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The SAARC Journal of Tuberculosis, Lung Diseases and HIV/AIDS is the official journal of the STAC. The Journal's main aim is the continuing education of personnel and the dissemination of the most up-to-date information in the field of tuberculosis, lung diseases and HIV/AIDS. It is devoted to dissemination of knowledge concerning various aspects of tuberculosis, lung diseases and HIV/AIDS. All articles relevant to the practice of this Journal and quality health research are published. The Journal is an appropriate forum for the publication of articles concerning the social, economic, public health, epidemiology, diagnostics, genetics etc. in the area of tuberculosis, lung diseases and HIV/AIDS. The scientific manuscripts presenting the results of public health importance are encouraged. The novel case reports which adds to the existing knowledge and consistent with the scope of Journal will be considered for publication. The Journal accepts review/mini-review, case report, short communications, and letters to editors within the scope of the journal.

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Editorial

A DEVELOPMENT PRIORITY- SAARC Region

Tobacco use is a significant hurdle to development gains worldwide. It is the leading cause of preventable death. Smoking-related illness costs billions of dollars each year, imposing a heavy economic toll on countries, both in terms of direct medical care for adults and lost productivity.

The tobacco epidemic is one of the biggest public health threats the world has ever faced, killing around 6 million people a year. More than 5 million of those deaths are the result of direct tobacco use while more than 600 000 are the result of non-smokers being exposed to second-hand smoke. Nearly 80% of the more than 1 billion smokers worldwide live in low- and middle-income countries, where the burden of tobacco-related illness and death is heaviest. Tobacco users who die prematurely deprive their families of income, raise the cost of health care and hinder economic development.

The use of tobacco by adolescents remains a major public health concern worldwide. There are 1 billion smokers globally, of which more than 50% are young people. South Asia Region contributing large amount of the global burden of tobacco users. India alone has about 35 million tobacco users. There are variations in trends of tobacco use among the SAARC countries, which largely reflects cultural differences, values, and norms toward use of tobacco and tobacco related products in these societies.

Evidence of the harmful effects of tobacco has existed for centuries, at first in relation to oral cancer and then to vascular diseases and lung cancer or Non Communicable Disease (NCD). However, even though smoking is often initiated early in life, its most obvious health consequences are not seen until later stages in life, when they manifest as various chronic problems in adulthood through old age. Because of late onset of symptoms, most smokers are oblivious of the harmful effects of cigarette smoking. One of the obvious implications of tobacco use is addiction or dependence, which is a state of drug-seeking behavior. It is well established that multiple nicotinic receptors reside in the central nervous system that are stimulated on nicotine intake; hence cigarette smokers have higher levels of brain nicotine receptors than do nonsmokers. Another implication of serious consequences of tobacco use is the link between smoking and cancer.

Another implication is the influence of cigarette smoking on other respiratory illnesses. Smoking cigarettes is a known risk factor for chronic obstructive pulmonary disease (COPD), asthma, interstitial lung diseases, respiratory tract infections, and pulmonary tuberculosis. Smoking substantially increases the risk of TB and death from TB. More than 20% of global TB incidence may be attributable to smoking according to WHO report. Smoking is the most important risk factor for COPD in Asia, which therefore makes smoking indirectly responsible for the increased disability life adjusted years (DALY) and the mortality due to COPD in the region. Current statistics shows smoking-related diseases kill 1 in 10 adults, and if the current trend continues, smoking-related diseases will kill 1 in 6 adults by the year 2030 globally.

Tobacco smoking remains a source of public health concern in Asia despite some success in achieving a gradual decline in prevalence rates among countries in the region. More vigorous target-oriented goals are needed to address rising trends of smoking among girls and young smokers in general. Global governance is a prerequisite on the regional countries to uphold the World Health Organization framework convention on tobacco control, is required to strengthen the regional effort in containing this serious public health problem

The public health community must recognize that tobacco use is a global problem that needs international collaboration as well as regional consolidation. Policy Maker, Researcher public health program managers in the region need to consolidate actions toward active, evidence-based interventions needed to effectively control the lethal public health problem of tobacco and make tobacco free SAARC Region

ASSESSMENT OF GENE-XPERT MTB RIF PROGRAM IMPLEMENTATION AND THE CHALLENGES FOR ENHANCED TUBERCULOSIS DIAGNOSIS IN NIGERIA

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ABSTRACT

Introduction: Gene-Xpert MTBRIF, rapid tuberculosis and rifampicin resistance diagnostic technology is implemented in Nigeria to enhance public health response to tuberculosis diagnosis in HIV patients with presumed tuberculosis (TB), and presumed cases of drug resistant TB. The aim of the paper is to share experience on programmatic issues on Xpert MTB RIF roll-out.

Methodology: Program implementation data from 22 Xpert laboratories for period between September 2011 and December 2013 were analyzed to evaluate outcomes and identify challenges and opportunities for strengthening tuberculosis detection in Nigeria.

Results: A total of 12249 patients received single gene-Xpert test at 10 secondary (S), 10 Tertiary (T) and 2 private (P) health facilities over 25 months. The tests were valid in 10948 patients, and 3669/10948 (33.5%) were positive for *Mycobacterium tuberculosis* (MTB). In 815/3669 (22.2%) of the MTB cases, the bacteria were resistant to rifampicin. Rifampicin resistance was inconclusive (indeterminate) in 509/12249 (4.2%) while the test failed in 792/12249 (6.5%). The program was noticeably limited to health facilities above primary centers; there were prolonged delays in the diagnosis and treatment with limited on-site synergy between TB/HIV services. Reducing diagnostic delays and integrating TB/HIV services into the gene-Xpert program will enhance early case detection and enrollment for care in Nigeria.

Conclusion: The model Gene-Xpert MTBRIF program implemented in Nigeria targets specific risk groups with high number of cases detected. Diagnoses of tuberculosis and resistance to rifampicin could be enhanced by offering integrated TB/HIV services; improving patient and sample flow/referral; proper documentation of test outcomes and alignment with DR-TB management

Key words: Gene-Xpert, Implementation, Challenges, Nigeria

INTRODUCTION

Few studies have reported the different ways Gene-Xpert MTBRIF; rapid tuberculosis and rifampicin resistance diagnostic technology is implemented in different settings.[1] In Nigeria, the program targets specific groups at risk of tuberculosis and cases of tuberculosis at risk of resistance to one of the most powerful drugs currently in use for treating the disease. In 2010, the World Health Organization (WHO) endorsed GeneXpert® MTB/RIF (Xpert) (Cepheid Inc. New Jersey, USA) for Mycobacterium tuberculosis (MTB) detection in settings with high burden of tuberculosis (TB), and HIV. Since then, access to Xpert

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services has risen in resource limited settings.[1-3] Available data show that the test is effective and reliable for the rapid diagnosis of pulmonary tuberculosis especially in HIV positive suspects, and multi-drug resistant tuberculosis (MDR TB) in TB cases.[2,4,5] The massive deployment of Xpert to some resource limited high burden settings is however matched with few reports so far on the program outcomes and challenges.

Xpert is a point-of-care diagnostic test that provides a platform for the integration and scale-up of TB-HIV services in settings where diagnostic delays reduce access to clinical care services.[6,7,8] Such delays are associated with increased morbidity and mortality among HIV positive clients, and among TB cases infected with multi-drug resistant mycobacteria.[9,10] Rifampicin resistance is a precursor to the development of MDR TB, and a reliable predictor of MDR in settings where the prevalence of rifampicin resistant mycobacterium tuberculosis is high.[11,12,13]

Whether Xpert is used as a primary screening tool or as an add-on test for cases with negative smear microscopy outcomes, the uptakes of TB-HIV and MDR-TB services at facility level depends on a number of factors such as effective HIV counseling and testing services (HCT), coordination between TB and HIV programs, timely sample transfer and retrieval of results and effective documentation. Successful implementation of the Xpert program in resource limited settings may be hampered by high cost of the test, poor maintenance, underutilization and hard operational conditions (high temperatures, irregular power supplies and low capacity human resources).[14,15] Nationwide implementation of Xpert program requires high level of advocacy, adequate preparation, sites selection and in-depth trainings.

Xpert program in Nigeria is largely implemented by the KNCV Tuberculosis Foundation in partnership with the government of Nigeria, with support from the U.S agency for international development (USAID). The implementation program is supervised by the national TB control program (NTP) through an advisory committee of experts: the country GeneXpert advisory committee (C-GAT). The C-GAT is responsible for the coordination of Xpert implementation activities by all implementing partners. The C-GAT is assisted by technical staff from the KNCV foundation and Cepheid Inc., in the planning, facility assessment and selection; development of strategies for the program roll-out; establishment of diagnostic algorithms, standard operating procedures and reporting formats according to the WHO recommendations.

In this article we evaluate the model Xpert program implemented in Nigeria with reference to the program's data generated to assess outcomes and challenges faced in the roll-out and scale-up of the program in Nigeria.

METHODOLOGY

A retrospective Xpert program data from the 22 sites (10 secondary, 10 tertiary, and 2 private health facilities) supported by KNCV/TB CARE I project in Nigeria between September 2011 and December 2013 were reviewed. One Xpert machine per site (facility) was installed in the sites from September, 2011 to September, 2013. Patients were offered Xpert tests at these sites if they had HIV with presumptive tuberculosis or if they had poor response to category I and, or II tuberculosis treatment regimen; relapsed after tuberculosis treatment; returned after treatment interruption; or had contact with a known case of MDR-TB. As part of the standard of care, documentation of patients' HIV status was required. All program report forms, monitoring and evaluation report sheets, site planning, preparations and take-off reports from the date a site was activated until December, 2013 were reviewed. The quarterly C-GAT meetings and evaluation reports were also reviewed.

De-identified quantitative data on the number of patients enrolled at different sites including their Xpert and HIV test outcomes were abstracted. Xpert tests were valid if MTB and rifampicin resistance (RIFr) presence or absence were determined. Indeterminate if only MTB presence or absence was determined, and failed if the presence or absence of MTB cannot be determined (invalid) or test error or no result signals were shown. HIV status was classified as positive, negative or unknown (if undocumented). The various sites were coded as follows: S1 through S10, for the 10 secondary sites; T1 through T10 for the 10 tertiary sites and P1, P2 for the 2 private sites.

The abstracted data were organized into cell counts in which descriptive values were provided along with frequencies and proportions. In computing proportions, failed and, or indeterminate results were carefully excluded or included from the denominators depending on what was reported. In comparing the test outcomes, we pooled data from the same type sites into three

groups: S, T and P; representing data from the 10 secondary, 10 tertiary and 2 private sites respectively. We then constructed 2-way table: variables of interest by group type (3 types), and performed a Chi-square test; if it was significant we followed with pair wise 2 by 2 table and a Chi-square test. Data consistencies with the hypotheses of no difference were assessed by the *p*-values (level of significance = 0.05) reported while the strength of associations was given by the odds ratios and 95% confidence intervals of the odds ratios estimated. Qualitative data reporting challenges with program implantation were tabulated with frequencies and pattern of reported challenges summarized to which workable solutions or recommendations provided.

RESULTS

GeneXpert Test outcomes

From September, 2011 to December, 2013, 12249 presumptive cases of drug resistant (DR) TB and presumed TB in HIV infected patients were offered single Xpert tests at 22 sites. The number of tests and yields of MTB and RIFr at the 22 different sites were summarized in table 1. Of those, 7567 (61.8%), 3419 (27.9%) and 1263 (10.3%) were enrolled at secondary, tertiary and private level health facilities (sites) respectively. The tests were valid in 10948 patients, and of those, 3669 (33.5%) had *Mycobacterium tuberculosis* (MTB) infection with rifampicin resistance (RIFr) in 815/3669 (22%). Among the resistant cases, 119 (14.6%) had co-infection with HIV, 444 (55.5%) were negative of the HIV while in 252 (30.9%) cases the HIV status was not documented (see table 2).

Table 1. The prevalence of tuberculosis (TB) and resistance to rifampicin (RIFr) among Xpert testing clients by site

Site	Site	Valid Xpert	MTB Cases	
	S_{AT}	Nc	*n*	%
Total		10948	3669	33.5
S1	10.2011	1156	352	30.5
S2	10.2011	534	215	40.3
S3	4.2012	1121	547	48.8
S4	4.2012	784	259	33.0
S5	10.2011	509	249	48.9
S6	10.2011	1388	413	29.8
S7	10.2011	588	200	34.0
S8	10.2012	537	162	30.2
S9	10.2013	73	34	46.6
S10	10.2013	56	23	41.1
T1	10.2012	206	67	32.5
T2	10.2012	232	75	32.3
T3	10.2012	219	93	42.5
T4	10.2011	1057	292	27.6
T5	10.2012	201	40	19.9
T6	10.2012	849	251	29.6
T7	7.2013	155	49	31.6
T8	7.2013	123	28	22.8
T9	10.2013	33	15	45.5
T10	10.2013	25	8	32.0
P1	10.2011	1087	293	27.0
P2	10.2013	15	4	26.7

S_{AT} = Month and year the site was activated
N_c = Total number with valid Xpert test
S = Secondary; T= Tertiary; P= Private

Table 2. The prevalence of tuberculosis (TB) and resistance to rifampicin (RIFr) by HIV status among Xpert testing clients by site

Site	RIFr		RIFr HIV+		RIFr HIV-		RIFr HIV ±	
	n	%	*n*	%	*n*	%	*n*	%
Total	815	22.2	119	14.6	444	55.5	252	30.9
S1	64	18.2	11	17.2	29	45.3	24	37.5
S2	69	32.1	9	13.0	60	86.7	0	0.0
S3	106	19.4	15	14.2	60	56.6	31	29.2
S4	43	16.6	5	11.6	10	23.3	28	65.1
S5	80	32.1	3	3.8	55	68.8	22	27.5
S6	102	24.7	8	7.8	45	44.1	49	48.0
S7	32	16.0	7	21.9	19	59.4	6	18.8
S8	24	14.8	6	25.0	9	37.5	9	37.5
S9	7	20.6	0	0.0	2	28.6	5	71.4
S10	2	08.7	1	50.0	1	50.0	0	0.0
T1	14	20.9	1	7.1	5	35.7	8	57.1
T2	13	17.3	0	0.0	10	76.9	3	23.1
T3	13	14.0	4	30.8	2	15.4	7	53.8
T4	109	37.3	16	14.7	61	56.0	32	29.4
T5	8	20.0	1	12.5	06	75.0	1	12.5
T6	56	22.3	11	19.6	28	50.0	17	30.4
T7	6	12.2	1	16.7	5	83.3	0	0.0
T8	9	32.1	2	22.2	7	77.8	0	0.0
T9	6	40.0	0	0.0	6	100.0	0	0.0
T10	1	12.5	0	0.0	1	100.0	0	0.0
P1	50	17.1	17	34.0	23	46.0	10	20.0
P2	1	25.0	1	100.	0	0.0	0	0.0

RIF HIV+ = HIV positive TB cases resistant to rifampicin
RIF HIV- = HIV negative TB cases resistant to rifampicin
RIF HIV± = HIV unknown TB cases resistant to rifampicin
S = Secondary; T= Tertiary; P= Private

The Xpert tests were indeterminate in 509/12249 (4.2%), and failed in 792/12249 (6.5%). Of all patients tested the proportion of MTB cases with undocumented HIV status was 1058/12249 (8.6%). However, within the MTB cases, the proportion of cases with undocumented HIV status was 1058/3669 (28.8%). The distribution of the indeterminate test findings, failed Xpert tests, and

MTB cases with undocumented HIV status by site-type among all patients tested is summarized in figure 1.

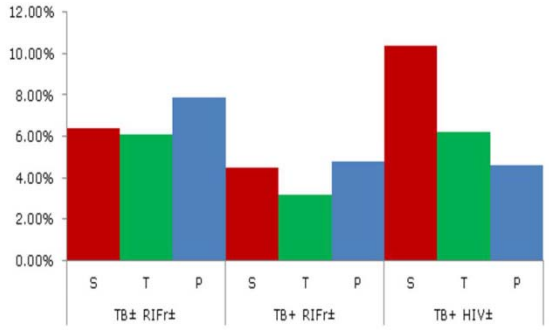

Figure 1. Distribution of Failed (TB± RIFr±), Indeterminate (TB+ RIFr±) Xpert test results and MTB cases with undocumented HIV status (TB+ HIV±) across the secondary (S), tertiary (T) and private (P) site

Comparisons of the site-type with respect to indeterminate, failed result and undocumented' HIV status showed the three sites to differ significantly. While the tertiary site was less likely to yield test results that were indeterminate compared to the secondary and private sites (OR= 0.72, 95% CI: 0.58, 0.90; p=0.03; OR=0.66, 0.48, 0.91; p=0.01), the non-documentation of HIV status was more likely among patients who visited secondary site than tertiary, and private (OR=1.75, 95% confidence interval (CI): 1.49-2.04, *p*=<.0001; OR=2.44, 95%CI: 1.85-3.20; *p*= <.0001) (table 3).

Challenges in the roll-out of Xpert services

A review of the reports on program monitoring and evaluation showed that the program was implemented in selected secondary, tertiary and private levels health facilities .None of the primary health care facilities assessed by the program implementers met the criteria selection, mainly based on the suitability for Xpert machine installation. Logistical issues, such as, lack of alternative power supply, limited laboratory space and inadequate human resources were listed as the reasons for the failures of the primary health facilities. However, even among the secondary and tertiary facilities selected for the program, alternative sources of power supply were lacking in some. There were frequent reports of power inverter failures from more than half of the selected sites, in addition to insufficient human resources and poorly equipped laboratories (without work bench, air-condition, refrigerator etc.).

Machines utilizations were generally suboptimal because the program selectively targets presumptive cases of drug resistant TB and HIV cases with presumptive TB. There were delays in getting cases of MDR-TB enrolled into drug treatment despite increase in MDR-TB treatment centers from a single facility (24 beds capacity in 2010) to ten hospitals with over 285 beds capacity nationwide according to the 2013 Ministry of Health's annual report on tuberculosis and leprosy captured in one of the program's reports. Codes were not provided for some of the error results and indeterminate outcomes were often labelled invalid in some sites.

Documentation of HIV status was also inconsistent and no reasons were given for client whose HIV status was

Table 3. Comparison of frequencies of indeterminate (Indetr) Xpert tests, failed results and undocumented HIV status between secondary (S), tertiary (T) and private (P) Xpert program sites in Nigeria

Outcome	Site Type	Yes, Yes	Yes, No	No, Yes	No, No	OR	95% CI	P-value
Indetr	T vs. S	111	337	3308	7230	0.72	0.58, 0.90	0.030
	S vs. P	337	61	7230	1202	0.99	0.69, 1.21	0.548
	T vs. P	111	61	3308	1202	0.66	0.48, 0.91	0.010
Failed	S vs. T	484	208	7083	3211	1.05	0.89, 1.25	0.532
	S vs. P	484	100	7083	1163	0.79	0.64, 0.99	0.042
	T vs. P	208	100	3211	1163	0.75	0.59, 0.97	0.021
HIV ±	S vs. T	787	213	6780	3206	1.75	1.49, 2.04	<.001
	S vs. P	787	58	6780	1205	2.44	1.85, 3.20	<.001
	T vs. P	213	58	3206	1205	1.38	1.02, 1.86	0.030

OR: odds ratio, CI: confidence interval, HIV ±: HIV status undocumented

not documented. Patient HIV status is coded and reflected in the laboratory requests forms that accompany the sputum specimens, in situations where the sputum samples were collected and brought to the center from clinics without Xpert services, or in program sites where patients walk in with the request form to provide sputum samples. The non-reflection of HIV status was more frequent with samples coming from centers other than where the machines were located. for samples brought to the site from collection centers that were remotely located. Logistical delays in getting the data collection tools to the sites were a frequent complaint. Finally, there were concerns of lack of awareness of the existence of Xpert services among clinicians at different service points within and outside where the machines were installed. Some of these challenges and suggested ways to address them were summarized in table 4.

Table 4. Key challenges in the rollout and scale-up of Xpert program in Nigeria

Challenge	Comments	Suggestions
Sample transfer and results retrieval strategies	No standardized sample transfer mechanisms between sites with machines and those without, and sites that are farther located.	Consider equipping and decentralizing services to Primary Health Centers in densely populated areas lacking Xpert services.
Proper documentation and reporting of test outcomes	Non-adherence to protocol and occasional delays in the supply of data collection tools may have contributed to the inconsistencies in test results documentation.	Regular supervision and training of site staff on proper documentation of results, sample collections, processing, and testing.
Non-documentation of patients HIV status and poor integration of HIV-TB services at site level.	HIV infection is an eligibility criterion for access to Xpert services. Screening TB cases for HIV and vice-versa is also part of the standard of care.	Offer HIV counselling and testing services at the point of Xpert testing to cases with unknown HIV status. Provide reasons for unknown status; example, refusal of HIV test.
Frequent power interruption	All the machines at the secondary sites run on alternative source of electricity for most of the working hours in a day	Collaborate with site HIV program. Generators supporting the CD4 count machines in some sites could be used to support Xpert program. Consider solar energy as an alternative source of power.
Long programmatic turnaround time	Takes days and even weeks from sample collection to diagnosis.	Internet based GxAlert is being introduced which sends instant results via text messages to both patients and clinicians. Improve flow of patients, samples, and results at facility level.
Low awareness of Xpert program and services among clinicians	Xpert is not part of routine TB and TB/HIV training program in many sites. Many clinicians in such sites were unaware of the existing Xpert program at their sites	Create awareness through presentations at clinical meetings and updates trainings. Integrate of Xpert into all TB & TB/HIV training manuals.
Inefficient Xpert cartridges supply management system	While some sites were low or running out of cartridges others have expired stock of cartridges	Cartridges supply should match site needs. GxAlert provides daily utilization of cartridges by site.

However, even among patients from the program sites, missing data on HIV status was common.

In many sites, inefficient sample and result retrieval flow system resulted in prolonged time to diagnoses after samples were collected. Programmatic turnaround time from sample collection to diagnoses varied with some running into several weeks due to logistical delays in sample transportation and result retrievals particularly

DISCUSSION

The phased introduction and scale-up of Xpert program in Nigeria is yielding encouraging outcomes from testing specific population groups. Access to the program is limited to cases at risk of drug resistant tuberculosis (DR-TB) and HIV infected patients with suggestive symptoms of tuberculosis unlike in several other countries where the test is offered to all

presumptive cases of tuberculosis.[16,17.] The high proportion of the MTB cases resistant to rifampicin indicates that risk groups for DR-TB are being well targeted. Rifampicin resistance is used as a proxy for MDR-TB and the predictive value of positive Xpert rifampicin resistance for MDR-TB improves greatly with increasing prevalence of resistance to rifampicin.[13]

The scale-up of DR-TB treatment centers mentioned, to match the demand created by increased detection of the resistant cases, from a single 24 beds capacity facility in 2010 to over 285 beds capacity in 10 facilities in 2013 will improve access to treatment for resistant cases. Care should however, be taken to ensure that this apparent success of improved access to treatment is not diminished by delays in treatment initiation due to poor flow of samples and test results. As the program expands, resistant TB case detection will continue to rise. Addition of treatment sites may not provide the needed solution to the delays in treatment initiation if the logistical problems associated with sample transfer, diagnosis, results retrieval and processing of patients for enrollment are not addressed. Long programmatic turnaround time is a challenge with Xpert implementation in most settings[3] but diagnostic delays exceeding a few days and getting into several weeks could significantly impact on the quality of care and synergy with other programs.[8]

The failure of any of the primary care facilities inspected to qualify for the program is a concern because the long-term objective is to make these services more accessible at the community level. Meeting the infrastructural and operational needs of the primary sites is an important consideration for the decision-makers. A recent study indicated that Xpert test can successfully be run by a nurse in primary-care clinics in settings with limited resources.[17] With adequate infrastructure, sufficient capacity and strong supervision, more patients will have access to the services at the community level.

For effective program evaluation and the use of Xpert for intensified TB case findings among patients with HIV co-infection, it is essential that HIV counseling and testing (HCT) services are offered to all patients in Xpert program and their status documented.[18-20] One in three of all the TB cases identified by Xpert in this program have no documented evidence of access to HCT. This makes it hard to evaluate the uptake and impact of the program among all HIV cases with presumptive TB. The proportion of MTB cases without documented HIV status is higher among patients tested at secondary health facilities, the sites where the majority accessed Xpert services at the moment. This calls for improve co-ordination in such centers between the Xpert program and the HIV services, at the sites and from sputum collection centers to enable tracking of patients HIV status and capturing that information into the Xpert program database. Additionally, HIV test could be offered to patients who walked in to provide sputum specimen and whose HIV status is not reflected on their test request forms.

The focus on specific groups could be programmatically efficient. The high number of cases with drug resistant TB attests to this. However, the more the target groups are narrowed, the less is the number of eligible patients to take the test. The machine and the expensive cartridges are then underutilized. Given the setting, interruption in power supply and excessive temperatures are anticipated. However, with the existing complementary programs such as the US President's Emergency Program for AIDs Relief (PEPFAR) in some of the sites, working out modalities to link Xpert machines to generators supporting other programs where feasible could minimize the effect of frequent power interruption on the test uptakes and outcomes.

Xpert rollout and scale up program in Nigeria is recording considerable successes, however, limiting the services to health facilities above primary centers; prolonged delays in the diagnosis and treatment; lack of on-site synergy between TB/HIV services and in efficient sample and result retrieval flow system are challenges to the program implementation. Equally, the sole objective of obtaining same day result to initiate treatment may be hard to achieve given the delays from poor sample and patient flows which are likely to worsen when the algorithm is altered to target all suspected TB cases. Program decentralization should consider equipping and building capacity in facilities nearest to the people especially the primary health care sites.

CONCLUSION

Despite the fact that Xpert MTB RIF machines was aimed to be place at the lowest health care delivery level for ease of access, lack of infrastructural support and human resource were key barriers in Nigeria. Diagnoses of tuberculosis and resistance to rifampicin could be enhanced by offering integrated TB/HIV

services; improving patient and sample flow/referral; proper documentation of test outcomes and alignment with DR-TB management

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FREQUENCY OF ADVERSE EFFECTS OF FIXED DOSE COMBINATIONS, IN TUBERCULOSIS AND THERE EFFECTS ON TREATMENT OUTCOME

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ABSTRACT

Introduction: This study was designed to assess the frequency, types and impact of adverse drug reactions (ADR) to category 1 anti-tubercular therapy using fixed drug combinations (FDC). Patients with tuberculosis started on anti TB treatment from 01st of July 2011 to 30th of June 2012 were recruited

Methodology: Patients were followed up for development of ADR. Frequency of ADR, number of patients who required prolongation of therapy, who had alternate regimes, and there treatment outcome were recorded.

Results: Out of 280 patients with tuberculosis 67 (24%), 37 (55.2%) males, 30 (44.8%) females ADR. Thirty three out of 74 (44%) of total population above the age of 60 had ADR, while only 34 out of 206 (16.5%) of patients below the age of 60 had ADR (Chi= 23, p <0.0001). Incidence of ADR were - Dyspeptic symptoms 31(11.1%), itching 20 (7.1%), hepatitis 9 (3.2%), arthralgia 1 (0.4%), vertigo 1 (0.4%), peripheral neuropathy 1 (0.4%), visual impairment 1 (0.4%), rash 1 (0.4%).

Out of 27 patients who had prolongation of therapy 22 (81.4%) were due to ADR (Chi = 54, p <0.0001). Nine (3.2%) were given alternate regimes (Fishers exact p = 0.000017) [6 hepatitis, 1 rash, 1 vertigo, 1 visual impairment]. None of the patients with ADR had relapses or treatment failures.

Conclusion: Adverse reactions were commoner among the elderly, and were associated with prolongation and modification of anti tuberculosis therapy but over all treatment outcomes were not adversely affected.

Key words: Tuberculosis, Fixed Drug Combinations, Adverse Reactions, Alternative Regimes

INTRODUCTION

Tuberculosis is still a major cause of death and one of the most challenging public health problems worldwide. Two billion individuals, about one-third of the total human population, are infected with the causative agent of tuberculosis, *Mycobacterium tuberculosis*.[1] According to the World Health Organization's 2014 global report on Tuberculosis (TB), there were 9 million estimated cases of TB 2013, with a loss of 1.5 million human lives.

Once diagnosed, patients with tuberculosis must undergo immediate treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months and subsequently, patients with newly detected pulmonary tuberculosis should receive isoniazid and rifampicin for another four months. For an optimal outcome, the treatment should be according to Directly Observed Treatment Short course (DOTS).[3]

Many adverse effects are associated with anti tubercular treatment (ATT). As TB requires long-term treatment, many adverse effects and patient non adherence remains the most important reason for treatment failure.[4]

In the management of TB patients, fixed-dose combination (FDC) anti-TB drugs are recommended over individual drugs.[2] Sri Lanka has introduced FDCs for TB treatment since 2005. There are several advantages as well as disadvantages of using fixed dose combination tablets over individual drugs in the treatment of tuberculosis.[5] Our national policy is to use FDC 4 tablets (INAH – 75mg, Rifampicin 150mg, ethambutol 275mg and pyrazinamide 400mg) for

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intensive phase and FDC 2 (INAH – 75mg, Rifampicin 150mg) for continuation phase, according to weight bands in the category 1 regime.

Since FDC are in wide use now, it is important to have a better understanding of the adverse reactions in order to detect them in time and to study their impact on the treatment outcome. The objectives of our study were to assess the frequency and types of adverse reactions to FDC and to find out the impact of adverse reactions on the treatment regimen. We also aimed to assess the impact of occurrence of adverse reactions and the subsequent changes in the treatment regimens on the treatment outcome in patients with tuberculosis.

METHODOLOGY

This prospective descriptive study was carried out on patients whose anti TB treatment was started from 01st of July 2011 to 30th of June 2012 at Respiratory unit 01, Chest Clinic-Kandy. Ethical approval for this study was granted by the Ethical Committee of Teaching Hospital Kandy. Written informed consent was obtained from all participants of the study.

All patients who were confirmed to have Tuberculosis and were initiated on FDC [FDC4 (HRZE) x 2 months and, FDC2 (HR) x 4 months] with a plan to be treated for six months during the study period of one year were recruited. This population included pulmonary and extra pulmonary TB, but excluding TB meningitis, CNS TB, bone TB and military TB. Both bacterially positive as well as negative patients were included. Only the new cases were included. Case definition given by the national guideline was used to diagnose tuberculosis in this study. They were managed according to daily DOTS strategy.

Patients who met the following exclusion criteria were excluded from the study. Exclusion criteria were: patients on regimes other than the standard (CAT 1) regime, patients who were on individual drugs, patients on long term steroids and anti-histamines, patients with active skin diseases prior to drug treatment, patients with HIV, and patients with TB meningitis, CNS TB, bone TB and military TB who would any way receive ATT for more than 6 months due to the site of infection.

Patients who were started on ATT were educated on the following symptoms at the commencement of ATT for adverse reactions.

Major reactions

Nausea, vomiting, yellow discoloration of eyes and urine, skin rashes, oliguria, dizziness, confusion, visual impairment and features of shock.[3]

Minor reactions

Epigastric discomfort and pain, itching of skin, numbness of feet, joint pain and swelling, flue like symptoms and orange colored urine.[3]

Patients with major reactions were advised to stop treatment and report to the local treatment facility immediately and those who had minor reactions were advised to report to local treatment facility but continue treatment.

All were screened for diabetes, and all patients underwent full blood count (FBC) liver biochemistry, and renal functions before the start of ATT.

Patients were followed up weekly or earlier if they develop adverse reactions.

They were screened for the development of adverse reactions using an interviewer administered questionnaire which evaluated itching, rash, gastritis, hepatitis, visual impairment, arthralgia, vertigo, peripheral neuropathy and acute renal failure.

WHO definition for the diagnosis of ATT induced hepatitis was used in this study to diagnose drug induced hepatitis.FDC induced hepatitis was defined as elevation of serum transaminases more than 2 folds of the normal and elevated serum bilirubin level in symptomatic patients (i.e. patients with nausea, vomiting with or without icterus or hepatomegaly) after clinical exclusion of other causes of hepatitis.[4]

Patients with visual symptoms underwent ophthalmic assessment by an ophthalmologist for diagnosis/exclusion of optic neuritis. Patients with features of peripheral neuropathy underwent nerve conduction studies.

Patients who developed adverse reactions were managed according to WHO guideline for treatment of tuberculosis 2009.[3]

All patients were followed up for a year since the commencement of treatment and patients with adverse reactions were followed up with sputum cultures for Mycobacterium tuberculosis at 6 months and 12 months to confirm that cultures are negative. WHO treatment outcome definitions were used to categorize the treatment outcomes in our study.[3]

Data was entered in excel spread sheets and descriptive analysis was done using percentages. Chi square statistics was used to asses if adverse reactions act as a risk factor for prolonged or altered therapy.

DISCUSSION

Adverse reactions to anti tuberculosis medications have been the subject to many researches. According to a study done by WHO anti-tuberculosis drugs are known to be associated with number of adverse effects and that can lead to drug discontinuation in up to 23% of patients.[4]

Studies done on individual drugs were found but, fixed dose combination (FDC) therapy related data were not available in Sri Lanka. Since FDC therapy is being widely used in Sri Lanka since 2005, data related to it would be essential in the program for TB control. Since adverse reactions can lead to significant morbidity and loss of compliance it's vital for a national TB control program to have an assessment of the problem.

Hepatotoxicity is the most common major adverse reaction found in our study (3.2%). This is a significant proportion given the seriousness of the condition and the time taken to desensitize such patients. Overall incidence of hepatotoxicity was 3% in a study done by Daphne Yee et al. Incidence of ATT induced hepatitis is comparable in our study compared to the study done by Daphne.

However the study done by Senarathna et al in pre FDC era in Sri Lanka show an incidence of drug induced hepatitis of 9.5%.[7] The same study showed that 6 out of 74 patients who had drug induced hepatitis died, but none of the patients in our study died during the study period. One of the most important finding in our study is that the incidence of drug induced hepatitis is less compared to pre FDC era. There are no previous studies done on FDC to find out the adverse reactions in Sri Lanka. Whether incidence of drug induced hepatitis is less with FDC compared to individual drugs is an important finding which should be assessed further. One good reason for this could be the lower doses of isoniazid and pyrazinamide against the standard doses of rifampicin included in FDC used in Sri Lanka.

Efficacy of FDC in treatment of tuberculosis has been comparable to individual drugs as shown in a study done by Christian Lienhardt et al. [8] This study confirms non inferiority of FDC to individual drugs. The same study shows that incidence of severe adverse reactions were similar between individual drugs. Therefore it's interesting to know if a low dose of INAH (225 mg) in FDC is enough to treat tuberculosis compared to 300 mg. Similarly proportion of pyrazinamide is lesser in FDC (1200mg instead of 1500mg). Whether this lowered dose is responsible for lower incidence of ADR is a possibility. A further study is suggested to investigate this interesting finding.

The overall incidence of dermatological reactions has been estimated at 5.4%.[3] Incidence of skin reactions was higher in our study (7.5%). However most of the patients were having pruritus (7.1%) which did not warrant alternate regimes or discontinuation of treatment. Their treatment regime was continued under antihistamine cover. The only patient who had a rash was secondary to pyrazinamide and the drug was discontinued.

Gastrointestinal symptoms such as loss of appetite, nausea, mild abdominal pain, vomiting and diarrhea have been reported with rifampicin and which may lead to modification of the regimen in up to 9% of patients.[9] Dyspepsia was the commonest adverse reaction (11.1%) shown in our study.

It is estimated that rifampicin associated acute renal failure occurred in 0.05% of patients treated for TB, but in our series we didn't find any patient with this ADR.

Twenty three percent of patients in our study had adverse reactions which is comparable to the study done by Schaberg T et al.[10] Therefore nearly one fourth of the patients commenced on ATT develop ADR which is quite a significant proportion. Although data on overall incidence of adverse reactions to ATT in Sri Lanka is lacking, one of the previous preliminary study done by same authors has shown that incidence of major adverse reactions is 15%.[11] Same study showed that among the patients who needed hospital admission 48% had drug induced hepatitis.

Male female ratio was similar to studies done in Sri Lanka previously.[12] Proportion of females in the adverse reaction group was higher but this difference was not statistically significant.

Patients who had ADR were slightly older compared to patients who didn't have ADR. A significant proportion of patients (44%) above the age of 60 had adverse reactions. This finding is comparable with past studies which identifies age as a risk factor for adverse

reactions. This emphasizes the importance of closely following up elderly patients for adverse reactions.

A significant finding in this study is that patients with ADR were more prone to have a prolonged therapy for >6 months. That means having an ADR considerably increases morbidity. Although there were many studies looking into adverse reactions this knowledge is new and highlights the importance of monitoring patients closely for development of ADR. However having adverse reactions did not adversely affect the overall treatment outcome. In fact the failures were zero among ADR group this could be due the better supervision and more interaction with the health care workers in patients who had ADR. All patients with ADR underwent sputum cultures for mycobacterium tuberculosis which was negative at 6 and 12 months which confirms that the alternative regimes were safe and effective. This study provides valuable new information regarding adverse reactions to anti tubercular treatment in Sri Lanka as there are only few studies done on this field despite the number of patients with tuberculosis.

RESULTS

A total of 280 patients were on study 168 (60%) males and 112 (40%) females. The mean age of the total 280 patients was 48 years (SD 18.7), 67 (24%) had adverse reactions out of which 12 (4.3%) were major reactions and 55 (19.6%) were minor reactions.

Mean age of patients with adverse reactions was 51.3 years (SD 16.54; range 18 to 91) while mean age of patients without ADR was 45y (SD 18).Thirty seven males (21.8%) and 30 females (27%) had adverse reactions (Chi = 0.68) (p= 0.51).

Thirty three out of 74 (44%) of total population above the age of 60 had adverse reactions in our study, while only 34 out of 206 (16.5%) of patients below the age of 60 had adverse reactions (Chi= 23) (p =<0.0001).

Frequency of adverse reactions is shown in table 1.

Table 1. Frequency of adverse reactions

ADR (Major)	n	%	incidence
Hepatitis	9	13.4	3.2
Vertigo	1	1.5	0.4
Vision	1	1.5	0.4
Rash	1	1.5	0.4
ARF	0	0.0	0.0
ADR (Minor)			
Dyspeptic	31	46.3	11.1
Itching	20	29.9	7.1
Arthralgia	3	4.5	1.1
Peripheral	1	1.5	0.4

Twenty seven patients had prolonged treatment of >6 months out of which 22 81.4%) were due to adverse reactions (chi = 54, p<0.0001).

Treatment outcome and ADR is shown in table 2

Table 2. Treatment outcome and ADR

Outcome	With ADR	%	Without ADR	%
Treatment successful	67	100	190	89.2
treatment interrupted	0	0	4	1.9
failures	0	0	6	2.8
not analyzed	0	0	13	6.1
Total	67	100	213	100.0

Nine patients (13.4%) out of 67 who had ADR had to be given alternative regime while none of the patients out of 213 who did not have adverse reactions were put on alternative regimes [Fishers exact p = 0.000017].

Out of 22 who had prolonged therapy 9 (40.9%) received alternate regimes while rest of the 13 (51.1 %) were successfully desensitized or the same regime was continued. For majority of patients with pruritus same regime was continued with antihistamines.

Table 3 shows the frequency of patients who required alternate regimes due to ADR.

Table 3. Frequency of ADR that required alternate regimes

ADR	n
Itching (with skin eruption)	1
Hepatitis	6
vertigo	1
visual impairment	1

Three patients with hepatitis were successfully desensitized. None of the patients died due to ADR.

CONCLUSIONS

Adverse reactions were associated with prolongation of anti tuberculosis therapy and altered regimes, but overall outcome was not adversely affected. Adverse reactions are commoner among the elderly.

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KNOWLEDGE AND AWARENESS OF TUBERCULOSIS AMONG PULMONARY TUBERCULOSIS PATIENTS IN A RURAL AREA OF WEST BENGAL

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ABSTRACT

Introduction: India has more new tuberculosis (TB) cases annually than any other country and contributing of about twenty percent to the global burden of TB. The objective of the present study was to understand the knowledge and awareness of TB among adult male pulmonary TB patients in a rural area of West Bengal.

Methodology: The present cross-sectional study was carried out among the TB patients registered under the Revised National Tuberculosis Control Programme (RNTCP). A structured questionnaire was used for data collection.

Results: The mean age of the study participants was 41.46 (14.3) years.52% of the subjects never heard of TB before diagnosis of their disease. Majorities of the participants thought that smoking and chewing tobacco was the cause of TB. With regard to the mode of spread, 21% thought that TB spread through unclean food and water followed by through sharing materials for drink (21%). Most of the participants were unaware or had no idea about the fact that transmission of TB is preventable. With regard to the occurrence of TB in life time, 64% had no idea. With regard to the curability of TB, 38% said that it is curable and majorities (60%) said don't know, 40% subjects thought that good food and drinking water can reduce the chance of getting TB.

Conclusion: This study showed that lack of knowledge and misconceptions regarding TB were widespread among the TB patients. Thus, the present study emphasizes the need for health education programmes to improve knowledge, awareness and removing misconceptions about TB.

Key words: Awareness, Knowledge, Pulmonary tuberculosis, West Bengal

INTRODUCTION

Tuberculosis (TB) has reached epidemic proportions in many developing countries including India.[1] India has more new TB cases annually than any other country with a contribution of over twenty percent to the global burden of TB.[2] Among different types, pulmonary TB is one of the leading causes of adult mortality.[3] Studies also demonstrated that the prevalence of TB was more common among men than women of economically productive age groups,[4] indicating variation in infection and progression of disease.[5]

Study shows that HIV positive individuals are more susceptible to develop TB compared to HIV negative individuals and it is the leading cause of death among HIV positive individuals.[6] The association of pulmonary TB with diabetes mellitus.[7,8] and rheumatoid arthritis [9] is also well established. Study also shows that TB patients had a significantly higher risk of developing chronic kidney disease than the controls.[10]

Since the introduction of National Tuberculosis Control Programme (NTP) in 1962, the Government of India has taken different steps to controlling TB on a mass basis.[11,12] However, the lack of awareness regarding TB impeding progress toward TB control. Because, the incidence of TB was inversely associated with increasing awareness.[13,14] Moreover, lack of awareness

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can worsen the epidemiological situation by increasing drug resistant patients, who may increase the risk of infection with drug-resistant bacilli.[12]

Literature review revealed that some studies in India have been done to understand the knowledge and awareness about TB both in patient[15-17]and in general populations.[18,19] However, to best of our knowledge, study related to knowledge and awareness about TB among TB patients of rural areas of West Bengal is yet to be made. With this view of context, the objective of the present study was to understand the knowledge and awareness of TB among adult male pulmonary TB patients in a rural area of West Bengal.

METHODOLOGY

The present cross-sectional study was carried out among one hundred adult male pulmonary TB patients, selected at random from the patients registered under Revised National Tuberculosis Control Programme (RNTCP) of Rampurhat Tuberculosis Unit (TU), West Bengal, about 250 km. from Kolkata city. Informed consent was obtained from each participant before commencement of the study. The participants in the present study were restricted in male because studies revealed that the prevalence of TB was higher in males than females.[20] Moreover, a recent study[21] based on NFHS-2 and NFHS-3 data demonstrated that the prevalence of TB had significantly declined in female, but not in male.

A structured questionnaire was used for data collection. The questionnaire was first pilot tested and after a few modifications the questionnaire was implemented. The questionnaire consisted of two sections; first section was about the subject's socio-economic characteristics including age, sex, education, occupation, monthly household income etc. Second section was about the knowledge and awareness on TB like heard of TB disease, cause of transmission, symptoms, parts of the body affected by TB bacilli, etc. Statistical analyses were performed using SPSS software version 9.0 (Statistical Package for Social Science, SPSS Inc, Illinois, USA).

RESULTS

Mean age of the study participants was 41 years. The average monthly household income of the participants was Rs. 2548 (1627). Characteristics of the studied population are presented in table 1. It shows that majority (84%) of the study participants were married. With regard to the educational status, 59% participants were able to read and write, 38% were illiterate, 3% were only able to read. The distribution of occupation indicated that most of the participants occupation were either daily labor (35%) or agriculture labor (33%), followed by business (12%) and others including driver, service, pastoralist (3%). However, 17% individuals were unemployed. The result also revealed that most (72%) of the participants are residing in the study area since birth.

Table 1. Characteristics of the studied population

Characters	Specified characters	Percentage
Marital status	Married	84
	Single	14
Education	Reade and write	59
	Read only	3
	Illiterate	38
Occupation	Daily labor	35
	Agriculture labor	33
	Unemployed	17
	Business	12
	Others	3
Duration of residence	Birth place	72
	Migrated from other places	28

Knowledge and awareness about TB in the studied population are presented in table 2. It revealed that, 52% of the subjects never heard of TB disease before diagnosis of their disease. When they were asked about the source of information about TB, 26% individuals replied health worker, 11% replied patient, followed by friend (6%), family member (3%) and, media and neighbor 1% each as a source of information about TB. With regard to the cause of TB, 19% participants think that smoking and chewing tobacco was the cause of TB. 17% participants think that poor nutrition was the cause of TB, followed by, drinking alcohol (12%), cold air (9%), dust (8%), shortage of food (7%), bacteria/germ (6%), drinking raw milk (3%), evil eye (2%) and work load (2%). However, 15% subjects had no idea about the cause of TB. When

participants were asked about the symptoms of TB, 21% answered that cough for 2 or more weeks was the symptom of TB. However, 17% participants answered that sputum with blood was the symptom of TB. 15% participants thought that cough for 2 or more weeks, sputum with blood and weight loss were the symptom of TB, followed by fever and sweat at night (14%), cough for 2 or more weeks and fever and sweat (6%), fever and sweat at night and sputum with blood (5%), chest pain (4%), cough for 2 or more weeks and chest pain (4%), sputum with blood and chest pain (3%), fever and sweat at night and chest pain (3%), sputum with blood, weight loss and loss of appetite (3%), weight loss and chest pain (2%), cough for 2 or more weeks, fever and sweat at night and chest pain (2%), and cough for 2 or more weeks, loss of appetite and chest main (1%). With regard to the mode of spread, 21% thought that TB spread through unclean food and water. Another 21% thought that the mode spread was through sharing materials for drink, followed by through cough, sneeze and breadth (14%), drinking raw milk (11%), through sharing materials for feeding (10%), heredity (8%), through contact with patient (4%). However, 11% subjects have no idea about the mode of spread. When the participants were asked about the transmission of TB preventable or not, only 15% answered yes and 62% answered as don't know. When the subjects were asked about the source of information on TB treatment, 55% replied that the source of information was health workers, 30% replied as patient, 14% replied as family and 1% replied the source of information was media. With regard to the duration of TB treatment, 66% replied that the duration of TB treatment was 6 months, 10% replied 7 months, 11% replied ≥8 months, 5% < 6 months. When the participants were asked about the occurrence of TB in life time, 29% replied that TB can re-occurred, 7% replied that TB occurs only once in life time. 64% replied that they don't know. With regard to the organs affected by TB, 72% thought that only lung is affected by TB and 26% replied don't know. With regard to the curability of TB, 38% said that it is curable. With regard to the question, what reduces the chance of getting TB, 40% subjects replied that good food and drinking water can reduce the chance of getting TB, 10% subjects replied that good environment can reduce the chance of getting TB, 15% subjects replied that avoiding of smoking and alcohol can reduce the chance of getting TB, followed by drink lots of water (3%), avoid dust (3%), supplementary nutrition (2%), take care of cold (2%), keep distance from TB patient (2%), protection against germ (1%), take care of health (1%).

Table 2. Knowledge and awareness about tuberculosis in the studied population

Characters	Specified characters	%
Heard of TB, before diagnosis	No	52
	Yes	48
Source of information about TB	Health worker	26
	Patient	11
	Friend	6
	Family member	3
	Media	1
	Neighbor	1
Cause of TB	Smoking and chewing tobacco	19
	Poor nutrition	17
	Drinking alcohol	12
	Cold air	9
	Dust	8
	Shortage of food	7
	Bacteria/Germ	6
	Drinking raw milk	3
	Evil eye	2
	Work load	2
	Don't know	15
Symptoms of TB	Cough for 2 or more weeks	21
	Sputum with blood	17
	Fever and sweat at night	14
	Cough for 2 or more weeks, sputum with blood and weight loss	15
	Cough for 2 or more weeks and fever and sweat	6
	Fever and sweat at night and sputum	5

	with blood	
	Chest pain	4
	Cough for 2 or more weeks and Chest pain	4
	Sputum with blood and chest pain	3
	Fever and sweat at night and chest pain	3
	Weight loss and chest pain	2
	Sputum with blood, weight loss and loss of appetite	3
	Cough for 2 or more weeks, loss of appetite and chest main	1
	Cough for 2 or more weeks, fever and sweat at night and chest pain	2
Mode of spread	Through unclean	21
	Through sharing	21
	Through cough,	14
	Drinking raw milk	11
	Don't know	11
	Through sharing	10
	Heredity	8
	Through contact	4
Transmission of TB preventable	Yes	15
	No	23
	Don't know	62
Source of information on TB treatment	Health worker	55
	Patient	30
	Family	14
	Media	1
Duration of treatment	6 months	66
	7 months	10
	≥8 months	11
	Don't know	8
	< 6 months	5
Occurrence of TB in life time	Re-occurred	29
	Only once	7
	Don't know	64
Organ effected by TB	Lung	72
	Don't know	26
	Bone	1
	Whole body	1
Curability of TB	Yes	38
	No	2
	Don't know	60
What reduces the chance of getting TB	Good food and drinking water	40
	Good environment	10
	Avoid smoking and alcohol	15
	Drink lots of water	3
	Supplementary nutrition	2
	Take care of cold	2
	Avoid dust	3
	Keep distance from TB patient	2
	Protection against germ	1
	Take care of health	1
	Don't know	21

DISCUSSION

Poverty and lack of awareness are considered the most important factors that increase the risk of exposure to TB as well as health-seeking behavior. Moreover, it also affects earlier diagnosis, effective treatment and prevention strategy.[14] In order to understand the knowledge and awareness on TB among adult male pulmonary TB patients of a rural area of West Bengal, the result revealed that majorities of the subject never heard the disease TB before diagnosis of their TB disease. However, it was 27.6% in Pakistan who never heard about the disease, before diagnoses of their TB[1] and 83% in South West Ethiopia.[22]

Primary source of information about TB and its treatment in the present study was health worker, followed by patient. However, the contribution of media in increasing awareness was very low. This was in corroboration with the study by Khan et al.[1]. Contrary to that, health facility was the least source of information while relatives and friends were the most important sources in central Tanzania.[3]

Interestingly, most of the subjects had misconception about the cause of TB, they think that smoking and chewing tobacco, poor nutrition, drinking alcohol, cold air, dust, shortage of food, drinking raw milk, evil eye and work load were the causes of TB. However, very small number of individuals answered that bacteria/germ was the cause of TB. Similarly in a study in Delhi, Singh et al.[23] reported that only 2.3% of the participants knew that TB was caused by a germ. Similar to the findings of the present study a previous study in Ethiopia also observed misconceptions about the causative agent of TB in majorities of the participants.[14]Study in central Tanzania also observed smoking cigarette or tobacco as the most important cause of TB infections.[3]Smoking as the cause of TB was also perceived by the majorities of South Africans.[24] The findings of the present study indicated that the subjects had basic awareness about the symptoms of TB, which was comparable to the results of previous studies from West Bengal,[12] North East Ethiopia,[14] South West Ethiopia[22] and Nepal. [25]The results also demonstrated that the participant's knowledge about the mode of spread of TB varied widely. Most of the participants thought that socio-cultural factors like sharing materials for drink and feeding are the mode of spread of the disease. However, some community-based studies showed that social-cultural factors may increase the risk of acquiring TB.[26,27] Sharing of domestic utensils was also considered as an important modes of TB transmission in central Tanzania.[3]

In contrary to some other studies[14, 28] most of participants in the present study were either unaware or had no idea about the fact that the transmission of TB is preventable. This was only 10% in Pakistan, who was not considered TB as a preventable disease.[1]We also noted that majorities of the participants were aware about the duration of treatment, but had no idea about its occurrence in life time. Similar study by Khan et al.[1] also observed that only 17% responders in Pakistan thought that TB occurred only once in a life-time and did not recur for a second time after treatment. The participant's awareness about the duration of treatment was in corroboration with the study in Tanzania.[28]

It was also observed that most of the participants in the present study thought that only lung is affected by TB. Similar result was observed in the study conducted in Southwest Ethiopia,[22] where, 91.6% of the TB suspects thought that the lungs were the most affected part of the body. Majorities of Nepalese people also thought lung as the main part affected by TB.[25]Contrary to that, only 23% Pakistani patients considered lung as the only organ affected by TB.[1] With regard to the curability of TB, most of the patients had no idea about the curability of TB. Only 38% said that it is curable. Contrary to that a previous study in Tanzania by Kilale et al.[28] showed that all respondents in that study knew that TB was a curable disease. Majorities of the TB patients in Nepal also aware that TB is curable disease.[29]Interestingly,majorities of the TB patients in the present study thought that good food and drinking water can reduce the chance of getting TB, followed by avoiding smoking and alcohol, and good environment.

CONCLUSSION

This study showed that both lack of knowledge and misconceptions regarding TB were widespread among the TB patients. For example, majority of the subjects never heard the disease TB. A considerable number of the participants had misconceptions about the cause and mode of spread of TB. Most of the participants in the present study were either unaware or had no idea about the fact that the TB is curable and transmission of TB is preventable. Surprisingly, a large number of participants thought that good food and drinking water can reduce the chance of getting TB. Thus, the present study emphasizes the need for health education programmes to improve knowledge, awareness and removing misconceptions about TB. Because, poor knowledge of TB patients concerning their disease may obstacle in effective cure, prevention and control of the disease, and thus will contribute more burden of TB disease in the country. However, the main limitations of the present study are the relatively small sample size, restricted to males, and it is not representative of the Indian population. Further studies are needed in a larger sample for effective planning of TB control and prevention strategies.

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PREVALENCE OF DIABETES AMONG TUBERCULOSIS PATIENTS AND ASSOCIATED RISK FACTORS IN KATHMANDU VALLEY

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ABSTRACT

Introduction: Diabetes among tuberculosis patients is a growing concern. The prevalence of diabetes among tuberculosis patients in Nepal is not known. The objective of this study was to determine the prevalence of diabetes among tuberculosis patients and to identify the associated risk factors.

Methodology: A descriptive, cross-sectional study was conducted in Kathmandu valley of Nepal. Face to face interviews using structured questionnaire were conducted to collect socio-demographic and behavioral risk factors. A random blood sugar test was carried out using glucometer. Measurements on height, weight and waist circumference were taken to obtain the anthropometric information.

Results: Out of 407 tuberculosis patients recruited in the study, 37 (9.1%) were found to have diabetes. Among them 28 (6.9%) were self reported cases of diabetes while 9 (2.2%) were found with random blood sugar level >200mg/dl. Tuberculosis patients aged 50 years and above (OR 7.5; 95% CI 2.72-20.66), ever tobacco users (OR 3.5; 95% CI 1.19-10.74), high income status (OR 5.2; 95% CI 1.59-17.26) and self history of high blood pressure (OR 20.0; 95% CI 5.07-79.50) were found significantly associated with diabetes.

Conclusion: Overall, the prevalence of diabetes among tuberculosis patients was 9.1%. Older age, tobacco use, high income status and history of high blood pressure were identified as associated risk factors.

Key words: Diabetes; Prevalence; TB; Nepal

INTRODUCTION

World Health Organization (WHO) stated that 350 million people were living with diabetes in 2011.[1] It is predicted to increase by 50.0% till 2030. The prevalence of diabetes is similar in both high and low-income countries. Likewise, in 2011, there were 8.7 million estimated new cases of tuberculosis (TB) and 1.4 million had died from TB.[2] South-East Asia and Western Pacific regions accounted for 60.0% of total TB cases. TB in Nepal remains to be a major public health problem. About 45.0% of the total population is infected with TB, of which 60.0% are adults.[3]

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Diabetes leads to the faster progression of latent TB infection (LTBI) to active TB disease and poor TB treatment outcomes such as death during treatment, relapses and delayed sputum smear conversion.[1] The prevalence of diabetes among TB patients varies between countries and limited evidences are drawn from low-income countries.[4] Studies in several countries showed varied results regarding the prevalence of diabetes among TB patients. Some revealed 3.3% while others reported up to 44.0%.[5-18] In Nepal, however no studies were found on prevalence of diabetes among tuberculosis patients and its associated risk factors. Thus, the aim of this study was to determine the prevalence of diabetes among tuberculosis patients and to identify the associated risk factors.

Study variables:

Dependent variable: Diabetes among TB patients

Independent variable: Independent variables were divided into 3 major domains:

1. Socio-demographic factors (Age, Sex, Education and Income)
2. Anthropometric measurements (Body Mass Index (BMI) and waist circumference)
3. Behavioral and other risk factors (tobacco use, alcohol use, family history of diabetes, physical activity, food habit, type of TB and history of high blood pressure)

Operational definition of variables:

Diabetes: Respondent who self reported of having diabetes and/or those with random blood sugar level >200 mg/dl at the time of the study enrollment tested by using glucometer was considered to have diabetes.[10]

TB patient: Respondent who was diagnosed and registered as a tuberculosis patient under National Tuberculosis Control Program and was on TB treatment during the study period.

Age: Age of the respondent was in completed years

Income: Income status of the respondents was obtained using principle component analysis method. Respondents were classified into three groups: High, Middle and Low income status. A total of 15 components were included in the analysis to find out the income status of the respondents.

Education: Respondents highest level of education. For the purpose of this study, it was classified as:

No education: Never attended school

Primary: Formal education up to five classes

Secondary: Formal education from 6-10

Intermediate (10+2) or above, 12 class passed or above

Place of Residence: Those respondents who were living in VDCs and municipalities for at least more than 6 months from the interview date were classified as rural residents and urban residents respectively.

Tobacco Use

Ever user: Respondent who revealed that they had ever used tobacco products (cigarettes and/or *bidis*, *khaini, surti, gutkha, pan with jarda* and others) but was or was not using at the time of the study.

Current user: Respondent using tobacco products (cigarettes and/or *bidis*, *khaini, surti, gutkha, pan with jarda* and others) at the time of study enrollment.

Alcohol Use

Ever user: Respondent who answered that they had ever used alcohol but was or was not using at the time of the study.

Current user: Respondent using alcohol at the time of study enrollment.

Family History of Diabetes: Respondents with any one of their parents/grandparents/siblings suffered or suffering from diabetes.

Food Habit: Respondents being a vegetarian (with eggs or without eggs) and a non vegetarian.

Physical Activity: Respondents meeting WHO recommendations of 600 MET minutes per week were considered as physically active and those not meeting the recommended value were categorized as physically inactive. Metabolic Equivalent (MET) is the ratio of a person's working metabolic rate relative to the resting metabolic rate. One MET is defined as the energy cost of sitting quietly and is equivalent to a caloric consumption of 1 kcal/kg/hour.[19]

METHODOLOGY

Study design: A descriptive, cross-sectional study was carried out.

Study population: All TB patients aged 15 years and above who were registered under National Tuberculosis Control Program and on treatment during the study period were the study population. The association between DR TB and diabetes was found unclear, thus DR TB was excluded.[20] Pregnant/lactating mothers were also excluded in the study.

Study setting: The study was conducted in Kathmandu valley comprising three districts viz. Kathmandu, Lalitpur and Bhaktapur which consists of a total of 107 DOTS units. The sites were purposively selected.

Sample Size

Sample size was calculated with following values:

- Two sided confidence level = 95.0%
- Prevalence of diabetes among tuberculosis patients = 14.0%[10]
- Sample size (n)= z2pq/l2
- n = 1.96*1.96*0.14*0.86/(.05)2 = 185.01 =185
- n = 185*2 = 370 (Adding design effect 2)
- Non response rate: 10.0%
- Total sample size = 407

Sampling Design: Each DOTS unit was considered as a cluster. Out of the total 107 DOTS units in the valley, 17 DOTS units were visited which included 9 from Kathmandu, 4 from Lalitpur and 4 from Bhaktapur to get the sample of 407 participants. Seven of those visited DOTS units were hospital run clinics, 5 were municipality run urban health clinics (UHCs), 2 were health posts (HPs), 2 were primary health care centers (PHCCs) and 1 was NGO run DOTS unit.

Data collection procedure: Data was collected from 15th of September to 23rd of November 2013. Research Assistants visited the DOTS units and requested TB patients for participation. Those who provided verbal as well as written consent were included in the study. Face to face interviews using pretested structured questionnaire was done to collect the information on socio-demographic characteristics, behavioral and other risk factors along with a history of diabetes. For self reported diabetes, patients were asked to collect the medication slips /patient cards /diagnosis slips to ensure the confirmation of self reported diabetes. In case the DOTS center is hospital run DOTS centers and if the patient was diagnosed with diabetes in the respective hospital, laboratory records were also reviewed. Height and waist circumference were measured using non stretchable linen tape while well calibrated floor weighing scale was used to measure weight to get the anthropometric information by the trained research assistants. The measurements were used to derive the Body Mass Index (BMI) and the BMI 18.50 to 24.99 kg/m^2 was categorized as normal. Random capillary blood sugar test was conducted using glucometer by research assistants with clinical background (One of them is staff nurse and other is Health Assistant). The glucometer used for the purpose of this study was named Gmate Mini, a product of PHILOSYS (a korean company). Various studies showed different results for varied values in regard to the sensitivity and specificity of using glucometer for random capillary blood glucose level test. The sensitivity and specificity of a glucometer for random capillary blood sugar test for the value more than 7.8mmol/l (140.4 mg/dl) is 75.0% and 88.0% respectively.[21] Those patients with blood sugar level >200mg/dl taken randomly at the time of study enrollment were considered as diabetic.[10]

Study Instrument:

- Interviewer administered structured questionnaire including Global Physical Activity Questionnaire (GPAQ) developed by WHO for assessing physical activity. [19]
- Floor weighing scale for weight, and Linen tape for height, and waist circumference measurement were used.
- Gmate Mini, a product of PHILOSYS (Glucometer) for random capillary blood sugar test.

Pretesting of questionnaire: Pretesting of questionnaire was done in Baneswor DOTS clinic. A total of 20 TB patients had undergone pretesting for diabetes. As a result minor changes were made in a questionnaire.

Ethics Statement: Approval was taken from Institutional Review Board (IRB), Institute of Medicine (IOM), Tribhuvan University, Maharajgunj, Nepal. TB patients aged 15 years and above were the study participants. Both written and verbal consent was obtained prior to the test. The consent form was priorly designed and approved from the IRB, IOM before its application in the field. The written consents obtained were kept in an individual patient files and were documented. Patients with self history of diabetes were advised on lifestyle modification measures and those found on medication for both diabetes and TB were advised to continue both medication. Patients with blood sugar level >200mg/dl were advised to go for the confirmatory test of diabetes. They were also notified to the respective DOTS units' in-charge for follow up.

Data management and analysis: Data was entered in EpiData 3.1 and analysis was done in three sections using Statistical Package for Social Sciences (SPSS) full version 16. Descriptive analysis was done in the form of frequencies, percentages, mean, median and standard deviation. Chi-square/fischer's exact test was done to test the association. Variables with p value <0.05 were considered to be significant and

were subjected to multivariate analysis. Prevalence odds ratio with confidence interval was also calculated.

RESULTS

Out of 407 TB patients enrolled in the study, 37 (9.1%) were found to have diabetes. Of which, 28 (6.9%) were self reported cases and 9 (2.2%) were identified by the test. Twenty five (89.3%) out of 28 self reported cases had a history of diabetes prior to the TB diagnosis while 2 (7.1%) had known at the time TB was diagnosed and 1 (3.6%) knew after TB was diagnosed. Major proportion of TB patients with diabetes were 50 years and above (54.0%), male (56.8%) and living in urban part (94.6%) of the valley. Likewise, most of the diabetic TB patients (73.0%) had normal Body Mass Index (BMI) (18.50-24.99)kg/m^2 and waist circumference <90 cm (96.5%). Majority had ever used tobacco (78.4%), were non vegetarian (91.9%) and pulmonary TB patients (73.0%). Under bivariate analysis, TB patients aged 50 years and above (P =0.000), high income status (P =0.000), waist circumference >90cm (P =0.000), ever tobacco users (P =0.001), ever alcohol users (P =0.002), positive family history of diabetes (P =0.012), self history of high blood pressure (P =0.000) and pulmonary TB (P =0.030) were found associated with diabetes. However, when these variables were subjected to multivariate analysis, TB patients aged 50 years and above (Prevalence odds ratio [POR] 7.5, 95% CI 2.72-20.66), high income status (POR 5.2, 95% CI 1.59-17.26), ever tobacco users (POR 3.5, 95% CI 1.19-10.74) and self history of high blood pressure (POR 20.0, 95% CI 5.07-79.50) were identified as associated risk factors of diabetes among TB patients.

Table 1. Respondents by their diabetic status

Characteristics	Frequency	Percent (%)
Diabetes (n = 407)		
Yes	37	9.1
No	370	90.9
Diabetic status (n = 37)		
Self reported	28	75.7
Random blood	9	24.3
History of diabetes prior TB diagnosis (n = 28)		
Yes	25	89.3
No	1	3.6
Don't know	2	7.1

Table 2. Respondents by their socio-demographic characteristics

Socio-demographic characteristics	TB-DM (n=37)	TB only (n=370)	Total (n=407)
Age group			
15-24	1 (2.7%)	168(45.4%)	168(41.3%)
25-34	1(2.7%)	114(30.8%)	115(28.3%)
35-44	9(24.3%)	41 (11.1%)	51 (12.5%)
45-54	14 (37.8%)	24 (6.5%)	38(9.3%)
Above 55	12 (32.5%)	23 (6.2%)	35(8.6%)
Mean±SD (yrs)	50.1±9.2	29.6±12.4	31.4±13.5
Sex			
Male	21 (56.8%)	178(48.1%)	199(48.9%)
Female	16 (43.2%)	192(51.9%)	208(51.1%)
Education level			
No education	15 (40.5%)	63 (17.0%)	78 (19.2%)
Primary (1-5)	7 (18.9%)	44 (11.9%)	51 (12.5%)
Secondary (6-10)	13 (35.1%)	178(48.1%)	191(46.9%)
Intermediate level (10+2) and above	2 (5.4%)	85 (23.0%)	87 (21.4%)
Place of residence			
Rural	2(5.4%)	44(11.9%)	46(11.3%)
Urban	35(94.6%)	326(88.1%)	361(88.7%)

Table 3. Respondents by their anthropometric characteristics

Anthropometric characteristics	TB-DM (n=37)	TB only (n=370))	Total (n=407)
BMI			
Underweight (<18.5kg/m2)	5 (13.5%)	103(27.8%)	108(26.5%)
Normal (18.5-24.99)kg/m2	27 (73.0%)	231(62.5%)	258(63.4%)
Overweight (>24.99kg/m2)	5 (13.5%)	36 (9.7%)	41 (10.1%)
Waist circumference			
Low (<90 cms)	357(96.5%)	29 (78.4%)	368(94.8%)
High (>90 cms)	13 (13.5%)	8 (21.6%)	21 (5.2%)

Mean ± SD (cms)	83.8 ± 7.9	76.5 ± 7.3	77.2 ± 7.6

SD = Standard Deviation; DM = Diabetes Mellitus

Table 4. Respondents by their behavioral characteristics and other risk factors

Characteristics	TB-DM (n=37)	TB only (n=370)	Total (n=407)
Tobacco use (Ever used)			
Yes	29 (78.4%)	112 (30.3%)	141 (34.6%)
No	8 (21.6%)	258 (69.7%)	266 (65.4%)
Alcohol use (Ever use)			
Yes	22 (59.5%)	102 (27.6%)	124 (30.5%)
No	15 (40.5%)	268 (72.4%)	283 (69.5%)
Food habit			
Vegetarian	3 (8.1%)	31 (8.4%)	34 (8.4%)
Non-vegetarian	34 (91.9%)	339 (91.6%)	373 (91.6%)
Physical activity			
Physically active (≥600MET minutes/week)	19 (51.4%)	230 (62.2%)	249 (61.2%)
Physically inactive (<600MET minutes/week)	18 (48.6%)	140 (37.8%)	158 (38.8%)
Median minutes spent on sedentary activities per day* = 120 minutes			
Self history of High blood pressure			
Yes	16 (43.2%)	8 (2.2%)	24 (5.9%)
No	21 (56.8%)	362 (97.8%)	383 (94.1%)
Family history of diabetes			
Yes	9 (24.4%)	30 (8.1%)	39 (9.6%)
No	24 (64.8%)	313 (84.6%)	337 (82.8%)
Don't know	4 (10.8%)	27 (7.3%)	31 (7.6%)
Type of TB			
PTB	27 (73.0%)	203 (54.9%)	230 (56.5%)
EPTB	10 (27.0%)	167 (45.1%)	177 (43.5%)

**Sedentary activities include sitting, watching TV, reading books and other idle activities while sleeping is not inclusive.*

Table 5. Results from bivariate analysis

Variables	TB-DM (n=37)	TB only (n=370)	P value
Age group			
<50 years	17	336	0.000*
≥50 years	20	34	
Sex			
Female	16	192	0.381
Male	21	178	
Place of residence			
Rural	2	44	0.410[a]
Urban	35	326	
BMI			
Underweight (<18.5)	5	103	0.121
Normal (18.5 - 24.99)	27	231	
Overweight (>24.99)	5	36	
Waist circumference			
<90 cms	29	357	0.000**
≥90 cms	8	13	
Income status			
Low	5	131	0.000*
Middle	5	130	
High	27	109	
Ever tobacco users			
No	8	258	0.001*
Yes	29	112	
Ever alcohol users			
No	15	268	0.002*
Yes	22	102	
Food habit			
Vegetarian	3	31	1.001[a]
Non vegetarian	34	339	
Physical activity			
Physically active	230	19	0.213
Physically inactive	140	18	
Family history of diabetes			
No	24	313	0.012[a]*
Yes	9	30	
Don't know	4	27	
History of high blood pressure			
No	21	362	0.000[a]*
Yes	16	8	
Type of TB			
Pulmonary TB	27	203	0.030*
Extra-pulmonary TB	10	167	

[a] Fischer exact test value, * P value < 0.05

Table 6. Results from multivariate analysis

	TB-DM (n =37)	TB only (n =370)	POR (95% CI)*
Age group			
≥50 yrs	20 (54.0)	34(9.2)	7.5 (2.72-20.66)

<50 yrs	17 (46.0)	336 (90.8)	Reference
Income status			
High	27 (73.0)	109 (29.8)	5.2 (1.59-17.26)
Middle	5 (13.5)	130 (35.1)	0.9 (0.22-3.99)
Low	5 (13.5)	131 (35.1)	Reference
Waist circumference			
<90 cms	357(96.5)	29(78.4)	2.2 (0.47-10.34)
>90 cms	13(13.5)	8(21.6)	Reference
Tobacco use			
Ever	29(78.4)	112(30.3)	3.5 (1.19-10.74)
Never	8(21.6)	258(69.7)	Reference
Alcohol use			
Ever	22 (59.5)	102 (27.6)	1.1 (0.40-3.11)
Never	15 (40.5)	268 (72.4)	Reference
Self history of high blood pressure			
Yes	16 (43.2)	8 (2.2)	20.0 (5.07-79.50)
No	21 (56.8)	362 (97.8)	Reference
Family history of diabetes			
Yes	9 (24.4)	30 (8.1)	2.8 (0.70-11.20)
Don't know	4 (10.8)	27 (7.3)	2.4 (0.60-10.38)
No	24 (64.8)	313 (84.6)	Reference
Type of TB			
Pulmonary	27 (73.0)	203 (54.9)	2.1 (0.76-6.07)
Extra-pulmonary	10 (27.0)	167 (45.1)	Reference

NA= Not Applicable; DM = Diabetes Mellitus; POR = Prevalence Odds Ratio; CI = Confidence Interval; Reference assigned for the reference category for categorical variables.

DISCUSSION

This is the first study conducted in Nepal aimed to determine the prevalence of diabetes among TB patients and to identify the associated risk factors to our knowledge. A total of 37 out of 407 (9.1%) TB patients in the study were found to have diabetes. This proportion was found lower than those of screening studies in India[17] and China,[14] however, it was found consistent with North India.[17] Self reported diabetic TB patients (89.3%) provided a known history of diabetes prior to the diagnosis of TB with a mean duration of 49 months. A systematic review of 13 observational studies have discussed that people with diabetes for longer period can have impaired immune responses required to oppose the progression of TB[22] but the study had not talked on duration of diabetes. This could be one of the possible explanations behind having higher proportion of previously known diabetes, however, there are no evidences about diabetes preceding TB or vice-versa.[23] Moreover, this can also be described with the observation that most (88.7%) of the TB patients were from urban part of the valley with easy access to diagnostic facilities. Older age is found consistently linked to diabetes[6-9,12,13,16,18] which was also observed in this study. The consistent linkage found could be illustrated with the fact that type II diabetes is often seen in older age. This study did not distinguish between type I and type II diabetes but has mostly considered type II diabetes, since the mean age of diabetic TB patients was 50.1 years while of those non diabetic TB patients was 29.6 years. High income status was also found associated with diabetes. We can expect that high income group of people have better, easy and early access to diagnostic and medical facilities. The amount of time spent in sedentary activities is positively associated with less glucose metabolic profile leading to higher risk of developing type II diabetes. On the contrary, increased physical activity causes increased peripheral insulin sensitivity which leads to more glucose uptake by muscles.[24] A systematic review on adult sedentary behavior[25] revealed that high income group will more likely to spent ample amount of time in sedentary activities. Interestingly, high income group of TB patients in this study was found spending longer time (164 minutes) compared to low income group (135 minutes) on sedentary activities. This observation could possibly describe the association, however, further research need to be done to make a relevant explanation. Likewise, tobacco use including smoking was also found significant with diabetes among TB patients. Smoking results in inflammation and oxidative stress in the body cells. Evidence showed that both inflammation and oxidative stress is related to the increased risk of diabetes. Smokers have 30.0% to 40.0 % increased risk of developing diabetes compared to non

smokers.[26] In the study, it is observed that majority of diabetic TB patients (78.3%) had ever used tobacco products including smoking compared to non diabetic TB patients (30.3%). Also a prevalence based cohort study (2000-2005) for diabetes among TB patients in Saudi Arabia[15] showed the association as well. Studies identifying tobacco use as a risk factor for type II diabetes[27,28] and for TB[29] had explained the positive association. . Accordingly, self history of high blood pressure was also identified as a predictor of diabetes among TB patients. This can be expressed in the studies which concluded that people with diabetes are more likely to have high blood pressure.[30] More significantly, prospective research might justify the relationship.

CONCLUSION

The prevalence of diabetes among TB patients in our study was 9.1%. The associated risk factors identified were older age, high income status, tobacco use and hypertension. It suggests for the universal screening of TB patients for diabetes.

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Case Report and Review of literature

SUBDELTOID BURSA TUBERCULOSIS WITH RICE BODIES FORMATION

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ABSTRACT

Introduction: We describe a rare case of a patient with unilateral musculoskeletal manifestation of tuberculosis presented as bursitis of the left shoulder with rice bodies, without coexisting active tuberculosis or tuberculosis in the previous history.

Case Report: A 21 year old patient was examined, who complained of pain and swelling in the left shoulder for 2 years. MRI showed a large amount of rice bodies with joint effusion in the left shoulder with intact rotator cuff. The histological examination showed a tuberculosis-specific inflammatory response with giant cells and epithelioid granulomas. Arthroscopic debridement and removal of the loose bodies was done.

Conclusion: We report a unique case of tuberculous sub-deltoid bursitis with rice bodies formation in absence of any other concomitant focus of tuberculous infection, managed with arthroscopic debridement and anti -tuberculous regimen with a long follow up of twelve months.

Key words: Subdeltoid Bursitis, Rice bodies, Arthroscopy

INTRODUCTION

Rice body formation is commonly observed in the joint and tendon sheaths among patients with rheumatoid arthritis[1,2] however only a few cases with rice bodies in sub-deltoid bursa of tubercular origin have been mentioned in the literature.[3,4] There are very few reports[5] about the arthroscopic management of cases with rice bodies in sub deltoid bursa with a long term follow up. The authors report the rare case of a patient with musculoskeletal manifestation of tuberculosis presented as bursitis of the left shoulder with rice bodies without coexisting active tuberculosis or tuberculosis in the previous history managed with arthroscopic debridement with follow up of one year .

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CASE REPORT

A 23 years young male with 2 years history of diffuse swelling of left shoulder was examined (Non dominant side). He was an athlete. Pain was gradual in onset. The pain was not aggravated by activities of daily living but terminal rotations were painful. There was no history of constitutional symptoms. There was no history of tuberculosis or any other major illness in the past.

He was a febrile with vital parameter within normal limits. There were no signs of acute or chronic inflammation. There was diffuse swelling over the shoulder. No point tenderness was elicited; external and internal rotations of the shoulder were terminally restricted.

The WBC count was 7,800/cmm. With lymphocytes being 39%, His ESR (erythrocyte Sedimentation Rate) was raised (68mm). C-reactive protein study was positive. Rheumatoid factor and HIV studies were negative.

Radiograph showed no abnormality of the humeral head. Chest x-ray did no show any evidence of healed primary lesion. Magnetic resonance imaging (MRI) scans figure 1 & 2 showed moderate joint effusions with multiple loose bodies on T2 weighted image & signal changes of humeral head near the synovial reflection along posterior aspect. The T1 weighted images showed homogenous images. The patient underwent arthroscopic debridement figure 3 for removal of loose bodies some of which were attached to the synovium. The loose bodies resembled rice bodies ranging from 3 to 10 mm length figure 4.

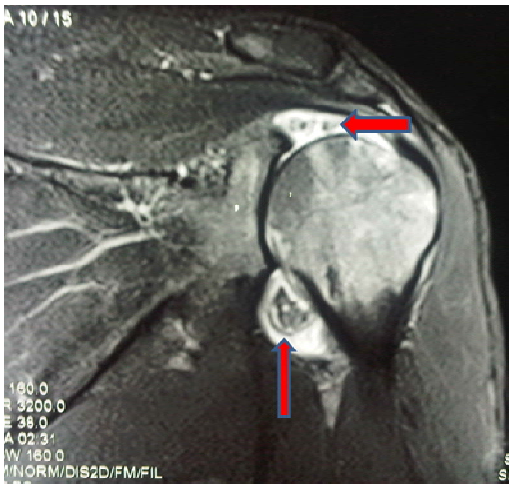

Figure 1. T2 fat suppressed coronal image showing intermediate intensity multiple rice bodies

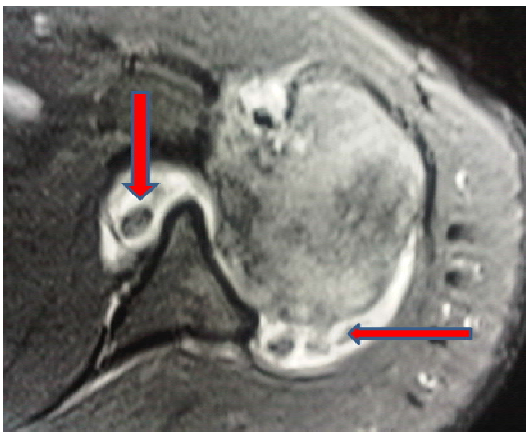

Figure 2. T2 fat suppressed axial image showing intermediate intensity multiple rice bodies

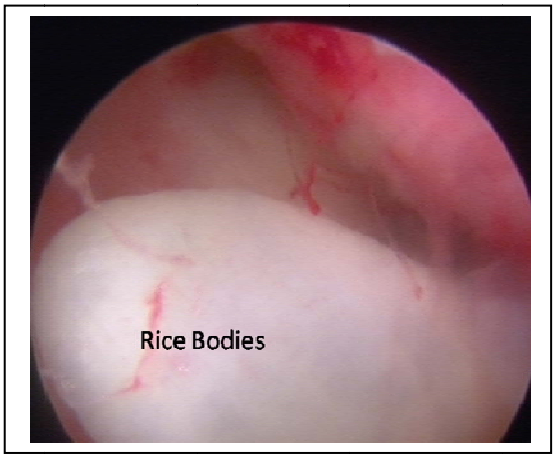

Figure 3. Arthroscopic Image of Subdeltoid Rice Bodies

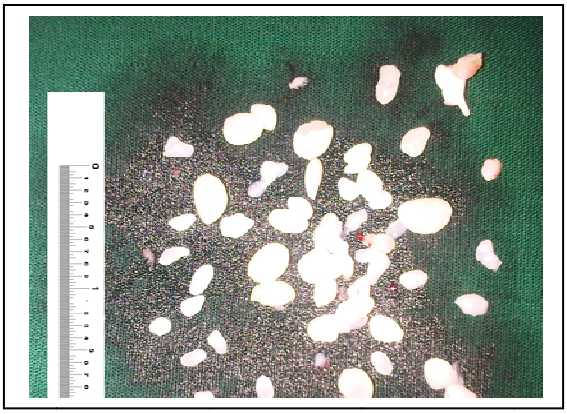

Figure 4. Rice Bodies gross anatomical presentation

Histo-pathological analysis confirmed caseous necrosis and Zheil-Neelson staining of the fluid from the bursa isolated mycobacterium tuberculosis. Microscopically they consisted of compact fibronous material; however the articular cartilage did not show evidence of tuberculosis.

The patient was treated with anti-tuberculosis medication for 12 months and he is disease free for the last 9 months after completion of ATT.

DISCUSSION

The formation of intra-articular rice bodies was first described in tuberculous arthritis. These nodules are a common finding in rheumatoid bursitis and arthritis; they are rare in other arthropathies.[6] The pathogenesis of these rice bodies remains obscure. The main theories depict the origin of the rice bodies from the synovial fluid due to aggregation of the fibronectin /fibrin.[7] A different theory proposes them to be of the synovial origin. The underlying disease condition leads

to micro infraction of the synovium which progresses to sloughing, and then the fibrin covering the infracted tissue as described by Cheung.[8]

The MRI findings in our patient revealed the rice bodies as intermediate intensity images on the T1 and T2 weighted images. They were better delineated on the T2 weighted images than T1 weighted images, on which they appeared homogenous. On arthroscopy they seemed attached to the synovial lining supporting the description of their origin by Cheung. Macroscopically they appeared similar to the rice bodies arising in rheumatoid arthritis. On microscopic analysis they were composed of fibrous tissue.

Tuberculous bursitis is always descried secondary to some other primary focus of infection in the bone or the nearby joint.[9] Tuberculous involvement have been described in the superficially situated bursa such as the olecranon and the pre-patellar bursa.[10-12] History of trauma and direct transmission has been thought as the underlying cause. Hematogenous spread is proposed as the cause of deep seated bursa involvement[13], for the hematogenous spread to occur there should be a primary focus of infection or a healed primary lesion in the lungs. In our patient there was no history of trauma and the chest x ray did not show any focus of infection.

So far very few studies have been published on sub-deltoid bursitis and its arthroscopic management with a long term follow-up. Jaovisidha et al[4] has published a case series of 3 cases with subdeltoid bursitis. Alkalay et al[3] has reported a case of patient with 30 year history of tuberculous subdeltoid bursitis. Kim et al[5] reported a case with subdeltoid bursitis in a 41 year old woman.

CONCLUSION

We report a unique case of tuberculous subdeltoid bursitis with rice body formation in absence of any other concomitant focus of tuberculous infection, managed with arthroscopic debridement and anti-tuberculous regimen with a long follow up of twelve months.

Clinical Message

Possibility of tuberculosis of sub-deltoid bursa in absence of a primary focus should be ruled out.

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CASE REPORT

NON HEALING ULCER OF SOFT PALATE: A COMMON ENTITY RARELY SEEN

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ABSTRACT

Oral Tuberculosis is a rare disease, accounting for less than 1% of all cases of tuberculosis. The most common manifestation is a non healing ulcerative lesion of the mucosa which is often misdiagnosed. The recent increase in the incidence of tuberculosis especially after the advent of HIV infection, combined with an emerging global resistance to anti-tuberculous drugs, warrants an increased awareness of the involvement of *Mycobacterium tuberculosis* in persistent or atypical lesions in oral cavity and oropharynx. Very few cases of oropharyngeal tuberculosis have been described in literature. We report a rare case of tuberculosis of soft palate secondary to pulmonary TB in an 8 year old child.

Key words: Tuberculosis soft palate, Oral and Oropharyngeal TB, Granuloma, Nonhealing ulcer

INTRODUCTION

Tuberculosis, one of the oldest diseases known to affect humans, is caused by bacteria of *Mycobacterium tuberculosis complex*. It usually affects lungs, although other organs are involved in up to one-third of cases. Oral TB may be primary or secondary. Secondary TB is usually seen after pulmonary TB. In secondary oral/oropharyngeal TB, the route of spread is either hematogenous or lymphatic spread. In primary oral TB, there is direct inoculation of the mycobacterium due to break or loss of the natural barrier. Predisposing factors for primary oral TB are: trauma; inflammatory conditions like dental abscess; leukoplakia; tooth extraction, or poor oral hygiene. We report a rare case of oropharyngeal tuberculosis involving soft palate secondary to pulmonary TB.

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CASE REPORT

An 8 year old female child presented to Otolaryngology department of our hospital with complaints of difficulty in swallowing and fever for past 3 months. Child also gave history of productive, mucopurulent cough for past 3 months. She had decreased appetite and weight loss for past 2 months. There was no past or family history of tuberculosis. Child was immunised for age. On examination, child appeared pale and weighed only

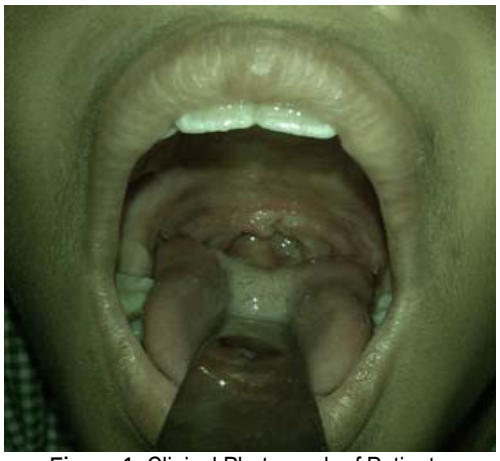

Figure 1. Clinical Photograph of Patients

15kgs. On oral cavity and oropharyngeal examination, 3x3cm irregular area of ulceration with granular surface was seen on uvula and soft palate (figure1). The rest of palatal mucosa was very pale. Rest of the oral cavity appears normal.

There was no significant cervical lymphadenopathy. In view of clinical presentation, a provisional diagnosis of granulomatous disease of soft palate with strong suspicion of tuberculosis was made. Complete blood count with ESR, montoux test, and chest x-ray were ordered. The results of investigations were: ESR was 77mm/hr, montoux test was positive (14mm), and chest x ray showed bilateral nodular and infiltrative opacities in upper zone (figure 2), suggestive of tuberculosis. Child was advised for sputum examination for acid fast bacilli but she did not cooperate for sample collection, hence sputum examination was not done. Serology for human immunodeficiency virus was negative. Her blood and urine culture were negative. Punch Biopsy of the lesion was done under local anesthesia and sent for histopathological examination The biopsy showed multiple tubercular granulomas with areas of caseation (figure 3). Thus, a diagnosis of tuberculosis of soft palate secondary to pulmonary TB was made and child was started on ATT and has been on regular follow up.

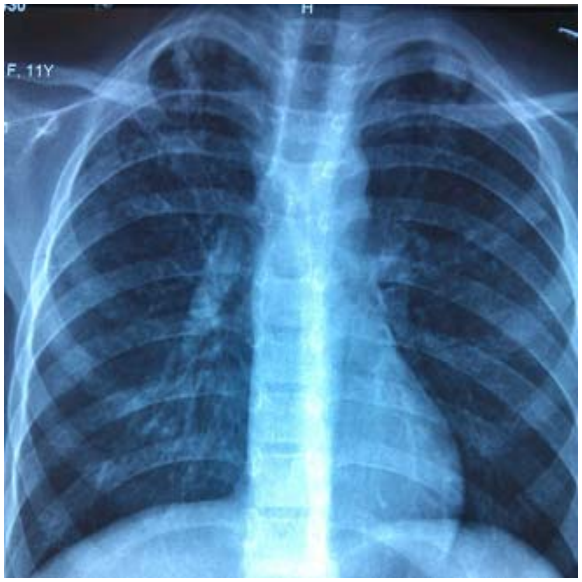

Figure 2. Chest X-ray showing Infiltrative Opacities in upper zone

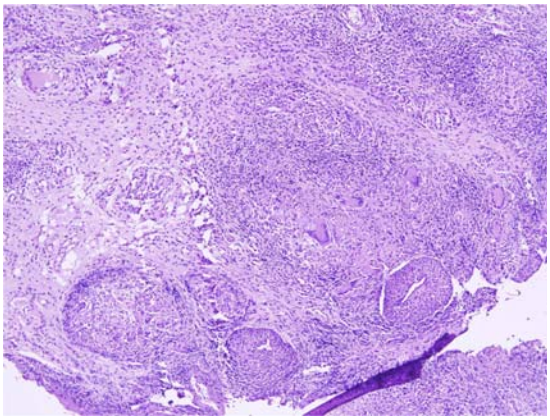

Figure 3. Histopathological Photograph showing Granulomas

DISCUSSION

Pulmonary tuberculosis is the most common manifestation of TB. Extra-pulmonary sites most commonly involved are lymph nodes, pleura, joints and bones, genitourinary tract and meninges. The risk of developing disease after being infected depends on individual's innate immunological and non immunlological defenses. A variety of diseases and conditions favor the development of active tuberculosis. The most potent risk factor for tuberculosis among infected individuals is HIV co-infection[2], which suppresses cellular immunity. With the advent of HIV infection, extrapulmonary tuberculosis is being increasingly seen.[2] Other risk factors are chronic renal failure, diabetes, immunosuppressive treatment, intravenous drug abuse, post organ transplantation and severe malnutrition. A case of tuberculosis of soft palate has been described in a 40 year old female on immunosuppressive medication for rheumatoid arthritis.[3] In our case, the serology for HIV was found negative.

Tuberculosis of upper airways nearly always occurs as a complication of advanced pulmonary tuberculosis. The prevalence of oral TB in cases of pulmonary tuberculosis ranges from 0.8 to 3.5%.[1] Different areas of oral cavity like floor of mouth, soft palate, gingiva, lips, hard palate can be involved. However, hard palate and tongue are the commonest sites of involvement for oral tuberculosis.[4] In a review from 1950 to 2010[5], secondary oral tuberculosis was found in 58% (54% pulmonary, 4% extra-pulmonary) of patients and as a primary in 42% of patients. Carcinomas are found to co-exist in the same lesion site in 3% of patients.

The lesions of oral and oropharyngeal tuberculosis manifest as non-healing ulcers, nodules, fissures, verrucous proliferation, erythematous patches or plaques, indurated lesions, or as jaw lesions.[6] The palatal lesions of tuberculosis may be seen as granulomas or ulcerations with undermined margins and are usually more common in the hard palate than in the soft palate.[3] In our case, lesion on the soft palate manifested as irregular ulceration.

Saliva plays a major protective role in oral tuberculosis. Very few cases of tuberculous oral lesions are seen, despite the large numbers of bacilli contacting the oral cavity mucosa in a typical case of pulmonary tuberculosis.[7] Other contributing factors are presence of saprophytes in oral cavity, striated muscles resisting bacterial invasion and thickness. Abbot *et al* were able to isolate the tubercle bacilli from mouth washings of 44.9 % of the patients with active pulmonary lesions, thereby signifying the importance of intact mucosal epithelium of oral cavity in providing protection against the disease.[8]

A distinct Indian social habit has been propsed for predisposing to primary uvular tuberculosis, s not commonly seen in the rest of the world. The habit of doing "datoon" i.e. brushing of the teeth with neem twigs in rural India has been proposed to cause tuberculosis.It causes trauma on the palate thereby predisposing to seedling of the wound with mycobacterium tuberculosis.[9]

The differential diagnosis of ulcerative lesions in oral cavity includes infection (syphilis, leprosy, leishmaniasis, or fungal infection), Wegener's granulomatosis, sarcoidosis, neoplasms (salivary or squamous cell), drug abuse (cocaine), and midline lethal granuloma. In our case, the above differentials were unlikely due to associated pulmonary tuberculosis and histopathological report.

Since oral TB is usually secondary to pulmonary infection, therefore it is essential to find underlying primary infection in a case of tuberculous oral lesion. Therefore, in all cases of oral and oropharyngeal tuberculosis, search for primary site of the disease should always be considered even in the absence of any signs and symptoms.[7] A case of multiple oral ulcers leading to diagnosis of pulmonary tuberculosis has been reported.[6]

The treatment of oral and oropharyngeal tuberculosis is ATT for 6 months duration. Medical personnel are also at risk, as elucidated by the case of a doctor who developed naso-labial infection after mouth-to-mouth resuscitation on a tuberculosis patient.[7] In the outpatient setup, caution is needed while dealing with such non healing chronic oral ulcers not only to miss an important medical entity but also to prevent transmission of infection to doctors.

CONCLUSION

Primary lesions of tuberculosis manifest in the oral cavity and oropharynx as non healing chronic ulcers. When diagnosing such lesions with non healing tendency, tuberculosis should be considered in the differential diagnosis especially in developing countries of Asia and Africa where there is a high prevalence of tuberculosis.

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Case Study

A STEP TOWARDS CONTROL OF MULTIDRUG RESISTANT TUBERCULOSIS: HOSPITAL BASED STUDY FROM NASHIK INDIA

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ABSTRACT

Introduction: The Global TB report (2012), estimates 73,000 MDR TB patients living in India, among them only 1,660 cases were notified and 68.4% cases were put on treatment. Hence, this study was conducted with objective to assess the treatment outcome of multi drug resistant Tuberculosis patients enrolled in DOTS plus (Cat-VI) site.

Methodology: It is a retrospective case series of MDR-TB cases conducted at Dr. Vasantrao Pawar Medical College, Hospital & Research Centre, Nashik (Maharashtra). Information was collected on age, gender, HIV status, previous treatment of TB, weight of patient, refused to take treatment for Cat IV. Outcome was recorded in terms of cure rate, rate of failure, defaulter, treatment completed, switch to Cat V and death.

Results: Among the study subject, majority of study subjects were male (65%) and highest proportion (49%) of MDR-TB was in 25-44 years of age. Out of 353 patient 241 (68.4%) were still on Cat IV in which 35% patient's on intensive phase and 65% put on continuation phase while 12.8%, 13.5%, 4%, 1.1%, 3.6% & 0.5% patient were found to be defaulted, died, refused to take treatment, treatment completed, transfer out & switch to Cat V, respectively.

Conclusion: In the present study, the majority of study subjects (99.4%) were previously treated for TB, we identified number of operational challenges in the treatment of MDR-TB like rate of defaulter, refuse to take treatment & deaths among MDR-TB patient was high. There is need to study correlates of these factors in details also need of operational research to improve MDR-TB treatment in India is considered as priority.

Key words: Outcome, Multi drug resistance, Tuberculosis, Treatment

INTRODUCTION

In the recent years, Multi-Drug Resistant Tuberculosis (MDR-TB) is being discussed globally for the reason of increase morbidity and mortality along with the challenges faced in treatment completion. MDR-TB as it is known, the Tuberculosis bacteria is resistant to at least one of the first line drugs Isoniazid and Rifampicin.[1] Drug resistance surveillance data indicate that in 2013, approximately 480,000 people developed MDRTB worldwide. Among TB patients reported by national TB programmes in 2013, there were an estimated 300 000 cases of MDR-TB. More than half of these cases were in India, China and the Russian Federation.[2]

Government of India, through Revised National Tuberculosis Control Programme (RNTCP) has proposed measures to implement and address the growing burden through its National Strategic Plan 2012-2017.[3] One of the key measure was to gather epidemiological and programmatic evidence to burden of MDR-TB in India. In this context, programme identified and operationalized DOTS-Plus sites exclusively for management of identified patients. Though DOTS-Plus sites were operational, from 2007,

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there are limited evidences to show the outcome of the treatment management at these sites. The paper here describes the outcome of those MDR_TB patients who were enrolled in DOTS Plus site of Dr. Vasantrao Pawar Medical College, Hospital & Research Centre, Nashik (Maharashtra).

METHODOLOGY

Study Design: The study was a retrospective case series of MDR-TB cases conducted at Dr. Vasantrao Pawar Medical College, Hospital & Research Centre, Nashik (Maharashtra). Which is the first private Tertiary care Institute where DOTS-Plus was started. Total sample size was 353 cases included in study from Jan 2012 to March 2014.

Data collection: Information was collected on age, gender, HIV status, previous treatment of TB, weight of patient, refused to take treatment for Cat IV. Outcome was recorded in terms of cure rate, rate of failure, defaulter, treatment completed, switch to Cat V and death.

Ethical approval: Data collection was done with prior permission from District Tuberculosis Officer, Nashik and Medical Director, Dr. Vasantrao Pawar Medical College, Hospital & Research Centre, Nashik.

Statistical analysis: Data was entered in Microsoft excel file & analyzed using Epi_info software package. The frequencies are expressed in percentages. Chi-square test was used to test the association. P-value <0.05 was taken as significant.

Operational definitions used for this study as per RNTCP guidelines are[4]

- Cured: An MDR-TB patient who has completed treatment and has been consistently culture negative (with at least 5 consecutive negative results in the last 12 to 15 months). If one follow-up positive culture is reported during the last three quarters, patient will still be considered cured provided this positive culture is followed by at least 3 consecutive negative cultures, taken at least 30 days apart, provided that there is clinical evidence of improvement.
- Treatment completed: An MDR-TB patient who has completed treatment according to guidelines but does not meet the definition for cure or treatment failure due to lack of bacteriological results.
- Death: An MDR-TB patient who dies for any reason during the course of MDR-TB treatment
- Treatment failure: Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12-15 months are positive, or if any of the final three cultures are positive.
- Treatment default: An MDR-TB patient whose MDR-TB treatment was interrupted for two or more consecutive months for any reasons.
- Transfer out: An MDR-TB patient who has been transferred to another reporting unit (DOTS Plus site in this case) and for whom the treatment outcome is not known. Till the time the DOTS Plus services are available across the country, the Cat IV patients can be transferred out only to those districts, within or outside the state, where these services are available. If a Cat IV patient moves from one district to another, both of which are covered by the same DOTS Plus site, transfer out will not be required.
- Treatment stopped due to adverse drug reactions: A patient on MDR-TB treatment who develops severe adverse reactions and could not continue the MDR-TB treatment in spite of the management of the adverse reactions as per the defined protocols and decision has been taken by the DOTS-Plus site committee to stop treatment.
- Treatment stopped due to other reasons: A patient on MDR-TB treatment who could not continue the MDR-TB treatment for any other medical reason (than adverse drug reactions), and a decision has been taken by the DOTS-Plus site committee to stop treatment.
- Switched to Category V treatment: A Category IV patient who during treatment is identified as an "XDR-TB suspect" and who is found to have XDR-TB on testing by an NRL, who subsequently has had their Category IV treatment stopped and RNTCP Category V treatment initiated.
- Still on treatment: An MDR-TB patient who, for any reason, is still receiving their RNTCP CAT IV treatment at the time of the submission of the RNTCP DOTS- Plus Treatment Outcome Report.

RESULTS

Among the study subject, highest proportion (49%) of MDR-TB was in 25-44 years of age followed by 27.5% in 15-24 years. It was minimum in the age group of 0-14

years. Proportion of MDR-TB was 230 (65%) among males as compared to 123 (35%) in females. The significant difference between age among MDR-TB patients except in the age of 25-44 years of age was ($p<0.05$). There is a significant difference in the gender among MDR-TB patients is mentioned in table 1.

Table 1. Age & gender wise distribution of MDR-TB patient.

Age in years	Gender		Total	P-value
	Male	Female		
0-14 year	1 (0.5)	2 (1.7)	3 (0.9)	0.58
15-24 years	53 (23.0)	44 (35.8)	97 (27.5)	0.01*
25-44 years	109 (47.3)	64 (52.0)	173 (49.0)	0.20
45-54 years	35 (15.2)	9 (7.3)	44 (12.5)	0.03*
55 years & above	32 (14.0)	4 (3.2)	36 (10.1)	0.01*
Total	230 (65.1)	123 (34.3)	353 (100)	0.001*

*statistically significant, figure in parenthesis are percentage.

Most of the patients 351 (99.4%) had a history of previous treatment for tuberculosis. Only 2 (0.6%) patients were new to anti-tubercular drugs.

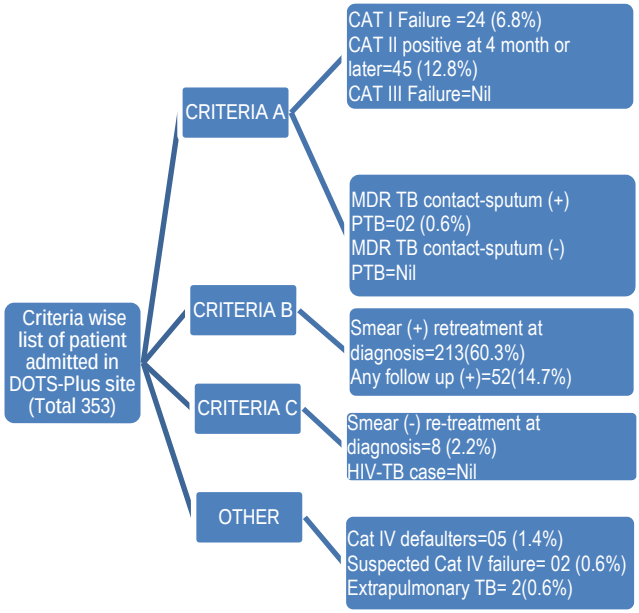

Figure 1. Criteria wise list of patient admitted in DOTS-Plus site

Outcome of MDR-TB treatment: Out of 353 patient 241 (68.4%) were still on Cat IV in which 35% patient's on intensive phase and 65% put on continuation phase while 12.8%, 13.5%, 4% 1.1%, 3.6% & 0.5% patient were found to be defaulted, died, refuse to take treatment, treatment completed, transfer out & switch to Cat IV, respectively. (See figure 2).

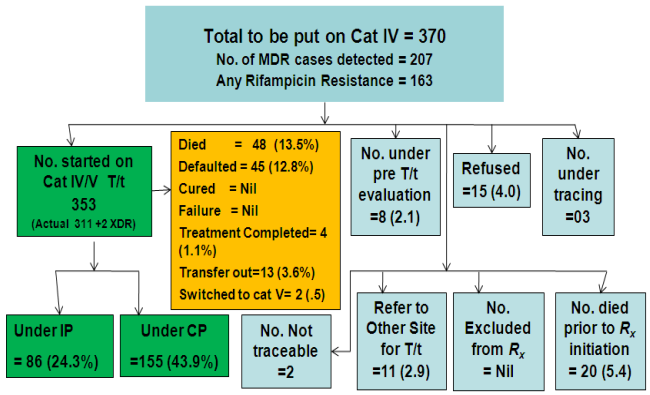

Figure 2. Outcome of MDR-TB patient at DOTS-Plus site

DISCUSSION

Government of India, implemented DOTS Plus under RNTCP program for the control of MDR TB. Despite of various activities in the present study we found that, rate of defaulter (12.8%) and death (13.5%) were high but treatment failure (Nil) was not reported. As per WHO Global supplementary report on MDR TB only 48% of the MDR-TB patients in the 2011 cohort of detected cases were successfully treated. 16% died, 24% did not have their treatment outcome documented or interrupted treatment, and 12% were not cured despite receiving treatment[2] while Jain K et al. found that, 13% of patients were failure, 23% defaulter, and 19% died.[5] As per N. Lytvynenko et al. (Ukraine), Cured (19%), treatment completed (1%), failure (16%), died (2%), and lost to follow up (16%).[6] Most of the studies have similar findings except treatment failure. The difference may be because of study design, place and implementation of program. The present study also reported switch to category V from Cat IV as well as refuse to take treatment.

In the present study, we found that MDR-TB was mainly seen in young age & male population.The proportion of drug resistance among younger age groups is more likely to be indicative of recent transmission than

among older age groups, which are more likely to be harboring older infections. Data on drug resistance stratified by age groups and sex but stratification cannot show effectiveness of programme.

Another interesting observation was that none of the patients with MDR-TB was HIV co-infected in the present study. This finding is in agreement with previous studies, although there are studies which contradict this finding.[5-10] (shown in table 2)

Table 2. Comparisons of finding of present studies with published research articles

Study	Setting	MDR Cases (n)	HIV status	Prevalence of XDR-TB (%)
In Present study	Tertiary care Centre, Nashik	231	All HIV-negative	1 (0.5)
Mondal and Jain, 2007	Tertiary care centre, Lucknow	68	All HIV-negative	5(7.4)
Jain et al, 2007	Teritiary care centre, Mumbai	326	All HIV-negative	36 (11)
Thomas et al, 2007	Field trial, Chennai	66	All HIV-negative	1(1.5)
Sharma et al, 2009	AIIMS, New Delhi, tertiary care hospital	211	All HIV-negative	5(2.4)
Ramchandran et al, 2009	Gujrat, Field study	216	All HIV-negative	7(3.1)
Singh et al, 2007	Tertiary care center, New Delhi	12	All HIV - infected	4 (33,3)

Strength of this study: this is the first study from India, assessing the treatment outcomes of MDR-TB (DOTS-Plus). Data collection & data entry was done by well qualified & trained staff. Limitation of study: end result of treatment outcome (cure) was unknown at the end of study.

This is secondary data analysis and only recorded information was used. Tuberculosis is major public health problem and MDR-TB is emerging threat in India. India is the second largest burden country after China. Government of India taken various innovative approaches to control the problem of TB and MDR-TB under RNTCP program but on the other side treatment of MDR-TB can take more than 2 years for cure; drugs are more toxic and expensive, less effective as compared to first line. There will be need to make shorter and effective drug regimen.

CONCLUSION

In this study we have identified number of challenges in treatment of MDR-TB like high rate of defaulter, deaths & refused to take treatment. There will be need to assess the treatment outcome of DOTS-Plus at both intensive phase as well as continuation phase. Operational research to improve programmatic management of MDR-TB in India is considered as priority.

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