the suspicion of Nocardia infection.[1] Nocardiosis, an uncommon infection of the past, is being increasingly reported in recent years with rise of immunosuppressed patients. Most patients have known underlying illness including renal transplantation, human immunodeficiency virus infection, and long-term steroid therapy.[2] Coincidence of pulmonary tuberculosis and nocardiosis increases from 1% for immunocompetent population to 6.25% among HIV-infected patients.[3–5] Diagnosis of pulmonary nocardiosis is dependent on the isolation or demonstration of the organism from respiratory secretions such as sputum or tissue specimens. It has been observed in cases of dual infection that mere ATT is not sufficient to treat mixed infections. Treatment for nocardiosis is to be initiated for complete recovery. Sulfonamides have been the agents of choice for the treatment of nocardiosis, however combination therapy with two or more agents is recommended.[6] A strong suspicion therefore could help in detection by various approaches if patients do not respond completely to ATT. Pulmonary manifestations of nocardiosis are quite similar to pulmonary tuberculosis. Consequently, physicians in endemic regions may treat the patients with compatible symptoms of tuberculosis, despite negative acid fast staining of the sputum.[1] Pulmonary nocardiosis is underdiagnosed or ignored.[1] This underscores the needs to consider pulmonary nocardiosis as a differential diagnosis or as co infection in bronchopulmonary diseases, especially when there is a failure of anti-TB therapy and as a possible cause of human infections.

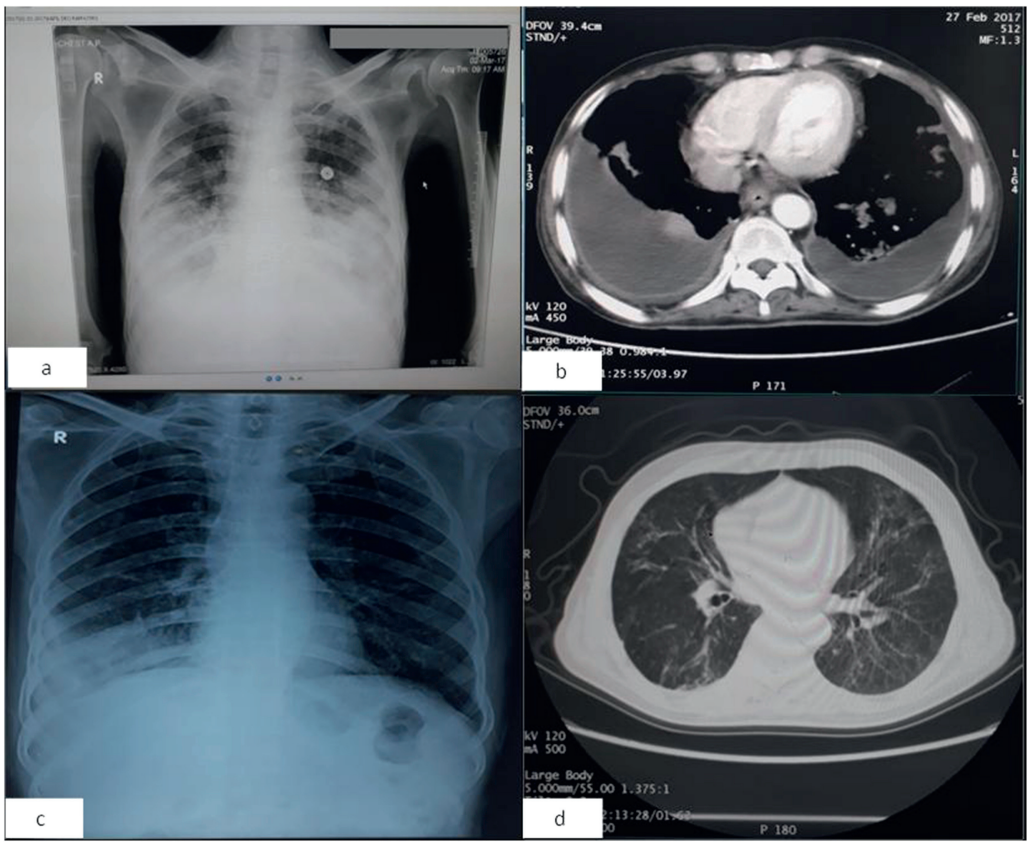

Fig. 1 – a: Chest radiolgraph frontal view showing B/L mid basal haziness with obscured CP angles. b: axial CECT mediastinal window showing B/L pleural effusion with posterobasal dependent consolidation. c: Chest radiograph showing patchy haziness in B/L (Rt > Lt) with obscured CP angles. d: Axial CT lung window showing patchy cosolidation with interstitial thickening.

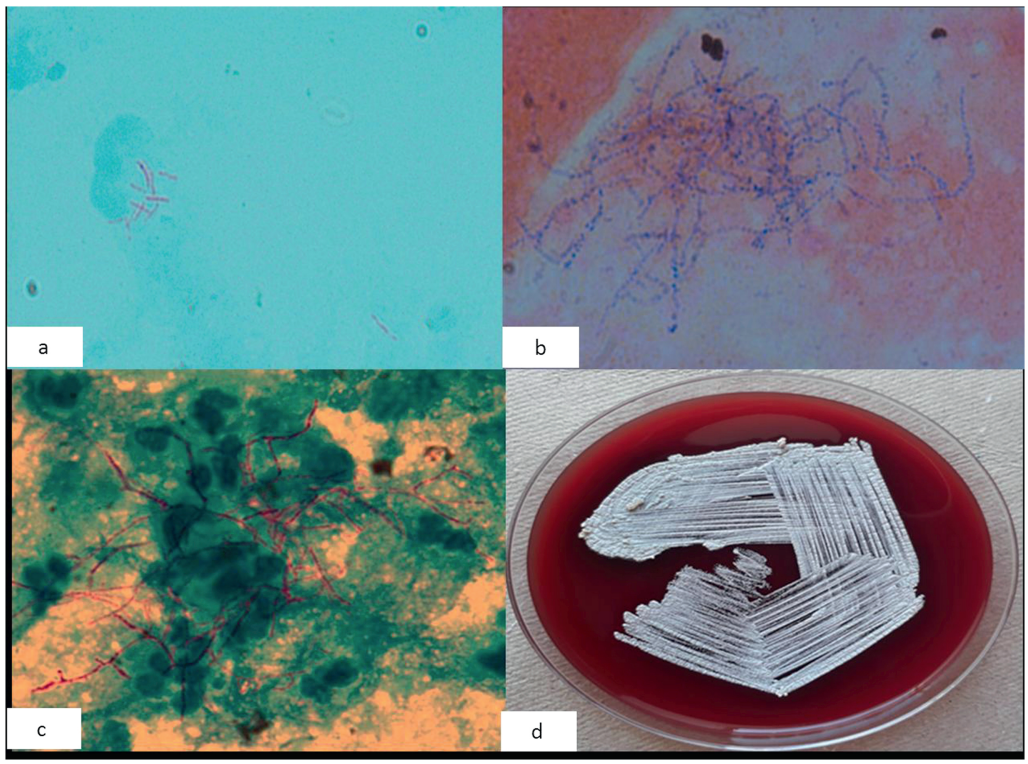

Fig. 2 – a showing Acid Fast Bacilli in the smear. b showing gram positive branching filamentous structure. c showing Acid fast branching filamentous structure. d showing dry white Nocardia colonies on blood agar plate.

Conflicts of interest

The authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.04.003.

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12 October 2018
Available online 18 April 2019

0019-5707/$ – see front matter

https://doi.org/10.1016/j.ijtb.2019.04.003

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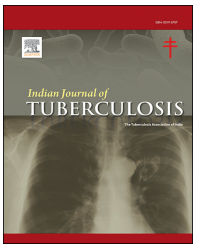

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Rice bodies in the ankle-a case of isolated tubercular tenosynovitis☆

Keywords:
Ultrasound
Magnetic resonance imaging
Tubercular tenosynovitis

ABSTRACT

Countries with tuberculosis as an endemic disease face many challenges. Isolated tubercular tenosynovitis is a rare presentation of extrapulmonary tuberculosis and involvement of the ankle is even rare. We present a case of isolated tubercular tenosynovitis of the ankle, the diagnosis of which was suggested radiologically and confirmed by histopathology. Clinicians dealing with tuberculosis infected patients need to be aware of such rare presentations for proper diagnosis and management.

A 36-year old Indian female, belonging to low socio-economic class presented with a complaint of swelling in the right ankle which gradually increased over 5 months. On examination, a soft, non-tender, dumbbell shaped swelling was palpated without any local rise of temperature with elevated ESR and CRP on laboratory investigations. Radiological examination was advised which revealed a cystic swelling with floating 'rice bodies' on ultrasound (Fig. 1) with normal underlying tendons. The cystic swelling was insinuating between the normal tendons with no flow on doppler study in the 'rice bodies'. MRI of the ankle joint was performed which confirmed the ultrasound findings depicting the 'rice bodies' within a cystic dumbbell shaped swelling with an intact extensor digitorum tendon (Fig. 2) passing through with no effusion in the ankle joint. The 'rice bodies' showed a hypointense signal on both T1 and T2 sequences, suggesting granulomatous tenosynovitis. As tuberculosis is endemic in the Indian subcontinent, tubercular tenosynovitis becomes the first differential diagnosis in cases of suspected granulomatous tenosynovitis. Surgical excision of the swelling was done to relieve the patient's symptoms (Fig. 3). Histopathological analysis of the rice bodies proved them to be tubercular granulomas (Fig. 4). The patient tested negative for any evidence of chest tuberculosis. The patient was started on anti-tubercular treatment and at 6 months follow up, she is asymptomatic.

Musculoskeletal tuberculosis involving the ankle comprises of less than 0.3% of cases of tuberculosis.[1,2] Tuberculosis is an endemic disease in developing nations and can have rare presentations like in this case, awareness about which is of utmost importance for appropriate diagnosis and management. Rice bodies are free shiny particle, synovial in origin, probably arising as a nonspecific response to synovial inflammation.[3] MRI examination helps in accurate pre-operative diagnosis, with the T2 weighted sequence being of utmost importance. The rice bodies in granulomatous inflammation have a low signal on T2 images in the background of hyperintense fluid and are differentiated from synovial chondromatosis in which the unossified cartilage appears more hyperintense. Rice bodies lack the hemosiderin cap when compared to pigmented villonodular synovitis.[4] Ultrasound also helped in characterisation as the surrounding fluid is more anechoic in tubercular tenosynovitis when compared to the hypoechoic soft tissue surrounding in synovial chondromatosis.

Radiological investigations helped in accurate and timely diagnosis of the patient, allowing proper management. This is a rare presentation of extrapulmonary tuberculosis in which clinical examination and radiological investigations provide a safe and definitive treatment and help in prevention of joint destruction.

Disclosure

There are no conflicts of interest.

☆ Author AA (1) conceived the idea of the manuscript. Authors AA and AC prepared the first draft. Author AC was the operating surgeon while AA looked into the radiological aspects of the patient. Author AA (2) undertook the literature review, medical management of the patient and was the primary physician.

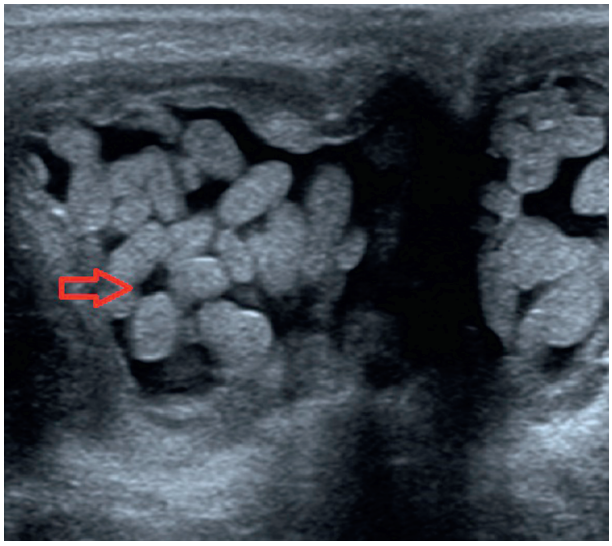

Fig. 1 – Red arrow shows echogenic rice bodies floating in the clear anechoic fluid insinuating around the extensor digitorum tendon.

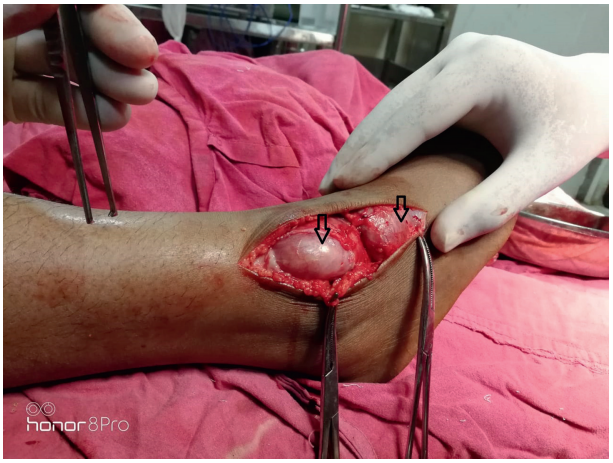

Fig. 3 – Intra-operative picture of the dumbbell shaped cystic swelling.

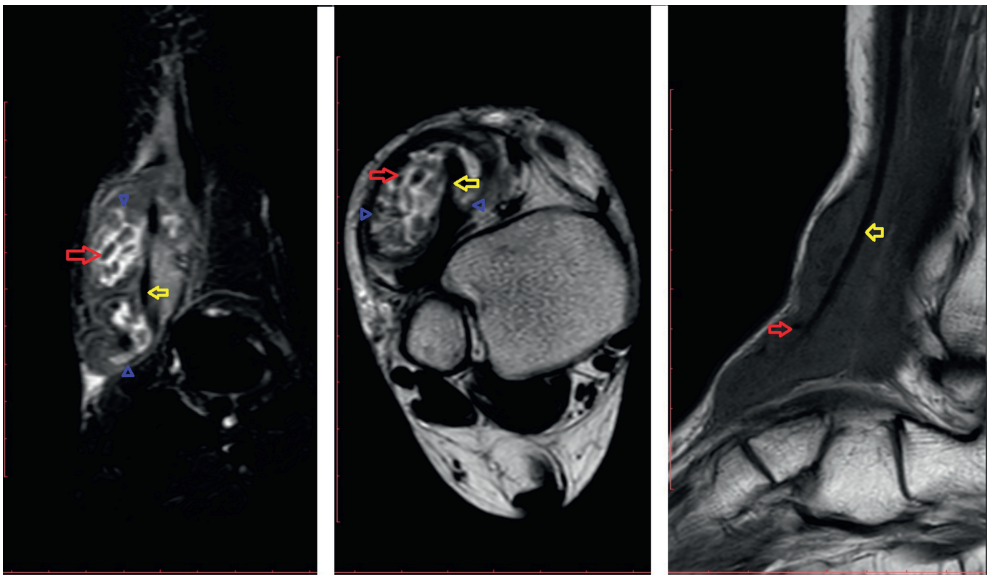

Fig. 2 – MRI shows the hypointense rice bodies (red arrow) on T2 weighted (first two panels) and T1 weighted image (third panel). Between the blue arrowheads is the clear hyperintense fluid contained in a well-defined dumbbell shaped pocket around the extensor digitorum tendon (yellow arrow) with normal signal intensity of the tendon.

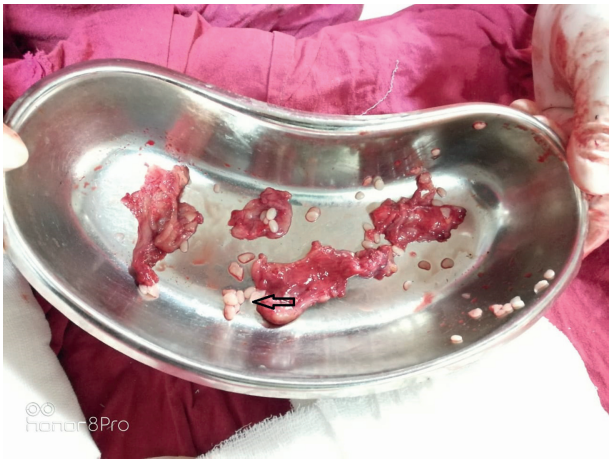

Fig. 4 – Rice bodies excised from the swelling which appear as glistening white structures which on histopathology revealed granulomatous inflammation with giant cells and lymphocytes, suggestive of tubercular granulomas.

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13 April 2019
Available online 18 May 2019

0019-5707/$ – see front matter

https://doi.org/10.1016/j.ijtb.2019.05.002

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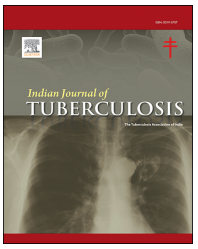

Tuberculous meningitis manifesting with neuroregression in a eleven month child

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ARTICLE INFO

Article history:
Received 21 December 2019
Accepted 1 January 2020
Available online 8 January 2020

Keywords:
Child
Infancy
Neuroimaging
Tubercular meningitis
Milestones

ABSTRACT

Tuberculosis (TB) is a disease of diverse manifestations. In children, neurotuberculosis is the severest form, which when left untreated can have deleterious consequences. There has been reports on pediatric TB meningitis manifesting with fever and seizures, altered sensorium or focal deficits. There are reports on TB meningitis presenting with cognitive decline in adults. We are reporting a eleven month old girl child who presented with acute regression of attained developmental milestones of one month duration as the only presenting complaint and MRI brain revealed basal exudates with hydrocephalus which nailed the diagnosis of tuberculous meningitis. CSF (Cerebro Spinal Fluid) tested by CBNAAT (Cartridge Based Nucleic Acid Amplification Testing) for TB was negative, but gastric aspirate tested for the same, came positive. Tuberculin skin testing was also positive. Chest X-ray was normal. The child had not received BCG (Bacillus Calmette Guerin)vaccine, thereby increasing her risk of complicated TB. The contact couldn't be traced. The child was started on ATT (Anti Tubercular Treatment) as soon as the diagnosis was made and she improved, thus signifying the better outcome with early initiation of ATT. This case reporting is intended to highlight the unusual presentation of TB meningitis in children, which when clinicians are aware of will lead to early treatment and better prognosis.

1. Introduction

Tuberculosis (TB) in children has multitude of presentations. The most severe form of extra-pulmonary TB is Tubercular meningitis, known to have an aggressive course, if left untreated.[1] We are presenting a eleven month girl who had regression of developmental milestones for one month duration and her MRI (Magnetic Resonance imaging) brain led to the diagnosis of Tubercular meningitis.

2. Case report

It was a eleven months old girl child with regression of previously attained developmental milestones of one month duration. The child was first born to non-consanguinous parents with a smooth perinatal transition and was developmentally normal till this presentation. The mother described that the child who was creeping and sitting without support was not able to do so over the last one month and that the child doesn't rollover or crawl now. Other domains were lost

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https://doi.org/10.1016/j.ijtb.2020.01.001

too, with no pincer grasp or reaching out for objects, no social smile and no monosyllables. There was no history of fever or seizures. BCG (Bacillus Calmette Guerin) vaccine was not given at birth. There was no history suggesting contact with TB. On examination, the child was irritable, afebrile, moderately underweight and had neck stiffness. Head size was normal for age. There were no neurological deficits or signs of raised intracranial pressure. There were no significant findings in other systems.

With the above scenario, MRI brain (Fig. 1) was done which revealed basal exudates, non-obstructive hydrocephalus and tubercles in the brain stem suggestive of tubercular meningitis.[3] The child was investigated further with lumbar puncture, and CSF(Cerebro Spinal Fluid) showed moderately elevated protein (173 mg/dl)and a mild decrease in glucose (30 mg/dl), with predominance of lymphocytes (270 cells/cu mm, 90% were lymphocytes). CSF for CB NAAT (Cartridge Based Nucleic Acid Amplification Test) for TB by GeneXpert MTB/Rif came negative, but CB NAAT for TB in resting gastric aspirate came out positive. Chest X-ray was normal, Mantoux test was positive (18mm). Complete blood counts and liver function tests were normal. HIV testing was negative. The child was thus started on treatment as per RNTCP guidelines.[2] Category 1 ATT (Anti Tubercular Treatment) – intensive phase consisting of HRZE (Isoniazid, Rifampicin,Pyrazinamide and Ethambutol) for 2 months, daily regimen, followed by continuation phase of HRE for 8 months, daily regimen along with tablet pyridoxine 50 mg once daily. Oral prednisolone and oral acetazolamide were given for 4 weeks and tapered over the next 3 weeks.

The child improved with ATT on regular follow up and has completed ATT treatment. She has attained age appropriate milestones. She runs well, self feeds and enjoys domestic mimicry. Her repeat MRI done after a year of completing ATT, showed resolution of hydrocephalus. Parents and younger sister of the child were screened for TB and was negative. Hence contact couldn't be traced in this case. The child had not received BCG vaccine and hence this had made her prone to develop a complicated form of TB. However, early initiation of ATT has helped in better survival and outcome.

3. Discussion

Of all the extra-pulmonary complications of TB, neurotuberculosis is the worst one, having significant morbidity and mortality if not treated.[3] Tuberculous meningitis (TBM) occurs in 0.3% of untreated tuberculosis infections in children, commonly seen in the age group of 6 months to 4 years.[4] The first stage has low grade fever with irritability, headache, drowsiness, and malaise. It has been described that in infancy, there could be stagnation or loss of developmental milestones. The second stage is characterised by nuchal rigidity, seizures, hypertonia, positive Kernig sign and Brudzinski sign, vomiting, cranial nerve palsies and other focal neurologic signs. The third stage has coma, hemiplegia or paraplegia, hypertension, decerebrate posturing, deterioration of vitals and eventually death.[4]

This child had presented in stage two, with neck stiffness and neurological features in the form of acute regression of milestones. The typical CSF findings and neuroimaging showing basal exudates which is highly specific for TB,[5] with Mantoux positivity directed to a diagnosis of probable TBM.[6] Henceforth she was started on ATT as per RNTCP guidelines. CBNAAT testing by GeneXpert was positive in gastric aspirate but was negative in CSF, given the low yield of CSF.[7] BCG vaccination was not given at birth again reinforcing the importance of BCG vaccine in preventing severe forms of TB. Absence of the usual prodromal presentation of fever with lethargy, seizures was a rarer presentation in our setting, thus signifying the cautious approach in children presenting with acute neuroregression. Early initiation of treatment has a good outcome.

We need to be more prudent in a child presenting with acute neuroregression and have a suspicion of tuberculous meningitis and corroborate accordingly with CSF analysis, neuroimaging, Chest X ray, Tuberculin skin testing, BCG vaccination status and TB contact positivity. The uniqueness in this case is the presentation with acute neuroregression with absent prodromal symptoms, and no contact history for TB in this child.

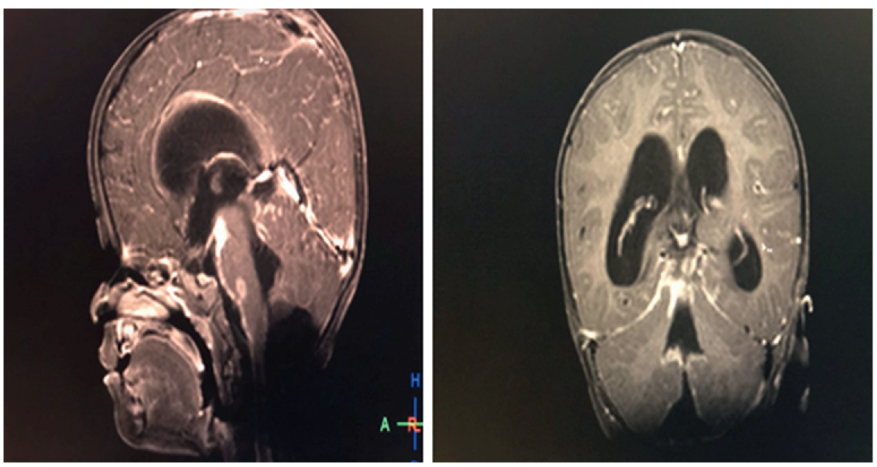

Fig. 1 – MRI brain showing basal exudates and non obstructive hydrocephalus.

Conflicts of interest

The authors have none to declare.

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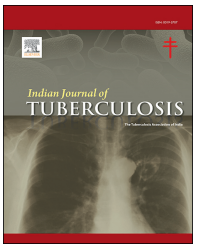

Tuberculous meningitis: An unlikely cause of Guillain-Barre syndrome

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ARTICLE INFO

Article history:
Received 28 November 2019
Accepted 26 December 2019
Available online 7 January 2020

Keywords:
Tuberculosis
Meningitis
Nervous
Immune

ABSTRACT

Guillain–Barre syndrome (GBS) is a life-threatening immune-mediated acute inflammatory polyneuropathy and is associated with various antecedent infections. Its association with tuberculosis is very uncommon with only a handful of cases being reported in the literature. It's association with tuberculous meningitis is even more scarce with only one case reported in literature till date. We report a 40-year-old lady with GBS associated with tuberculous meningitis. GBS was confirmed with clinical examination and nerve conduction studies.

1. Introduction

Guillain-Barré syndrome (GBS) is a common and potentially life threatening acute paralytic neuropathy, with an estimated annual incidence of 0.8–1.9 cases per 100,000 per year.[1] Various antecedent infections and non-infectious causes like drugs and vaccines have been implicated to be potential triggers probably due to aberrant immune response.[2] Tuberculosis which is virtually epidemic in African and South east Asian countries has rarely been seen as a trigger for development of GBS with only a few cases being reported.[3,4] GBS in association with tuberculous meningitis is even rarer entity with only a single case reported till date.[5] We report here one such case of a 40-year-old lady with GBS in associated with tuberculous meningitis.

2. Case report

A 40-year-old previously healthy lady presented with a chief complaint of fever for two weeks and altered sensorium for two days. Signs of meningitis were present on clinical examination. A non-contrast computerized tomography of brain revealed no abnormality. Cerebrospinal fluid (CSF) examination after lumbar puncture revealed a protein of 167mg/dl, 200 cells/ml with 90% being lymphocytes. CSF adenosine deaminase (ADA) level was 51 IU/L and polymerase chain reaction test was positive for mycobacterium tuberculosis. CSF was negative for viral etiology. Her chest X-ray and ultrasonography of abdomen were found to be normal. Other causes of fever were ruled out with relevant investigations. Patient was initiated on anti-tubercular drugs along with steroids. She became fully conscious by day three with no neurological deficit.

However, seven days following admission, she developed motor weakness, initially involving both lower limbs and progressing to involve both upper limbs, within next 12 hours. The neurological examination revealed hypotonia in all limbs, power of 1/5 in lower limbs and 2/5 in upper limbs with absent deep tendon reflexes. The plantar reflexes were absent and cranial nerves were normal. Sensory, bowel and bladder functions were normal.

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https://doi.org/10.1016/j.ijtb.2019.12.002

On investigations magnetic resonance imaging (MRI) scan of brain and spine (Figs. 1 and 2) was normal. Electrodiagnostic studies were suggestive of acute motor sensory demyelinating poly-radiculo-neuropathy (Fig. 3), a type of GBS. Apart from the CSF findings all other variables of the diagnostic Brighton's criteria were fulfilled in our case. CSF findings were not typical of those found in GBS due to presence of tuberculous meningitis which itself was the trigger for development of GBS.

Intravenous immunoglobulins (IVIG) was administered and improvement in the power of limbs to 4/5 in both upper and lower limbs was noticed after five days. Patient continues to receive anti-tubercular therapy and is currently undergoing rehabilitation.

3. Discussion

GBS is an immune-mediated acute inflammatory polyneuropathy associated with antecedent infection. Its worldwide incidence is estimated as 0.8–1.9 cases per 100,000 per year.[1] Both viral and bacterial infections are commonly implicated. Protozoal infections and non-infectious causes such as sarcoidosis, drugs, immunization and surgical procedures have also been implicated.[2] GBS associated with tuberculosis is an extremely rare entity with only a few cases reported in the literature.[3] Its association with tuberculous meningitis is rarer with only a single reported case till date.[4]

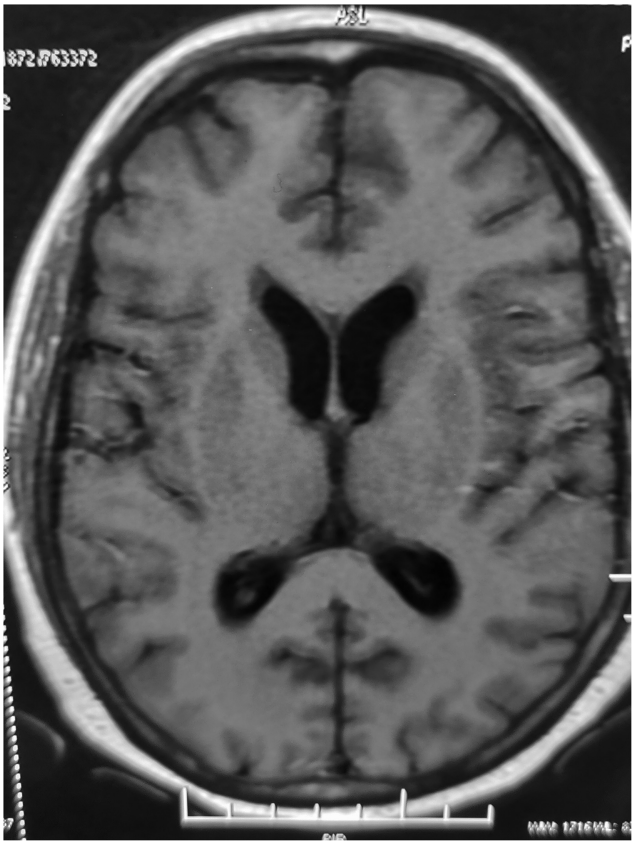


Fig. 1 – Magnetic resonance image of brain showing normal study.

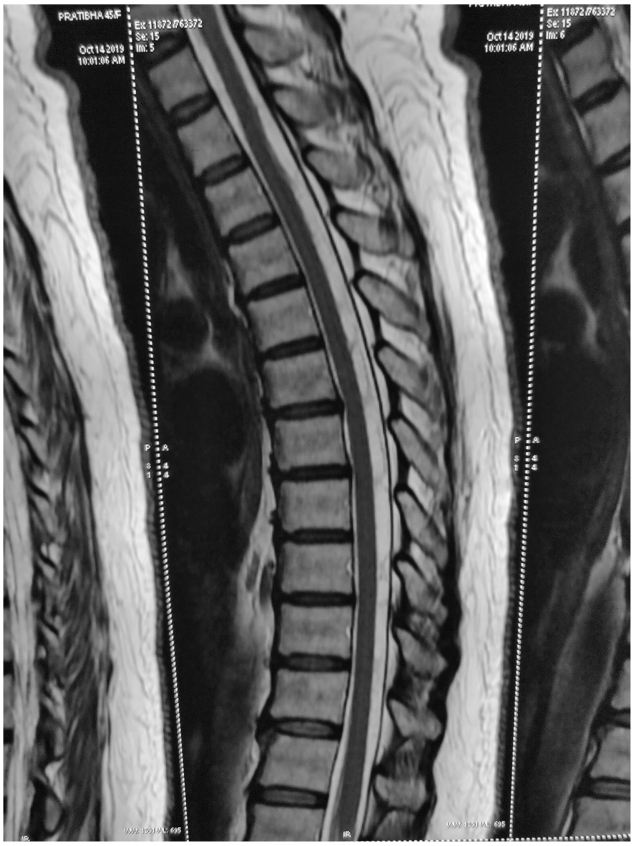
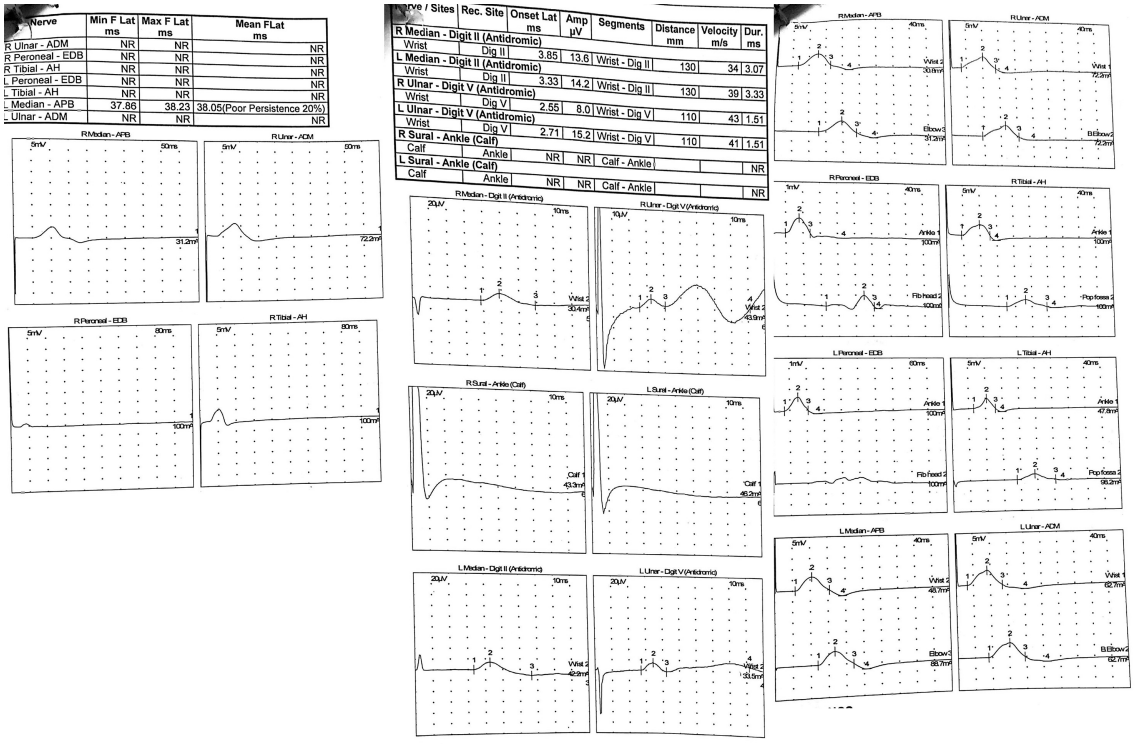


Fig. 2 – Magnetic resonance image of spine showing normal study.

The pathogenesis of tuberculosis associated GBS is not completely elucidated and it is believed to be due to molecular mimicry which in turn leads to an immunological response against the nerves. The proposed mechanism is also based on the fact that there is clinical improvement following administration of immune modulatory agents like immunoglobulins.[5] The immunological response may also be augmented by release of various inflammatory markers including cytokines and tumor necrosis factor alpha which may be caused by the tubercular bacilli protein following anti-tubercular therapy.[6] Another proposed mechanism suggests direct invasion of the nerve roots by tubercle bacilli as demonstrated at necropsy by Peiris J B et al.[7]

GBS is a rapidly progressive monophasic disease with varying outcomes. It can be a potentially life-threatening condition with as many as 20–30% of patients needing ventilatory support due to involvement of the respiratory muscles leading to respiratory failure. Despite optimal care, the mortality rate can be as high as 5%.[2]

Brighton criteria is commonly used for establishing the diagnosis of GBS which includes the clinical assessment, CSF findings, nerve conduction studies and exclusion of other causes.[8] The clinical examination commonly reveals bilateral flaccid paralysis of limbs with diminished or absent deep tendon reflexes. The CSF examination reveals elevated protein which is seen in almost 50–66% of cases in the first week and in more than 75% of cases in the third week. This raised



Nerve	Min F Lat ms	Max F Lat ms	Mean FLat ms
R Ulnar - ADM	NR	NR	NR
R Peroneal - EDB	NR	NR	NR
R Tibial - AH	NR	NR	NR
L Peroneal - EDB	NR	NR	NR
L Tibial - AH	NR	NR	NR
L Median - APB	37.86	38.23	38.05(Poor Persistence 20%)
L Ulnar - ADM	NR	NR	NR

Nerve / Sites	Rec. Site	Onset Lat ms	Amp µV	Segments	Distance mm	Velocity m/s	Dur. ms
R Median - Digit II (Antidromic)	Wrist	Dig II	3.85	13.6	Wrist - Dig II	130	34	3.07
L Median - Digit II (Antidromic)	Wrist	Dig II	3.33	14.2	Wrist - Dig II	130	39	3.33
R Ulnar - Digit V (Antidromic)	Wrist	Dig V	2.55	8.0	Wrist - Dig V	110	43	1.51
L Ulnar - Digit V (Antidromic)	Wrist	Dig V	2.71	15.2	Wrist - Dig V	110	41	1.51
R Sural - Ankle (Calf)	Calf	Ankle	NR	NR	Calf - Ankle			NR
L Sural - Ankle (Calf)	Calf	Ankle	NR	NR	Calf - Ankle			NR

Fig. 3 – Nerve conduction study suggestive of acute motor sensory demyelinating polyradiculoneuropathy.

CSF protein without an elevation in white blood cells provides supporting evidence for the diagnosis.[9] However, the CSF picture may be normal in first week of disease and may be different from the typical findings as seen in GBS in various clinical settings. A typical CSF picture could not be found in our patient due to the presence of tuberculous meningitis, and hence could not be used for making the diagnosis of GBS. Other modality used for making the diagnosis includes nerve conduction studies which also help to categorize GBS into various types.[10]

The optimal treatment approach includes use of intravenous immunoglobulin or plasma exchange is, alongside supportive care. An early initiation of intravenous immunoglobulins or plasma exchange is crucial, especially in patients with rapidly progressive weakness. Admission to intensive care settings is warranted owing to high percentage of them needing ventilator support and autonomic disturbance. The recovery is highly variable and take months to years with endogenous repair of the peripheral nerves following waning of the immune response.[2]

Our patient developed a clinical picture of tuberculous meningitis two weeks following symptom onset and was eventually diagnosed to have GBS one week after the initiation of anti-tubercular therapy. Although one cannot rule out anti-tubercular drugs and steroids as potential causes of GBS in our case, clinical improvement following administration of immunoglobulins along with continuation of steroids and anti-tubercular therapy for TBM suggests tuberculous meningitis to be the trigger for development of GBS.

The rare association is being reported to sensitize the physicians about the possible association which can be life threatening and has significant neurological morbidity. Early diagnosis is imperative to minimize the complications and neurological sequalae.

Contribution

ND: Concept, data collection, analysis, review of literature, manuscript preparation and review; RK: Concept, data collection, analysis, review of literature, manuscript preparation and review; AK: Concept, data collection, analysis, review of literature, manuscript preparation and review; SC: Concept, data collection, analysis, review of literature, manuscript preparation and review.

Conflicts of interest

The authors have none to declare.

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Case Report

Immune reconstitution inflammatory syndrome in non-HIV patients with tuberculosis. A case series

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ARTICLE INFO

Article history:
Received 3 January 2019
Accepted 28 February 2019
Available online 6 March 2019

Keywords:
Immune reconstitution inflammatory syndrome
Paradoxical reaction
Tuberculosis
Immunocompetent
Right middle lobe syndrome

ABSTRACT

Tuberculosis associated Immune reconstitution inflammatory syndrome (IRIS) in a HIV negative patient can present with a multitude of clinic-radiological presentations that are often confused with drug resistance/treatment failure. Being a diagnosis of exclusion, this clinical entity is often prone to under-diagnosis. We present a series of 5 patients who presented with varied but uncommon IRIS manifestations. High index of suspicion coupled with clinical reasoning and judicious use of phenotypic and genotypic culture methods helped in their timely detection and successful treatment.

1. Introduction

Immune reconstitution inflammatory syndrome (IRIS) is an exaggerated and/or dysregulated host's inflammatory response to invading micro-organism that presents as paradoxical worsening of the pre-existing infection after the initiation of treatment. It has classically been described as the worsening of tuberculosis infection in HIV positive patients after initiation of anti-retroviral therapy (ART).[1–3] However, it has also been seen in non-HIV patients following corticosteroid withdrawal, discontinuation of anti-TNF therapy or recovery of neutropenia

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https://doi.org/10.1016/j.ijtb.2019.02.018
0019-5707/

after cytoyoxic chemotherapy. Rarely, it can also occur in TB patients without any underlying predisposing factor.

Despite a well acknowledged entity, it is often missed while managing TB patients presenting with apparent disease worsening. With a rising burden of mono and multi drug resistant TB, differentiating paradoxical reactions from drug resistance is often a difficult task, especially in patients with extra-pulmonary tuberculosis. The present series describe 5 uncommon presentations of paradoxical reactions in immunocompetent patients with drug sensitive and resistant TB involving different sites that were managed successfully. Factors predisposing to it and intricacies in its management have been discussed that might help in better management of this condition.

2. Case 1

An 18-year-old male presented with low-grade fever, cough and weight loss since 1 month. Chest x-ray and contrast enhanced computed tomography (CECT) thorax showed a significant right hilar and mediastinal lymphadenopathy (Fig: 1a). Trans-bronchial needle aspiration (TBNA) of subcarinal lymph node revealed epithelioid cell granulomas and a positive stain for acid fast bacilli (AFB). Anti-tubercular treatment (ATT) was started that lead to gradual improvement with a weight gain of 4 kg in 2 months. However, the initial response was followed by worsening of cough. Repeat CECT thorax revealed a right middle lobe segmental collapse with consolidation along with increase in the lymph node size (Fig: 1b). Bonchoalveolar lavage (BAL) and TBNA aspirate (from station 7 lymph node) showed rifampicin sensitive *Mycobacterium tuberculosis* (Mtb) DNA on Cartridge based nucleic acid amplification test (CBNAAT) and a negative culture for AFB. Patient was diagnosed with IRIS presenting as right middle lobe syndrome. ATT was continued and a short course of oral steroid (Prednisone 30 mg/day for 2 weeks) was added. The patient showed a gradual clinico-radiological improvement (Fig: 1c). He completed an extended ATT of 9 months with complete recovery.

3. Case 2

A 30-year-old immunocompetent male presented with right-sided exudative pleural effusion (protein 5.8g/dl, Lymphocytes 98%; ADA 88 IU/L). Anti-tubercular treatment resulted in gradual clinico-radiological improvement. However at 1.5 months, he started having increased breathlessness along with pleural fluid refilling on CXR. Repeat pleural fluid analysis was done that excluded drug resistance and bacterial co-infection (empyema). Oral corticosteroid (prednisone 0.5 mg/kg) was added to the ATT that resulted in gradual improvement. The steroid was tapered over a period of 4 weeks. The patient completed 7 months of ATT successfully.

4. Case 3

A 42-year-old diabetic male on treatment for multi-drug resistant (MDR) TB male was admitted in drug resistant TB (DRTB) center with acute onset left-sided hemiparesis. He was on CAT IV ATT (Fig: 2a) for the last 21 months with consistent clinical, radiological and microbiological (negative sputum cultures) improvement. Contrast enhanced CT brain showed a tuberculoma in the left basal ganglia (Fig. 2b). Cerebrospinal fluid analysis showed a low protein, ADA values and an absence of Mtb DNA on CBNAAT. Neurologist consultation was sought and the same drugs were continued along with the addition of oral corticosteroid (prednisone 1 mg/kg) for 6 weeks. Patient showed a significant clinical improvement with complete resolution of lesion at 2 months (Fig: 2c). He successfully completed a 26 months ATT course with a 2 month extension (Fig. 2d).

5. Case 4

A 24-year-old male presented with 2-week history of fever and cough. Thoracic imaging (CXR & CECT) showed significant mediastinal lymphadenopathy (Fig. 3a and c). Transbronchial needle aspirate from the sub-carinal lymph node showed caseous necrosis with rifampicin sensitive Mtb DNA (on CBNAAT). Anti-tubercular treatment (CAT I DOTS) was started that resulted in an initial clinical improvement. However at 4 weeks he started having high grade fever and breathlessness (grade III mMRC). Sputum microscopy showed scanty positive for AFB that was sensitive for rifampicin on CBNAAT. Repeat CECT chest and abdomen showed increase subcarinal lymph node size (36 mm in shortest axial diameter), a new right lung collapse/consolidation, hepatosplenomegaly and an enlarged

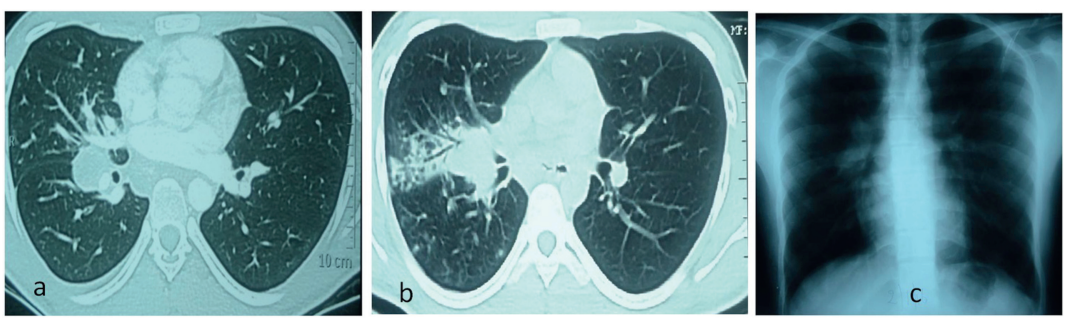

Fig. 1 – a) CECT thorax showing enlarged hilar lymph node b) increase in lymph node size with right middle lobe segmental collapse with consolidation c) X-ray chest showing resolution of the right mid zone shadow.

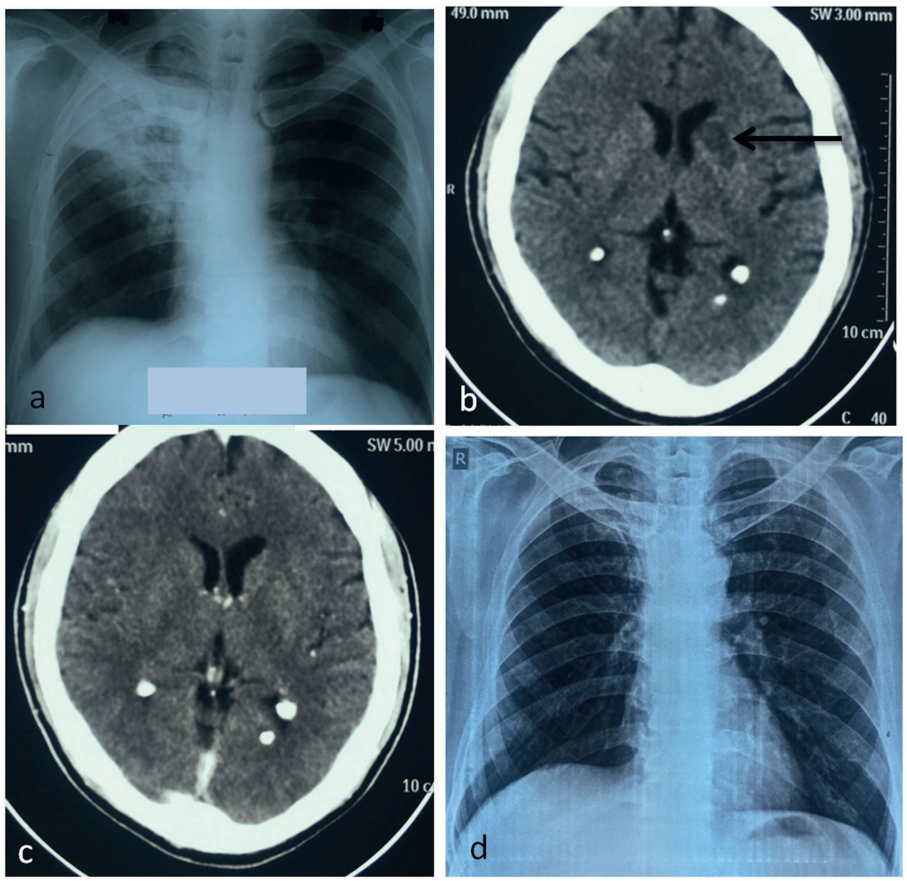

Fig. 2 – a) X-ray chest P-A view showing collapse with consolidation of the right upper lobe b) CT head showing a hypodense lesion (Black arrow) in the left basal ganglia c) follow up CT (after 2 months) showing complete resolution of the lesion d) X-ray at the end of treatment showing resolution of the parenchymal lesion with mild fibrosis.

periportal lymph nodes (largest size 21 × 11mm) (Fig. 3band d). BAL was taken that didn't show the growth of tubercle bacilli on liquid culture. Oral steroid (prednisolone 0.5 mg/kg/day) were added to ATT. Patient showed a gradual clinical and radiological improvement over a period of 6–8 weeks (Fig. 3e). Currently the patient is on ATT with satisfactory improvement.

6. Case 5

A 50-year-old diabetic male presented with fever and bilateral pleural effusion with mild pericardial effusion (Fig. 4a). Pleural fluid was exudative with high ADA (protein 5.4g/dl, ADA 45,

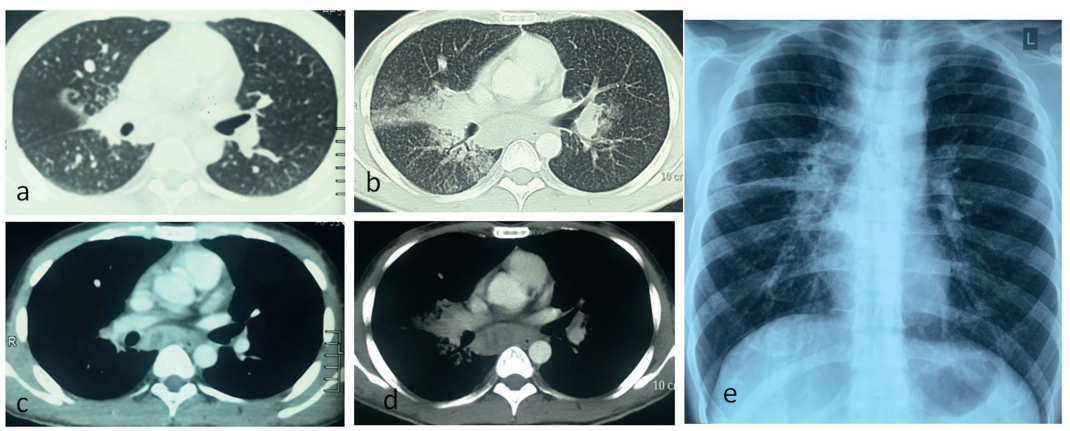

Fig. 3 – a) HRCT thorax showing few bilateral centrilobular nodules b) follow up CT (after 1 month) showing increase in parenchymal nodules along with a new consolidation with collapse involving right middle lobe medial segment c) CECT mediastinal window showing enlarged subcarinal lymph node at baseline d) CT (after 1 month) showing increase in the lymph node size e) follow up x-ray chest showing significant improvement in the parenchymal nodules and consolidation.

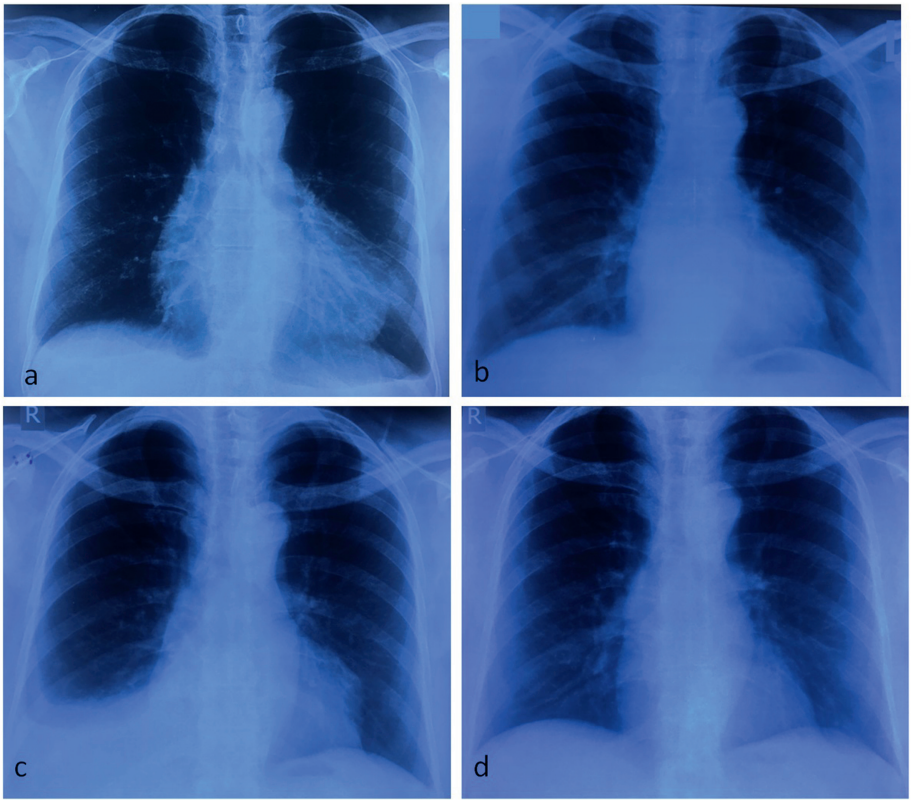

Fig. 4 – X-ray chest PA view a) showing mild bilateral pleural fluid and pericardial effusion at baseline b) At 2 weeks showing improvement c) Showing increase in the right sided pleural effusion d) At the end of treatment showing significant improvement.

neutrophilic (88%), sugar 140mg/dl, cytology-no malignant cells). He was started on anti-tubercular treatment (Cat I DOTS) and steroids (prednisolone 0.5 mg/kg/day) that was accompanied by resolution in fever and x-ray picture (Fig. 4b). However, after 3 weeks, the patients again started complaining of high grade fever and radiological worsening (Fig. 4c). Super-added infection and drug resistance was rule out by repeat thoracocentesis and blood/urine culture. With a working diagnosis of IRIS, the patient was continued on oral corticosteroid for 6 weeks along with ATT. The patient responded to treatment (Fig. 4d) and completed 9 months of extended ATT with significant improvement.

7. Discussion

Immune reconstitution inflammatory syndrome or paradoxical reaction has been widely described in tuberculosis from different geographical areas.[2,4] However, there is no conclusive data on its prevalence, with few studies showing 2–23% estimated frequency in HIV uninfected patients.[2–5] The condition is characterized by worsening of a recognized ("paradoxical" IRIS) or unrecognized pre-existing infection ("unmasking" IRIS) in the setting of immune function restoration. Besides tuberculosis, IRIS has also been seen in infections due to Pneumocystis, *Mycobacterium avium* complex, Cytomegalovirus, Cryptococcus and Herpes simplex virus.[6,7] In HIV infected patients, IRIS results from ART mediated fall in viral load and simultaneous increase in T-lymphocyte count resulting in immune function restitution. However, the exact mechanism in apparently immunocompetent patients is not well understood. It appears that host genetic susceptibility coupled by immune mediated change in the ability to respond to tuberculin proteins (released during rapid killing of Mycobacteria) leads to excessive and uncontrolled inflammatory response resulting in paradoxical reaction.

Certain factors like young age, male gender, anemia and low lymphocyte count at the initiation of ATT have also been shown to predispose to its development.[2,8–10] In the present series also, all patients were males in the age range of 18–40 years. Two of them were also anemic at the time of presentation.

Paradoxical reaction can have a variable presentations ranging from worsening in signs/symptoms (worsening of fever, cough or breathlessness) and/or transient worsening of primary lesions (increase in lymph node size, parenchymal lesions or pleural effusion) to the appearance of new TB foci at local or distant sites.[1,9] In the present series, clinical worsening was seen in all the patients. Increase in size of the primary lesion was seen in 3 patients, whereas appearance of

new lesion was seen in 2 cases (brain tuberculoma and new pleural effusion) and an apparent dissemination in 1 patient. Right middle lobe syndrome due to paradoxical mediastinal lymph node enlargement, as was seen in 2 patients, is a rare phenomenon, not reported previously. Paradoxical reaction occurring as a new neurological focus is also uncommon, especially in patients with drug resistant tuberculosis.[11]

Paradoxical reaction is a clinical diagnosis that is considered after exclusion of super-added or co-infections, anti-tubercular drug resistance and other co-morbid diseases mimicking TB. Factors affecting immunity like diabetes, HIV and long term corticosteroid use should be actively searched, as their uncontrolled interplay can result in paradoxical worsening, complicating the course of the disease. Nevertheless, high index of suspicion for IRIS should be maintained in all patients who worsen after initiation of treatment. Similar to the present cases, culture (for AFB, fungus and bacteria) and CBNAAT (for Rifampicin resistance) of the representative samples and imaging studies are the ancillary investigations that help in reaching the diagnosis.

There are no clear guidelines for the management of TB associated IRIS. A significant proportion of patients improve spontaneously with continuation of same ATT regimen only, in a few weeks time.[4,9,12] However, oral steroids (prednisolone 0.5–1 mg/kg/day) may be required in selected group of patients with marked/progressive clinical and/or radiological worsening accompanied by features of organ dysfunction. All patients in our series also received oral prednisolone for a duration ranging from 2 to 8 weeks. The duration of ATT can be extended in such cases as judged by the rate of clinico-radiological improvement.[7]

The present case series describe 5 varied and uncommon presentations of IRIS in non-HIV TB patients. It highlights the need for a high index of suspicion, in-depth clinical reasoning and systematic approach through judicious of phenotypic and genotypic culture methods that are the key to its timely detection and successful outcome.

Conflicts of interest

The author has none to declare.

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