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EDITORIAL

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The SAARC Journal of Tuberculosis, Lung Diseases and HIV/AIDS is the official journal of the SAARC TB and HIV/AIDS Centre (STAC). The Journal's main aim is to 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 and health research relevant to the practice of this Journal are published. This Journal is a 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.

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Editorial

On 26th September 2018, Heads of States of different countries gathered at the United Nation General Assembly for the first-ever UN High-Level Meeting (HLM) on tuberculosis (TB) to accelerate efforts in ending TB. The theme of the meeting was “**United to end tuberculosis: an urgent global response to a global epidemic**”. This was a landmark opportunity to marshal the political will and resources to end TB. Together we can defeat TB and overcome antimicrobial resistance by closing the funding gap for TB research and product development through equitable approaches, securing universal access to new medicines and fostering global collaboration.

TB is an infectious disease with high mortality, the most common form of antimicrobial resistance and leading cause of death in people living with HIV/AIDS. World Health Organization declared TB as global emergency. Still, TB is second leading cause of death worldwide. A good percentage of people in the developing countries continue to suffer from this menace because of poverty, gender inequality, vulnerability, discrimination and marginalization. Millions of people with TB do not have access to quality care, including affordable diagnostic test and treatment facility and is a precarious challenge to end TB globally, as well as in SAARC Region.

It is estimated that one quarter of the world’s population is infected with TB bacteria. SAARC Region has 36% of the global TB burden with 3.7 million new TB cases and 0.5 million death. Moreover these morbidity and mortality occur mainly in the economically productive age groups of 15-49 years. In order to eliminate TB from the SAARC Region before the global target, the SAARC TB and HIV/AIDS (STAC) has revised “**SAARC Regional Strategy on Elimination of Tuberculosis (2018-2023)**”.

This year the world TB day theme was “**Its time**”. So it is time to involve policy makers to advocate and take active participation in the TB control programmes. The affected and infected people with this disease can bring positive changes by combining their voices towards the elimination of the disease. Now it is time to intensify advocacy, social mobilization, partnership, research and inter-sectoral efforts to achieve the global target of ending the TB epidemic by 2030

Chief Editor
Director, STAC

AN OBSERVATIONAL STUDY OF FOLLOW UP OF MDR-TUBERCULOSIS PATIENTS AFTER SUCCESSFUL COMPLETION OF CATEGORY 4 TREATMENT UNDER RNTCP (PMT) IN ALLAHABAD DISTRICT

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ABSTRACT

Introduction: Drug-resistant TB is a persistent threat, with 490 000 million cases of multidrug-resistant TB emerging in 2016. The countries with the largest numbers of MDR/RR-TB cases were China, India and the Russian Federation. Given the prolonged nature of MDR-TB, one might expect higher rates of chronic disability among cured patients with MDR-TB. To explore these questions, we conducted an observational study focusing on: clinical, bacteriological, biochemical and various health parameter status of successfully treated MDR-TB patients.

Methods: Subjects enrolled in study as per inclusion and exclusion criteria were assessed by recording of demographic data and were subjected to a predetermined set of questions for determining the history of previous anti tubercular treatment and exposure to various type of risk factor for development of MDR TB. Physical parameters of health were determined and recorded.

Results: Total of 84 patients were enrolled in our study (57-males, 27 females). 69 subjects (46-males, 23-Females) were found apparently healthy. 25 subjects migrated outside. 6 patients (male-6, Female-2) died. 7 patients were diagnosed as XDR-TB (5-Males, 2-Females). 34 subjects (18- males, 16-females) (44.73%) were very under weight. Total 13 (Males-12, Females-1) out of 76 subjects (17.10%) were under weight. Mid arm circumference (MAC) of 35 out of 76 (21- males, 18-females) subjects (46.05%) was below 5th percentile. Majority of subjects showed moderate & severe obstruction in PEFV.

Conclusion: This study shows that the community based standardized treatment regimen is effective as only one of the patients was bacteriologically positive on follow up. However, significant numbers of treated MDR-TB patients suffer from clinical, nutritional and functional post-treatment adverse events leading to some morbidity.

Keywords: MDR-TB, XDR-TB

INTRODUCTION

Tuberculosis (TB) is as old as mankind¹⁻³ and prevails since antiquity. TB has coevolved with humans for many thousands of years, and

perhaps for several million years⁷ Oldest known human remains showing signs of TB infection are 9000 years old.⁸ TB remains a major global health problem and ranks as the second leading cause of death worldwide, second only to HIV/AIDS, as the greatest killer worldwide due to a single infectious agent.⁴ For the past 5 years, it has been the leading cause of death from a single infectious agent, ranking above HIV/AIDS.⁵ The disease is usually chronic with cardinal features like persistent cough with or without expectoration intermittent fever, loss of appetite, weight loss, chest pain and haemoptysis.⁶ In 2016, there were

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an estimated 10.4 million cases of tuberculosis with 1.67 million deaths, making tuberculosis the ninth leading cause of death worldwide.⁹ The 2017 WHO Global Tuberculosis Report estimated 490 000 cases of multidrug-resistant (MDR) tuberculosis, with less than 50% survival in patients who received recommended WHO treatment regimens.⁹⁻¹⁴ The Report reveals the dire need for new therapies and approaches for improving tuberculosis treatment delivery and management outcomes. Many challenges remain in developing optimal tuberculosis treatment regimens.¹⁵ As per the Global TB Report 2017,¹⁶ worldwide approximately 4.1% of new TB patients and 19% of previously treated TB patients have multidrug resistant-TB (MDR-TB), i.e. TB resistant to at least two of the first-line drugs – isoniazid and rifampicin. Extensively drug resistant TB (XDR-TB), defined as MDR-TB with additional resistance to at least one fluoroquinolone and one second line injectable aminoglycoside drug has been reported by 123 countries. The proportion of XDR-TB among MDR-TB patients is 6.2% worldwide. The estimated number of MDR/rifampicin resistant (RR)-TB in India is 147 000, accounting for one fourth of the global burden of MDR/RR-TB.¹⁶

Studies in India and other developing countries have focused on various causes and risk factors for default. Gender, alcoholism, treatment after default, poor knowledge of TB, irregular treatment and socio-economic status are some of the factors which have been found to be associated with higher default rates.¹⁷⁻²⁰ Once a drug resistant strain has developed it can be transmitted directly to others. Although there are some studies on follow up status of pulmonary tuberculosis patients, the information on post treatment status of the MDRTB patients successfully treated remains largely unknown and very few reports are available. Given the prolonged nature of MDR-TB, one might expect higher rates of chronic disability among cured patients with MDR- TB compared with those with drug susceptible TB. To explore these questions, we conducted an observational study focusing on consequences due to diseases, its management and other parameters.

MATERIALS AND METHODS

Ethics

Institutional ethics committee permission was procured prior to the start of the study. Subjects

were found with any co-morbid condition and/or were found deficient in nutrition were given proper treatment and nutrition supplement.

Study design

This is an observational study of follow up of MDR-TB patients after successful completion of Category 4 treatment in Allahabad District conducted over a period from July 2017 to September 2018.

Period of Study

Study was conducted over a period from July 2017 to September 2018

Subjects

MDR-TB patients enrolled in DOTS-Plus site (DRTB Centre) of Swaroop Rani Nehru Hospital of Allahabad District for pre treatment evaluation, from March 2013 to March 2015, and successfully completed Category 4 treatment, by second line anti TB drugs.

Case Selection

All patients aged >18 years of either sex who have undergone successful completion of Category 4 treatment under RNTCP, were enrolled in this study as per inclusion and exclusion criteria.

Inclusion criteria:

1. Patients who gave informed and written consent.
2. Patients aged > 18 years, who had successfully completed Category 4 treatment, for MDR Pulmonary TB, which was started in the period from March 2013 to March 2015 as per RNTCP criteria.

Exclusion criteria:

Patients were excluded from the study if they have any of the following conditions:

1. Patients who refused to give consent for participation in study.
2. MDR-TB in extra pulmonary TB patients
3. HIV infection
4. Any connective tissue disorders
5. Any Long-term steroid or cytotoxic drug therapy

Study Protocol

After obtaining written informed consent, patients qualifying inclusion criteria will be assessed as follows:-

- Recording of demographic data
- Were subjected to a predetermined set of questions for determining the history of previous anti tubercular treatment and exposure to various type of risk factor for development of MDR TB.
- Physical parameters of health was determined and recorded.

Investigations: Patients will be investigated for following parameters

1. Biochemistry (Hb, TLC, DLC, S.Bilirubin, SGPT, SGOT, S.ALP, S. protein, S. Albumin, S. Globulin, Thyroid profile, HBsAg, AntiHCV S.Urea, S.Creatinine, FPG).
2. Sputum for AFB Smear.
3. PEFR Test
4. Other investigation deemed necessary for any individual patient.

Analysis of Data

The data will be analysed using appropriate statistical methods.

RESULTS AND OBSERVATION

Between March (2013) to March (2015) a total of 121 patients were registered in DOTS PLUS centre S.R.N. Hospital Allahabad and declared "successfully treatment completed". Home visit was made to trace 121 subjects with the help of District T.B-HIV coordinator. Out of 121 subjects 112 patients could be currently traced. A Total of 84 subjects reported back to hospital and they were interviewed and investigated for various health parameters and their data was recorded. Thus a Total of 84 patients (57-males, 27-females) were enrolled and investigated in study. 9 subjects were lost to follow up due to inability to trace the address. 69 of the recorded subjects were found to be apparently healthy. 20 male subjects migrated outside for work. 5 female subjects migrated to their in-law's house after marriage. Hence these 25 subjects (20-males, 5-females) were interviewed telephonically with set of questions and were found to be apparently healthy. Hence including these subjects, 94 subjects (69+25) out of 112 traced subjects (83.92%) were found to be apparently

healthy. 3 patients were HIV positive and were not included in the study. Total 8 patients out of 84 (9.5%) died. 6 male patients (7.1%) and 2 Female patients (2.3%) out of 84 subjects died after successful treatment completion of CAT-4 MDR-TB.

Total 7 patients out of 84 (8.3%) were diagnosed as XDR-TB (5-Males (5.9%), 2-Females (2.3%)) with average duration of 8 months after successful MDR-TB Treatment completion. A Total of 69 (82.14%) subjects [46 males (54.76%), 23 Females (27.38%)] were found apparently healthy. The mean duration of follow up of subjects was 20.56 months with ± 7.94 S.D. ranging from 6 months to 38 months.

Table 1: Mean & Median age of the study participants males and females

AGE	MEDIAN	MEAN
MALES+FEMALES	25.5	29.75
MALES (M)	25	30.75
FEMALES (F)	26	27.62

Table 1 shows that the Median age of all the subjects was 25.5 years Median age for males and females were 25 and 26 years respectively. Mean age with S.D for all subjects were 29.75 \pm 11.49. Mean age for males and females were 30.75 \pm 12.58 and 27.62 \pm 8.56 years respectively.

Table 2: Mean & Median BMI of Males and Females in kg per m²

BODY MASS INDEX (BMI)	MEDIAN	MEAN \pm S.D
MALES+FEMALES	19.40	18.95 \pm 2.95
MALES (M)	19.5	19.48 \pm 2.42
FEMALES (F)	16.6	17.88 \pm 3.63

Table 2 shows that the 34 subjects out of 76 (44.73%) were very under weight. 18 out of 51 males (35.29%) and 16 out of 25 females (64%) were very underweight. Total 13 out of 76 subjects (17.10%), 12 out of 51 males (23.52%) and 1 out of 25 females (4%) were under weight. Weight of 29 out of 76 subjects (38.15%), 21 out of 51 males (41.17%) and 8 out of 25 females (32%) were within normal range.

Table 3: Median & Mean MAC of Males and Females in centimetres

MID-ARM CIRCUMFERENCE (MAC)	MEDIAN	MEAN +/- S.D
MALES+FEMALES	19.40	18.95 +/- 2.95
MALES (M)	19.5	19.48+/- 2.42
FEMALES (F)	16.6	17.88+/- 3.63

Table 3 shows that the Median MAC of all the subjects was 24.5 cm. Median MAC of males and females were 26 and 20 cm respectively. Mean MAC with S.D of all the subjects was 23.98+/- 4.27 cm. Mean MAC with S.D of males and females were 25.62+/-3.57 and 20.64+/-3.63 cm respectively.

Table 4: Percentile of mid-arm circumference of Males and Females as per age group

AGE GROUP	BELOW 5 th percentile		5 th percentile		15 th percentile		50 th percentile	
	M	F	M	F	M	F	M	F
GENDER	M	F	M	F	M	F	M	F
18-19	0	2	1	1	2	0	1	0
20-24	8	6	4	2	4	0	0	1
25-34	6	7	7	2	4	1	0	0
35-44	3	2	1	1	2	0	1	0
45-54	2	0	5	0	0	0	0	0
55-64	2	0	0	0	0	0	0	0
65-74	0	0	1	0	0	0	0	0

Table 4 shows that the Mid -arm circumference (MAC) of 35 out of 76 subjects (46.05%) was below 5th percentile. MAC of 21 out of 51 males (41.17%), 18 out of 25 females (72%) were below 5th percentile. MAC of 12 out of 51 males (23.52%) was in 15th percentile and 1 out of 25 females (4%) were in 15th percentile.

Table 5: Mean and Median PEFR of subjects in litres per minute (l/min)

PEFR	MEDIAN	MEAN+/-S.D
MALES+FEMALES	300	299.86+/-99.10
MALES	315	321.20+/-88.21
FEMALES	260	267.91+/-91.37

Table 5 shows that the Median PEFR of all subjects was 300 l/min and mean PEFR with S.D was 299.86+/-99.10 l/min. Median PEFR of males was 315 l/min and mean PEFR with S.D was 321.20+/-88.91 l/min. Median PEFR of females was 260 l/min and mean PEFR with S.D was 267.91+/-91.73 l/min.

Table 6: Observed percentage of predicted PEFR of subjects

OBSERVED % OF PREDICTED PEFR	MALES	FEMALES
< 33%	5	1
33%-50%	10	7
50%-80%	32	8
>80%	3	9

Table 6 shows that 32 males and 8 females had moderate obstruction (observed PEFR values between 50% to 80%). 10 males and 7 females had severe obstruction (their observed percentage of PEFR values between 33% to 50%). 9 females and 3 males had their observed percentage of PEFR values more than 80% (mild obstruction). 5 males and 1 female had their observed percentage of PEFR values less than 30% (very severe obstruction).

No of subjects with increased:

- Serum urea - 8
- Serum Creatinine - 6
- Serum Bilirubin - 36
- Serum SGOT - 13
- Serum SGPT - 12
- TSH - 4

No of patients with decreased

- Serum Protein - 17
- Serum Albumin - 16
- Serum Globulin - 2

Table 7: Mean with SD of various biochemical parameters

BIOCHEMICAL PARAMETERS	MEAN +/- S.D
Haemoglobin	13.13+/-2.18
Total Leucocyte Count	8054.21+/-3109.88
Fasting Plasma Sugar	94.66+/-14.37
HbA1C	5.43+/-0.601
Serum Bilirubin	0.876+/-0.42
Serum SGOT	29.90+/-12.53
Serum SGPT	29.93+/-16.29
Serum Protein	6.73+/-1.05
Serum Albumin	3.98+/-0.63
Serum Globulin	2.90+/-0.59
Serum TSH	2.24+/-1.49
Serum T4	1.35+/-0.33
Serum T3	2.73+/-0.65
Serum Urea	28.79+/-11.50
Serum Creatinine	0.79+/-0.39

Socio-demographic Data

Out of 84 subjects 46 were married (32-Males, 14-Females) and 38 were unmarried (26-Males, 12-Females). Out of 84 subjects, 20 were Graduate, 15 were intermediate pass, 15 were high school pass, 11 passed primary school and 14 were illiterate. History of ATT intake before the initiation of cat 4 treatment: Out of 76 subjects, 39 took from Government, 26 from Private health facility and 9 took from both Government and Private health facility. 9 out of 77 (11.68%) subjects had h/o contact with drug resistant TB (Primary MDR-TB). 1 out of 9 was diagnosed XDR and 8 were apparently healthy after successful cat 4 treatment.

Before initiation of CAT-4 MDR treatment number of patients out of 76 who took ATT regularly was 48 and number of patients who took ATT irregularly were 28.

Number of subjects who were

- Tobacco chewers - 23
- Smokers - 11
- Alcoholics - 10

DISCUSSION

With current short course chemotherapy (SCC) regimens, majority of the patients with tuberculosis are cured of the disease. However, the information regarding the long term sequelae remains largely unknown. Studies have documented that 30-47% of cured pulmonary TB patients continue to have respiratory symptoms at the end of treatment, (40%) after one year of treatment and (15.9%) after two and a half years after treatment.²¹⁻²⁴

The mean (+S.D.) age of study done by Neeta Singla, Rupak Singla et al²⁵ patients was 33.5+11, the age ranging from 15-69 years. Thirty five were men and 28 were women. In our study the mean (+/-S.D) age was 29.92(+/-11.79) the age ranging from 18-67. Fifty seven were men and 27 were women. In our study three patients were found to be HIV positive. In study done by Neeta Singla, Rupak Singla et al. there were no HIV positive patients²⁵

Twenty three (40%) of the patients had a normal Body Mass Index, 16 (34%) were underweight and 8 (17%) patients were found to be overweight in study done by Neeta Singla, Rupak Singla et al. In our study 34 subjects out of 76(44.73%) were

very under weight. 18 out of 51 males (35.54%) and 16 out of 25 females (64%) were very under weight. Total 13 out of 76 subjects (17.10%), 12 out of 51 males (23.52%) and 1 out of 25 females (4%) were under weight. Weight of 29 out of 76 subjects (38.15%), 21 out of 51 males (41.17%) and 8 out of 25 females (32%) had their weight within normal range.

Due to its prolonged nature, treated patients of MDR-TB are expected to have higher rates of chronic disability compared with those with drug susceptible TB. However, only few reports are available in the literature who have studied the post-treatment sequelae of MDR-TB patients.²⁶⁻²⁷

A recent study from India²⁴ among new drug susceptible TB patients treated with first line anti tuberculosis drugs observed that 14-18 years after treatment completion 29% participants had persistent respiratory symptoms, 86% had radiological sequelae and lung functions impairments were present in 65% of the patients. This again emphasizes the point that post treatment sequelae are more common among MDR-TB patients compared to drug susceptible TB patients. However a study from Peru followed 120 MDR-TB patients for a median 67 (47-88) months after initiation of treatment and reported favourable long-term outcome among 71% of patients.

In our study also most of the subjects, 94 subjects out of 121 traced were apparently healthy and were able to resume their work.

In our study 69 subjects were apparently healthy and only one was bacteriologically positive. In study done by Neeta Singla, Rupak Singla et al²⁵ none of the currently alive 51 patients was bacteriologically positive on follow up. The findings are similar to study from Peru where 4 years after initiation of MDR-TB treatment only one out of 86 cured patients relapsed.²⁸ However another study from Taiwan reported a relapse rate of 6.5% among 153 MDR-TB patients who were followed up for 6 years after cure.²⁷

Though our study was on the patients who successfully completed treatment of cat 4 MDR-TB, 8 patients died and 7 diagnosed as XDR within first year of follow up hence it indicates that there is requirement of close follow up within first year of successful cat 4 MDR-TB treatment completion.

In study done by Neeta Singla, Rupak Singla et al²⁵ among 63 traced patients mortality rate was 19%. Among 53 cured patients, 5 died, and among 9 patients who defaulted, 6 died. One patient considered as treatment failure subsequently died of TB. Thus mortality was more common among patients who default or fail to treatment compared to those who were successfully treated. Another study from Peru also reported higher mortality during follow up among MDR-TB patients who defaulted or failed during treatment.²⁸ In our study 8 patients out of 112 (7.1%) traced patients died.

In Neeta singla, Rupak single et al study Body Mass Index, 16 (34%) were underweight .In our study majority of patients had decreased percentile of mid arm circumference as per their age and decreased serum protein and albumin.44.73% patient were very under weight and 17.10% were under weight. It clearly indicates that there is need of protein supplementation during treatment and also after completion of cat 4 MDR-TB treatment.

In our study 32 males and 8 females had moderate obstruction (observed percentage of predicted PEFV values between 50% to 80%).10 males and 7 females had severe obstruction (their observed percentage of predicted PEFV values between 33% to 50%).9 females and 3 males had their observed percentage of predicted PEFV values more than 80% (mild obstruction).5 males and 1 female had their observed percentage of predicted PEFV values less than 30%(very severe obstruction). Though the PEFV measurement is crude method to measure pulmonary function, in our study we found that there is significant pulmonary dysfunction occurring as post-tubercular sequelae.

In our study though HIV positive patients were not included but it was observed they had no adverse follow up (no death, no XDR).

The major limitation of this study is that of the target 121 patients under study only 84 were investigated and recorded. Many were lost due to migration and 7.4% due to inability to trace the address. Another limitation was small number of patients.

Another limitation of this study is that the observations made need not be due to MDR-TB sequelae alone and could be due to other health related factors in some of the study population.

CONCLUSION

The current observational study has shown that the community based standardized treatment regimen is effective as only one of the patients was bacteriologically positive on follow up.

However significant number of treated MDR-TB patients suffer from clinical, nutritional and functional post-treatment adverse events leading to some morbidity.

These issues need to be addressed preferably under the programme guidelines itself.

The post-treatment pulmonary rehabilitation of MDR-TB patients should be an integral part of DOTS Plus programme and will improve the impact of the National programme in the community.

Further research studies are recommended as very little studies are done on follow up of patients of successfully completed category 4 MDR-TB treatment. There is need to expand the limited knowledge and to create effective interventions with an objective to decrease the suffering from clinical, nutritional and functional post treatment adverse events and morbidity.

CONFLICT OF INTEREST

None

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A COMPARATIVE STUDY OF PULMONARY AND EXTRA-PULMONARY TUBERCULOSIS IN BHUTAN (2015-2017)

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ABSTRACT

Introduction: Extrapulmonary Tuberculosis (EPTB) has been increasingly diagnosed and reported compared to Pulmonary TB (PTB) in Bhutan in the recent years. In this comparative study, our study describes the epidemiology, diagnostic modalities used, inconsistency in case-classification and treatment outcomes of PTB and EPTB cases diagnosed from 2015-2017.

Methods: A retrospective descriptive study was conducted by retrieving patient records maintained at the 11 TB Reporting Centres. Using two stage cluster sampling technique, nine primary sampling units (9-PSUs) were generated for the years 2015, 2016 and 2017 respectively. Based on the highest caseloads among 32 TB Reporting Centres, nine primary clusters were selected first and final sample of 350 for each year were drawn using systematic random sampling technique from the PSUs.

Results: We recruited a total of 1048 cases (PTB=555, EPTB=493) in the final descriptive analysis. The median age of the subjects was 27 years (range 1-87) with slight female predominance (53%). Students were the highest (23.85%) followed by farmers (17.94%). The proportion of PTB was (52.95%), EPTB of (47.08%) and clinically diagnosed EPTB accounted for (92%), which is extremely high. Twelve miliary/disseminated TB cases (1.15%) were miss-classified as EPTB and (56%) EPTB cases were not classified based on the body sites involved. The overall treatment success rate (TSR) of PTB and EPTB was (93.26%).

Conclusion: We recommend an expert team to revisit National TB treatment guidelines on diagnosis of EPTB and ensure EPTB site/s are properly identified and documented. Sensitize clinicians and other units (ENT, Surgery, Orthopedics, MCH, General OPD etc.) on the referral of EPTB cases to Medical Specialist/Chest Physician for consultation.

Key words: Extra-pulmonary tuberculosis, Pulmonary tuberculosis, Descriptive study, Bhutan

INTRODUCTION

Tuberculosis is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*, typically

affects lungs (PTB) and it can also affect other body sites (EPTB). The disease is spread through respiratory droplet infection when the infected patient coughs, sneezes or spits. It is estimated that a small proportion (5-15%) of the estimated 1.7 billion people infected with *M. tuberculosis* could develop TB during their lifetime. In general, the probability of developing TB is higher among people affected with HIV/AIDS, under-nutrition, diabetes, smoking and alcohol consumption ⁽¹⁾.

According to the World Health Organization (WHO), tuberculosis falls in one of the top 10

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causes of global death. About 10.4 million people has fallen sick with TB, and 1.7 million have died from TB (including 0.4 million among people with HIV) in 2016 with over 95% of TB deaths occurring in low and middle income countries (2).

The National Tuberculosis Control Programme (NTCP) in the Ministry of Health in Bhutan was established in 1986. In 2001 the proportion of EPTB of all the TB patients was 26%. In 2010 the proportion of EPTB has increased to 39% and an alarming increase was seen by the end of 2016, wherein almost half (49%) of all TB cases registered were classified as EPTB (3, 4) DoPH, Ministry of Health.

The availability of computerized tomographic scan (CT-scan), magnetic resonance imaging, laparoscopy, endoscopy and aspiration biopsy have tremendously helped in anatomical localization and sampling of EPTB sites in diagnostic confirmation (5).

As EPTB occupying about half of the tuberculosis infection proportion in Bhutan is a cause of concern and at the same time a huge economic burden for a small developing country like ours. We conducted this comparative study on PTB and EPTB to obtain baseline information on TB epidemiology, report on any miss-classification and understand TB treatment outcomes. In Bhutan we have a total 32 TB Reporting Centers with at least one each for a district and some bigger districts like Chukha, Samtse and Trashigang has two to three TB Reporting Centres (4).

METHODOLOGY

A retrospective descriptive study was conducted by retrieving patient records maintained at the TB Reporting Centres sampled as clusters in our study for the years 2015, 2016 and 2017.

Study period

The descriptive study was conducted from March to June 2018.

Sampling strategy

Target population

The whole of the Bhutanese people were the target population for this study. As the study was conducted

nationwide with samples across nine districts, the findings of this study could be extrapolated to the whole of the Bhutanese population.

Source population

All the PTB and EPTB cases registered at the 32 TB Reporting Centres formed the source population.

Study areas/sites

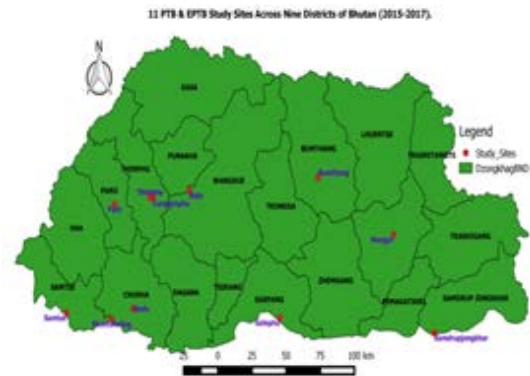


Figure 1. PTB and EPTB study sites, 2015-2017

We used two stage cluster sampling technique. Nine primary sampling units (9-PSUs) were generated using OpenEpi Version 3 software for the years 2015, 2016 and 2017. The actual samples required for each year from the nine clusters were 288. Based on the highest caseloads among the 32 TB Treatment Centres, nine primary clusters were selected first and final sample of 350 for each year were selected using systematic random sampling technique (SRS).

Definition and diagnosis of PTB and EPTB

PTB refers to any bacteriologically confirmed or clinically diagnosed case of TB that involved the lung parenchyma or trachea-bronchial tree with or without the involvement of any other organs in the body. Any bacteriologically confirmed or clinically diagnosed cases of TB involving other organs other than the lungs e.g. pleura, lymph nodes, abdomen, genitourinary track, skin, joints and bones, meninges, tuberculous pleural effusion without radiographic abnormalities in the lung parenchyma constitutes a case of EPTB (6).

Data collection and management

Data on patient demography, mode of diagnosis, TB case classification, sputum examination and

follow up, voluntary counselling and testing (VCT) and treatment outcomes were retrieved from the TB register, TB treatment card and Tuberculosis Surveillance and Information System (TbISS) online database system. Wherever feasible, we have contacted individual patients, for whom the data were incomplete in the above records maintained. Data base was built and entered in EpiInfo 7. STATA version 14 was used for data analysis, QGIS version 2.12.2 software for generating maps and excel for graph preparation. Mainly, descriptive statistical analysis was performed to generate counts and percentages. Results are presented mostly in tables, graphs and using maps.

Ethical Considerations

The study was approved by Research Ethics Board of Health (REBH) in Bhutan under the Ministry of Health vide its approval letter reference. No. REBH/Approval/2017/096 31st May, 2018.

RESULTS

Socio-demographic characteristics

The study included a total of **1048** (PTB=555 and EPTB=493) subjects from a total of 11 health centers from 2015-2017. PTB and EPTB combined socio-demography characteristics showed that the median age of the study participants was 27 years, which ranged from one to 87 years. Females were slightly more than (53%) than males. By occupation, students were the highest (23.85%) followed by farmers (17.94%). By ethnic group, *Sharchop* constituted the highest (48.09%) followed by *Ngalop* (32.54%) and (46.47%) of our participants were married. While the participants in PTB and EPTB showed significant difference by age groups (p value <0.05), other variables such as gender, place of residence, occupation, qualification, ethnicity and marital status between PTB and EPTB did not show any significant difference (p value >0.05) (Table 1).

Table 1. Distribution of PTB and EPTB by demographic characteristics in Bhutan, 2015-2017.

Demographic characteristics n (%)		PTB (n=555)	EPTB (n=493)	p-value
		n (%)		
Gender	Female	290 (52.25)	266 (53.96)	0.581*
	Male	265 (47.75)	227 (46.04)	
Age category	0 – 14	14 (2.52)	30 (6.09)	0.035*
	15 – 44	428 (77.12)	367 (74.44)	
	45 – 64	72 (12.97)	65 (13.18)	
	>65	41 (7.39)	31 (6.29)	
Residence	Rural	301 (54.23)	266 (53.96)	0.223 [†]
	Urban	245 (44.14)	211 (42.80)	
	Missing	9 (1.62)	16 (3.25)	
Occupation	Farmer	108 (19.46)	80 (16.23)	0.878 [#]
	Home-maker	73 (13.15)	67 (13.59)	
	Civil Servant	30 (5.41)	31 (6.29)	
	Corporate	22 (3.96)	17 (3.45)	
	Military	21 (3.78)	16 (3.25)	
	Students	127 (22.88)	123 (24.95)	
	Child	3 (0.54)	6 (1.22)	
	Monk	13 (2.34)	7 (1.42)	
	Construction worker	10 (1.80)	10 (2.03)	
	Private business	67 (12.07)	58 (11.76)	
	Health worker	4 (0.72)	6 (1.22)	
	National work force	1 (0.18)	1 (0.20)	
	Mining	1 (0.18)	0 (0.00)	

	Dependent	22 (3.96)	14 (2.84)	
	Prisoner	5 (0.90)	6 (1.22)	
	Missing	48 (8.65)	51 (10.34)	
Qualification	No schooling	152 (27.39)	123 (24.95)	0.144#
	Non-formal education	12 (2.16)	10 (2.03)	
	Primary school (<=6)	55 (9.91)	53 (10.75)	
	Lower secondary school	56 (10.09)	32 (6.49)	
	Higher secondary school	161(29.01)	139 (28.19)	
	Degree and above	45 (8.11)	54 (10.95)	
	Monastic	12 (2.16)	8 (1.62)	
	Pre-school	0 (0.00)	2 (0.41)	
	Missing	62 (11.17)	72 (14.60)	
Ethnicity	Indian	10 (1.80)	11 (2.23)	0.698*
	Sharchop	273 (49.19)	231 (46.86)	
	Ngalong	181 (32.61)	160 (32.45)	
	Lhotshampa	90 (16.22)	88 (17.85)	
	Missing	1 (0.18)	3 (0.61)	
Marital status	Unmarried	211 (38.02)	203 (41.18)	0.29*
	Married	267 (48.11)	220 (44.62)	
	Separated	7 (1.26)	7 (1.42)	
	Widow	18 (3.24)	8 (1.62)	
	Missing	52 (.37)	55 (11.16)	

*Pearson Chi-Square #Fisher's Exact

Mode of diagnosis of PTB and EPTB

Through 2015 to 2017, 98.66% of the PTB were diagnosed by smear microscopy. The next common bacteriological diagnosis was by culture (91.96%), followed by Line Probe Assay (LPA) (72.54%). About 85.05% of clinical diagnosed

cases of PTB were based on X-ray findings. CT scan and Ultrasonography (USG) were minimally employed (7.47% and 1.87% respectively). EPTB were mostly diagnosed by histopathology on the basis of biopsy and fine needle aspiration cytology (FNAC - 82.48%) (Table 2).

Table 2. Mode of diagnosis of PTB and EPTB in Bhutan, 2015-2017

Mode of diagnosis	Investigation types	Total tested	Positivity	
			n	%
PTB Diagnosis				
Bacteriology	Smear	447	442	98.66
	Culture	448	412	91.96
	GeneXpert	446	184	41.07
	LPA	447	325	72.54
	X-Ray	447	269	60.04
	MRI	448	5	1.12
	CT scan	448	5	1.12
	USG	448	1	0.22
Clinical	X-Ray	107	91	85.05
	MRI	106	0	0
	CT scan	107	8	7.48
	USG	107	2	1.87
EPTB Diagnosis				
Bacteriology	Smear	38	5	12.82
	Culture	38	2	5.13
	GeneXpert	38	4	10.26
	LPA	38	0	0
	X-Ray	38	10	25.64
	MRI	38	2	5.13
	CT scan	38	2	5.13
	USG	38	1	2.56
Clinical	X-Ray	449	169	37.22
	MRI	450	28	6.17
	CT scan	450	49	10.79
	USG	450	85	18.72
Histopathology	FNAC	137	113	82.48
	Biopsy	134	30	21.9

Classification of PTB and EPTB

The overall proportion of PTB was 52.95% (95% CI: 49.93% - 55.98%), while the proportion of EPTB was 47.08% (95% CI: 44.01% - 50.01%) (Table 3). The proportion of EPTB clinically diagnosed accounted for 92.09% ((440+14)/493*100), which is extremely high percentage with no evidence of

M. tuberculosis. Bacteriologically confirmed EPTB was very low at 7.91%. Similarly, the percentage of clinically diagnosed PTB was 19.28% and bacteriologically diagnosed PTB was 80.72% respectively. Relapsed cases (n=66) accounted for the maximum number of previously treated TB cases with (n=55, 83%) followed by treatment after failure (n=8, 12.12%).

Table 3. Classification of PTB and EPTB in Bhutan, 2015-2017.					
TB type <i>n</i>		New		Previously treated	
		%	<i>n</i>	%	
PTB	Pulmonary BC*	401	89.51	47	10.49
	Pulmonary CD**	104	97.20	3	2.80
	Overall PTB (%)	52.95 (95% CI: 49.93 – 55.98)			
EPTB	Extrapulmonary BC	37	94.87	2	5.13
	Extrapulmonary CD	440	96.92	14	3.08
	Overall EPTB (%)	47.08% (95% CI: 44.01 – 50.01)			

Classification of EPTB by body sites involvement

The most common EPTB sites involved was pleural effusion (17.56%), followed by lymphatic (13.17%) and gastrointestinal system (5.06%). More than half of the diagnosed cases of EPTB (56%) was not classified based on the body sites involved (Figure2).

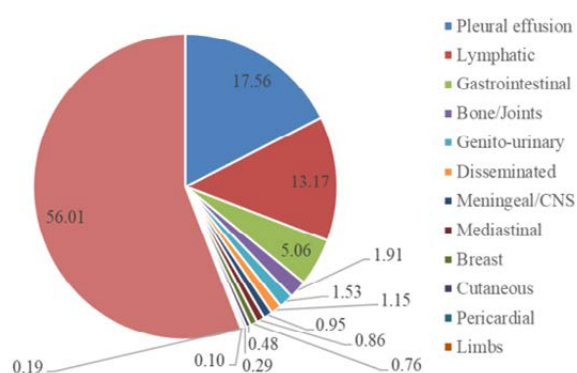


Figure 2. Classification of EPTB by body sites involvement (%)

Treatment outcomes of PTB and EPTB

Out of 555 PTB cases put on treatment, 409 have been declared successfully cured, with the overall proportion cured at (73.70%) and treatment completed at (17.50%). Out of 493 EPTB cases put on treatment, 471 have successfully completed treatment (95.53%) (Table 4).

Confirmed (PBC) was (91.29%) (i.e. 409/448*100) and Treatment completion rate for Extrapulmonary Clinically Diagnosed (EPCD) was (95.54%) (i.e. 471/493*100). TSR for PTB was (90.97%) and TSR for EPTB was (95.54%). The combined TSR of PTB and EPTB was 93.26% for 2015-2017.

Cured rate for Pulmonary Bacteriologically

Table 4. Treatment outcome of PTB and EPTB, 2015-2017.						
Treatment outcome	PTB			EPTB		
	<i>n</i>	%	95% CI	<i>n</i>	%	95% CI
Cured	409	73.7	70.02 - 77.37	---	---	---
Treatment completed	97	17.5	14.31 - 20.65	471	95.53	93.71 - 97.37
Died	12	2.16	00.95 - 03.38	8	1.62	0.50 - 2.74
Treatment failure	31	5.59	03.77 - 07.51	5	1.01	0.13 - 1.90
Lost to follow-up	4	0.72	00.00 - 01.43	5	1.01	0.13 - 1.90
Not evaluated	2	0.36	-00.13 - 08.74	4	0.81	0.02 - 1.61
Cure rate	---	91.29	88.68 - 93.91	---	---	---
Treatment completion rate	---	90.65	85.14 - 96.17	---	95.54	93.71 - 97.37
Treatment Success Rate (TSR)	---	90.97	87.03 - 94.97	---	95.54	92.16 - 99.84
Overall TSR	93.26 (91.70 - 94.75)					

DISCUSSION

In Bhutan, the overall proportion of PTB was 52.95% while the proportion of EPTB was 47.08% from 2015-2017. The proportion of EPTB diagnosed appears to be quite high with increasing trend observed till 2016. In 2017, the proportion of EPTB has dropped to about 40%, showing a declining trend. Globally and regionally, researchers have reported that percentage of patients with EPTB ranged anywhere from 15 to 55% (7-9). It is opinioned that successful treatment and cure of infectious cases may have resulted in a relative increase in annual EPTB case detection ⁽¹⁰⁾.

The proportion of clinically diagnosed EPTB in Bhutan from 2015-2017 was 92%, which is extremely high compared to proportion of bacteriologically diagnosed or smear positive EPTB at 8%, which is very low. Over diagnosis of EPTB is likely, which has led to reporting of a very high percentage of clinically diagnosed EPTB. In a study by Zenebe, Anagaw ⁽¹¹⁾, the overall prevalence of smear positive EPTB was reported as 9.9% (34/344), which is in close proximity to the smear positive EPTB reported in Bhutan.

Diagnosis of EPTB has always been a challenge. EPTB virtually affects all the organs and has a protean clinical manifestation depending on the anatomical sites involved. These often makes diagnosis difficult and presents with dilemma even for clinicians with great deal of experience in the field.

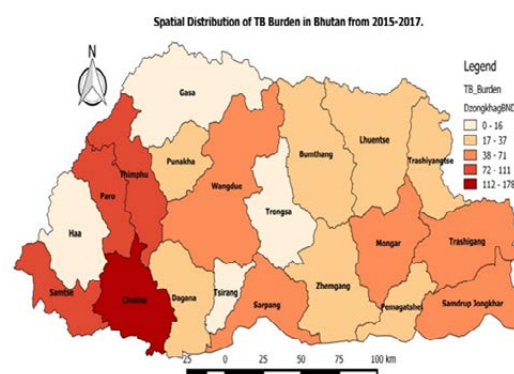
For a definitive diagnosis, it is essential to culture the mycobacteria. An appropriate specimens might be difficult to obtain from extrapulmonary sites due to pauci-bacillary nature of the disease, the bacteriological confirmation of EPTB is often more difficult than for pulmonary tuberculosis. Many of the affected sites may require an invasive procedure to get a biological sample to arrive at the diagnosis. Not all patients may agree for invasive procedures. Even for those who do, due to lack of diagnostic resources, poor yield of conventional diagnostic methods, and the lack of a universal sample processing technique for extra-pulmonary samples, all these can considerably lead to delay in starting the treatment ⁽¹²⁾.

We report misclassification of miliary TB/

disseminated TB as EPTB in a small percent (n=12, 1.15%) of our sample. EPTB site was not mentioned in (56%) of the patients, which was an important finding of our study. These type of misclassification error can be corrected by following standard diagnostic algorithm and proper documentation of the cases in the TB treatment card and the TB register, both by the treating clinician and the TB In-charges. We also need to sensitize other units (ENT, Surgery, Orthopedics, MCH, General OPD etc.) in the hospitals to refer the patients diagnosed as EPTB for X-ray chest to rule out miliary form of TB or lung involvement, which can avoid such misclassification.

In general, it was found that record keeping in the TB register, TB treatment card and on the TblSS online system was poor and many a times incomplete. We need to revisit all three forms of recording database, update if required and definitely train the new and re-train the existing TB In-charges so that their competencies to upload information present in the TB register onto the TblSS system is enhanced for better compliance and system efficiency in the future.

In terms of diagnostic workload, Jigme Dorji Wangchuk National Referral Hospital in Thimphu has catered to maximum of the TB patients. Thereafter, the patients were either transferred or returned to their place of residence to complete the treatment.



Chukha district followed by Thimphu, Samtse and Paro in the west and Mongar, Trashigang and Samdrupjongkhar in the east had the highest TB cases from 2015-2017 (Figure 3). These are logistic supply, manpower capacity building and programmatic intervention areas by the NTCP.

The combined TSR was 93.26% from 2015 to

2017. The overall TSR reported and maintained more than 90% by the NTCP form their program data has been confirmed and validated through this study.

LIMITATION OF THE STUDY

As our study was conducted retrospectively, historical data retrieval methods are potential sources of recall biases, missing information and incomplete recording. However, we have collected data by combining all these available sources and validated through rigorous supervision and monitoring process so as to obtain the best available data.

From a total of 31 eligible TB Reporting Centres, we have selected 11 TB reporting centres based on highest cases reported (9 PSUs each for 2015, 2016 & 2017). In total we had 11 PSUs which means a total of 11 TB reporting sites from nine districts were selected out of 19 eligible districts, representing all regions of the country. Although our sampling plan appears to have resulted in sampling bias, we are confident that results from this study can still be generalized as the TB treatment guidelines, case classification, sputum follow-up examination and treatment outcome standards are followed same throughout the country. On the other hand, mode of diagnostic and investigative procedures such as the sputum microscopy, X-ray and USG are practiced similarly across all centres, but advanced procedures such as the FNAC & biopsy, MRI & CT scan, LPA, GeneXperts and culture methods are limited to few centres only. In addition, the total sample size of 1048 retained in the final analysis is statistically robust/powerful enough for generalizability of the findings of the study.

CONCLUSION

We highly recommend the NTCP to revisit National Guidelines of Management of TB by an expert team on diagnosis of EPTB as very high percentage (92%) of EPTB was found to have been diagnosed clinically. Sensitize clinicians and TB In-charges on case detection, to ensure proper case classification, EPTB site identification and proper documentation in TB Register and patient Treatment card. All other units (ENT, Surgery, Orthopedics, MCH, General

OPD etc.) in the hospital should be sensitized on the referral of EPTB cases to Medical Specialist/ Chest Physician for consultation.

CONFLICT OF INTEREST

None

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ACCESS OF KEY POPULATION TO AVAILABLE HIV AND TB SERVICES IN NEPAL: A CROSS SECTION STUDY

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ABSTRACT

Introduction: TB is considered one of the opportunistic infection among PLHIV. The increasing burden of HIV/TB co-infection among key population cause problem to maintain adherence to ART and DOTS services. The emergence of MDR-TB is one of the greatest challenge to control and management of both diseases. However, having knowledge and information of both diseases are important role to access the available HIV/TB services.

Methods: A cross-sectional survey was conducted among key population who had HIV/TB co-infection in two-epidemic zone of Nepal. A pretested semi-structured questionnaire was used to collect data. ANOVA test was done to analyze the collected data by using SPSS version 20.0.

Results: A total of 343 HIV/TB co-infected individuals were enrolled to the study. Most of participants were from ART and DOTS clients. Therefore, the study found that there was significance difference found between knowledge about TB ($F=4.400, p=0.005$), causative agent of TB ($F=3.160, p=0.025$), risk of TB illness among PLHIV ($F=8.491, p=0.001$) and among key affected population. Moreover, there was significance difference found between access to OI treatment ($F=5.113, p=0.002$) and access to viral load ($F=4.642, p=0.003$) among key study population. In gender perspective, there was no significance difference to use and access to available HIV/TB services.

Conclusion: The general knowledge on HIV/TB co-infection was significant association with key population. The knowledge on HIV/TB and access to NGOs' help can significant effect to access the available HIV and TB services.

Key words: HIV/TB co-infection, available HIV and TB services, Nepal

INTRODUCTION

Human Immunodeficiency Virus/ Tuberculosis (HIV/TB) co-infection is a global public health problem and about 90% of cases are found in developing countries¹. Since the emergence of HIV epidemic, TB is the most opportunistic infection and considered the biggest (33%) killer among People Living with HIV (PLHIV)². The HIV/TB co-infection is common who have ($<200/ \text{mm}^3$) below Cluster of

Differentiation 4 (CD4) and WHO clinical stage II^{1,2}. The TB is responsible one third of deaths among PLHIV and it is found that about 40% of AIDS related deaths in Asia^{2,3}.

Despite the declining global burden of TB, there were 3,60,000 TB-related deaths occurred in 2013⁴. The HIV/TB co-infection epidemic is slowly emerging in the Asia-Pacific region but the impact of HIV/TB co-infection is poorly understood. The prevalence of HIV/TB co-infection is low at 17.2% in Asian countries, although HIV prevalence are highly found in key population^{2,3,5}. Data on HIV infection among TB patients are unreliable as universally testing of HIV is poorly implemented. Moreover, the dual burden of HIV and TB lead to complication and high rates of MDR-TB. Therefore,

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the management of both diseases are challenging to control and prevention of dual epidemic⁵.

Knowledge and information of HIV and TB are not satisfactorily in Nepal. The poor knowledge and existing socio-economic condition are important determinants of not health seeking behavior as well as adherence to ART and DOTS services^{6,7}. Patients' beliefs, knowledge and expectation of services are also strongly influence on adherence to medical decision⁶. On the contrary; stigma of either HIV and TB disease can lead isolation to infected person from their friends, family and that lead them to fear of seeking medical help. In fact, the knowledge and information of both HIV and TB diseases are believed to be an important role to access and adherence to care and support services^{6,7,8}. However; the lack of socio-economic support, stigma attached to HIV/TB disease and other behaviors factors are responsible to hide their disease and affecting to use of available health services^{9,10,11}. The poor socio-economic condition, financial access to care, poor health care delivery system, gender discrimination and unavoidable side-effect of drugs are demotivating to adherence HIV/TB services^{12,13}.

Although, it is usually expected that HIV/TB co-infected do not have sufficient knowledge about the availability of HIV and TB services and they do to adopt compliance behavior. To date, no study has been found regarding the knowledge and practice of HIV/TB services with regard to HIV/TB co-infection at community level. Therefore, this study was conducted to measure the knowledge of HIV and TB services and access on it. The findings of study could be beneficial to the decision makers and planners so as to design and implement the interventions to address shortcomings low coverage of HIV/TB services.

METHODS

The cross-sectional study was carried out covering two epidemic zone in five different districts such as Jhapa, Morang, Sunsari, Parsa and Kavre of Nepal. The participants of the study were enrolled from 12 HIV community care centers in state 1, state 2 and state 3 of federal democratic country Nepal. The main objective of the study to measure the knowledge and access of key population to available HIV/TB services in Nepal. The key study

population were approached who had previous background of Injecting Drug User(IDU), Sex Worker (SW) and their clients who travel high prevalence area of India, and Migrant Worker(MW). The all key study participants were adults having aged ≥ 18 to 55 years who were documented HIV diagnosis with TB infection according to national TB program guidelines. All HIV/TB co-infected individuals, including who were taking HIV/TB treatment from ART and DOTS centers were included. Before conducting of study, written consent was taken from each participants and ethical approval is taken from Nepal Research Health Council(NHRC). After taking verbal and written consent; the participants were approached and assessed their knowledge by asking knowledge about HIV/TB, causative agent, mode of transmission and along with their socio-demographic background, present and past health problems after having HIV/TB co-infection. The knowledge and information about availability and accessibility to HIV/TB services were also asked. The structured questionnaire was used to collect data and to analyze the data; ANOVA were done by using SPSS 20.0 version.

RESULTS

Table 1 shows analysis of F values and p-values of study variables. The analysis of ANOVA test shows there was significant difference between the knowledge of HIV before having HIV infection with key study population ($F=4.918$, $p=0.002$) and study districts ($F=3.344$, $p=0.006$). Similarly, significant difference was found between the knowledge on causative agent of HIV before illness with gender ($F=5.018$, $p=0.026$) and key study population ($F=2.754$, $p=0.043$). Likewise, there was significant difference between the knowledge on modes of transmission of HIV before illness with key study population. Analysis of ANOVA test shows that background variables like the key study population was a main determinant to have knowledge of HIV before having HIV infection of the respondents.

On the other hand, there was no significant difference between the knowledge on modes of transmission of HIV before having HIV infection and gender ($F=2.719$, $p=0.100$) and the knowledge on modes of transmission of HIV before having HIV and among study districts ($F=2.676$, $p=0.320$) as shown in table 1.

Table 1: Knowledge on HIV before infection				
Variables	Description	F values	p values	Remarks
Gender	Knowledge of HIV	0.006	0.937	Insignificant
	Causative agent of HIV	5.018	0.026*	Significant
	Modes of transmission of HIV	2.719	0.100	Insignificant
Key study population	Knowledge of HIV	4.918	0.002*	Significant
	Causative agent of HIV	2.754	0.043*	Significant
	Modes of transmission of HIV	5.657	0.001*	Significant
Study districts	Knowledge of HIV	3.344	0.006*	Significant
	Causative agent of HIV	2.158	0.073	Insignificant
	Modes of transmission of HIV	2.676	0.320	Insignificant
*Significant at the 0.05 level				

Table 2: Knowledge on TB before HIV/TB co-infection				
Variables	Description	F values	P Values	Remarks
Gender	Knowledge of TB	1.088	0.298	Insignificant
	Causative agent of TB	0.103	0.748	Insignificant
	Risk of TB illness among PLHIV	0.485	0.487	Insignificant
Key study population	Knowledge of TB	4.400	0.005*	Significant
	Causative agent of TB	3.160	0.025*	Significant
	Risk of TB illness among PLHIV	9.830	0.001*	Significant
Study districts	Knowledge of TB	4.612	0.001*	Significant
	Causative agent of TB	1.379	0.241	Insignificant
	Risk of TB illness among PLHIV	8.491	0.001*	Significant
* Significant at the 0.05 level				

Government of Nepal and various NGOs have been providing various types of HIV prevention and awareness services in the study districts. Table 2 gives F values and p-values to measure the significant difference of study variables. The analysis of ANOVA test shows that there was significant difference between the knowledge of TB before HIV/TB co-infection with key study population (F=4.400, p= 0.005), and study districts (F=4.612, p=0.001). Similarly, significant difference was found between the knowledge on risk of TB illness among PLHIV with key study population (F=9.830, p=0.001), and study districts (F=8.491, p=0.001). Likewise, there was significant difference between the knowledge on causative agent of TB

and respondents of key study population (F=3.160, p=0.025).

On the other hand, the knowledge on causative agent of TB among PLHIV had not significant difference with gender (F=0.103, p=0.748) and study districts (F=1.379, p=0.241). There was no significant difference between the knowledge of TB before HIV/TB co-infection and gender of respondents (F=1.088, p=0.298) as shown in table 2. Analysis of ANOVA test shows that background variables like the key study population and study districts were main determinants to have knowledge on TB before illness of the respondents.

Table 3: Availability and accessibility of NGO service				
Variables	Description	F values	p values	Remarks
Gender	Access to care home service	0.547	0.460	Insignificant
	Access to ART transportation cost	0.008	0.928	Insignificant
	Access to OI/CD4 transportation cost	0.031	0.860	Insignificant
	Access to capacity building training	0.007	0.935	Insignificant
Key study Population	Access to care home service	0.816	0.486	Insignificant
	Access to ART transportation cost	5.488	0.001*	Significant
	Access to OI/CD4 transportation cost	1.838	0.140	Insignificant
	Access to capacity building training	3.537	0.015*	Significant
Study districts	Access to care home service	2.912	0.022*	Significant
	Access to ART transportation cost	5.413	0.001*	Significant
	Access to OI/CD4 transportation cost	5.978	0.001*	Significant
	Access to capacity building training	7.483	0.001*	Significant

* Significant at the 0.05 level

Table 3 shows there was significant difference between the study districts with access to care home service ($F=2.912$, $p=0.022$), followed by access to ART transportation cost of NGOs ($F=5.413$, $p=0.001$), access to OI/CD4 transportation cost of NGOs ($F=5.978$, $p=0.001$) and access to capacity building training of NGOs ($F=7.483$, $p=0.001$). Similarly, significant difference was found between the respondents of key study population with access to OI/CD4 transportation cost of NGOs, and access to capacity building training of NGOs as shown in table 3. On the other hand, there

was no significant difference between the gender of respondents with access to care home service of NGOs ($F=0.547$, $p=0.460$), access to ART transportation cost of NGOs ($F=0.008$, $p=0.928$) and access to OI/CD4 transportation cost of NGOs ($F=0.031$, $p=0.860$). Likewise, no significant difference was found between the respondents of key study population and access to care home service of NGOs ($F=0.816$, $p=0.486$), the access to OI/CD4 transportation cost service of NGOs ($F=1.838$, $p=0.140$).

Table 4: Availability and accessibility of HIV/TB services				
Variables	Description	F values	p values	Remarks
Gender	Access to OI treatment	0.726	0.394	Insignificant
	Access to Viral load	0.008	0.928	Insignificant
	Access to CD4	2.112	0.147	Insignificant
	Access to ART service	0.001	1.000	Insignificant
	Access to DOTS	1.582	0.209	Insignificant
Key study population	Access to OI treatment	5.113	0.002*	Significant
	Access to Viral load	4.642	0.003*	Significant
	Access to CD4	1.187	0.314	Insignificant
	Access to ART service	2.157	0.093	Insignificant
	Access to DOTS	4.275	0.006*	Significant
Study districts	Access to OI treatment	20.09	0.001*	Significant
	Access to Viral load	20.56	0.001*	Significant
	Access to CD4	1.335	0.257	Insignificant
	Access to ART service	3.996	0.004*	Significant
	Access to DOTS	2.986	0.019*	Significant

* .Significant at the 0.05 level

HIV/TB co-infection, and availability and accessibility of health care services of the beneficiaries are important indicators of effectiveness of intervention of programme. So, the study had measured these indicators in study area. Table 4 presents the data of ANOVA which includes F value and p-values to measure the significance difference of variables of interest. The study also found that there was significant difference between the key study population with access to OI (F=5.113, p=0.002), access to viral load service (F=4.642, p=0.003), access to DOTS service (F=4.275, p=0.006). Likewise, significant difference was found between the study districts with access to OI treatment (F=20.09, p=0.001), access to viral load (F=20.56, p=0.001) and access to DOTS (F=2.986, p=0.019).

On the other hand, there was no significant difference between the gender of respondents with access to OI treatment (F=0.726, p=0.394), followed by access to viral load service (F=0.008, p=0.928), access to CD4 (F=2.112, p=0.147), access to ART service (F=0.001, p=1.000). Likewise, there was no significant difference between the respondents of key study population with access to CD4 population (F=1.187, p=0.314), the access to ART service (F=2.157, p=0.093).

DISCUSSION

Both HIV and TB infection are bound together early years of the HIV/AIDS pandemics. The collision of both HIV and TB disease have greatly added illness and loss of life among PLHIV^{12,14,15}. The synergy of HIV/TB co-infection can increase the pathogenesis, epidemiologic profile, social issues and decrease the socio-economic life of affected individuals and communities. Therefore, the burden of HIV/TB co-infection interface problem and it causes paucity of resources to control and prevention. Despite the abundant efforts of government and non-government sectors, the existing high level stigma, discrimination and other socio-cultural issues have limit the PLHIV access the HIV/TB services^{2,7,15}. But, our study found reverse result and in which the transportation support of NGOs found to be significant effect to access OI, viral load, ART and DOTS services.

This study assessed the general knowledge and access to available HIV/TB services and our study

found that the knowledge of TB, and risk of TB illness among were significant association with key affected population. This study is consistent with the study done by Yadav. et. al, which showed that general knowledge on TB was satisfactory whereas, in-depth knowledge on sign and symptom of disease was inadequate among PLHIV^{14,16}. Similar study was carried out by Bhatt CP et.al, have found that more than 83% of respondents had sound knowledge about TB and its prevention and treatment¹⁷. Our study result also revealed that there was significant difference about knowledge on HIV/AIDS among key study population. Compared to the previous study, it shows varied result. One previous study conducted in India found that gender differences in knowledge of HIV/AIDS were reported among college-going young population¹⁸. Similarly, another study conducted in India, showed there was higher knowledge on HIV prevention among active migrants than among returned migrants¹⁹.

In fact, the HIV/TB co-infected are living under unfavorable life with low accessing to treatment facilities. Despite the technological changes, those people do not get proper counselling and motivation and they have been living with low adherence to ART^{10,15,20}. Whereas, our study found that NGOs' contribution on transportation support to PLHIV, was significant association with accessing available of HIV/TB services in study districts. Similarly, a study done in Nepal and found that there is not uniform coverage ART service due to lack of transportation cost and fear of stigmatization^{6,15}. As a matter of fact, that the existing high level stigma and discrimination of both HIV and TB diseases cause late access timely diagnosis and treatment of illness especially to the female^{8,21}.

With regard to HIV/TB co-infection; the insufficient knowledge and not adherence to clinical practice guideline of health workers are significant effect on noncompliance treatment outcome²². Moreover, socio-cultural norms, structural and geographical location of treatment center also cause low treatment compliance rate among PLHIV^{15,20}. Our study findings also consistent with these previous studies and the study found that there was significant difference to access the available OI, viral load, DOTS service among key population. However, there was no significance difference

to access the available CD4 and ART services among key population. A recent study from Nepal has shown that socio-cultural and managerial issues limit to access the ART and DOTS services, although all services are offered free of cost^{6,15,17}.

This study has certain limitations. It included all registered HIV/TB co-infection cases in ART and DOTS centers and excluded all unregistered cases in DOTS and ART centres, and those who were diagnosed their co-infection in private doctors' clinics and taking drugs regularly. Their exclusion gives power of study to show relationship between HIV/TB co-infection and access to available its public health services. This study adopted cross-sectional survey that's why, the causal relationship could not be established. Some study participants might have felt hesitated to expose their feeling thereby responding to questions would be viewed low coverage of study. The study adopted snowballing and convenient sampling techniques and that limits generalizability of results. However, a strength of the study is that finding would be beneficial for planner to policy maker to execute control and prevention of HIV/TB co-infection among key population.

CONCLUSION

HIV/TB co-infection has been emerged as significant health problem in recent years. The adherence of ART services can reduce HIV and TB related morbidity and mortality. Despite the numerous effort of government, and Non-government sectors, the PLHIV still hides their HIV status and hesitate to access the available HIV and TB services. However, this study found that the general knowledge of HIV and TB have played significant effect to access the HIV and TB services among key population. Moreover, the use of available services of NGOs also contributing to scale up to access the HIV/TB services. The available transportation cost of NGOs have contributed in accessing OI, viral load, and DOTS service to the key population. Therefore, the expansion of HIV testing and counselling services could help to achieve high coverage HIV/TB services.

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CONFLICT OF INTEREST

None

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HIV VULNERABILITY AND SEXUAL RISK BEHAVIOR OF THE DRAYANG GIRLS IN BHUTAN

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ABSTRACT

Introduction: The rapid socio-economic development in Bhutan has brought changes in individual lifestyles resulting in increased risk behavior of the urban population, particularly the Drayang girls. This study investigated the underlying factors influencing the sexual risk behaviour of Drayang girls and their vulnerability to HIV and Sexually Transmitted Infection (STI). The Drayang are dance bars in Bhutan where the women perform Bhutanese songs/dances on the stage to entertain the bar patrons and making them pay for their performance.

Methods: This is a cross-sectional descriptive study conducted from May-July 2015 in three urban districts (Thimphu, Paro, and Phuentsholing) of Bhutan. The convenient non-random sampling method was used to recruit the respondents. We have collected the data using structured questionnaires including the taking of blood samples for HIV, Hepatitis B, and Syphilis testing.

Results: Of the 245 Drayang girls recruited for this study, 28.2% have engaged in transactional sex and 71.8% in non-transactional sex within last month. Condom use during transactional sex was 36.2% and non-transactional sex was 21.6%. The prevalence of HIV was 0.82%, hepatitis B 6.9%, and syphilis 2.8%. The factors such as marital status (divorced and unmarried), living arrangements, current living cities, and alcohol consumption were significantly ($p < 0.05$) associated with transactional sex among Drayang girls.

Conclusion: Although the prevalence of HIV and STIs is low among the Drayang girls, the presence of high risk behavior with low condom use still makes them vulnerable to HIV and STIs. The study recommends putting more effort in prevention of HIV and STI by increasing awareness of HIV and STI, targeted interventions like Behaviour Change Communications (BCC), condom promotion, condom negotiation skills and access for testing and treatment of HIV and STI.

Key words: Draying; HIV; vulnerability; transactional sex; Bhutan

INTRODUCTION

The national response to HIV and AIDS prevention in Bhutan dates to 1980s before the detection of the first case in 1993. As of December 2017,

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the cumulative number of 570 (296 male and 274 female) HIV cases has been detected with the majority (87%) between the ages of 15-49. Heterosexual remains the dominant route of HIV transmission in Bhutan. The increasing trends of HIV and STIs cases every year is one of the major public health concerns.⁽¹⁾The rapid socio-economic development in Bhutan has brought changes in social, political and cultural lifestyles of the Bhutanese population. As a part of the modernization, entertainment venues like discos, pubs, karaoke, and Drayang has emerged. The Drayang are dance bars in Bhutan where the women perform Bhutanese songs/dances on the stage to entertain the bar patrons and making them

pay for their performance.

The changes in lifestyles of the urban populations with such entertainment trends have increased individual's risk behaviour, particularly among the Drayang girls. The emergence of sex worker and growing transactional among the young girls in the entertainment venues were recorded in General Population Survey (GPS) 2006, Behavioural Surveillance Survey (BSS) 2008 in Bhutan.^(2,3) The GPS (2006) also reported that one-fifth of all the married people have engaged in extramarital sex within a year. This was higher among the urban areas (23%) as compared to the rural areas (14%).⁽²⁾ The qualitative study among Drayang girls by R. Lorway (2011) also showed a similar result.⁽⁴⁾ The Sexual Behavioural Network Study (SBNS) 2011 further revealed a large proportion (49%) of bar patrons in Phuentsholing and Thimphu had engaged in multiple sexual relationships in 12 months prior to the survey with an average of 2.5 partners. The study also confirmed risky sexual behaviour as a result of alcohol consumption in the entertainment venues.⁽⁵⁾

The findings from different qualitative studies and the reports in the local media⁽⁶⁻⁹⁾ on the issues of transactional sex among the Drayang girls has made many to perceive that these girls are at a higher risk of HIV and STIs infection. These negative perceptions of the society have brought some social stigma against their profession and may prevent them from seeking timely health care services including HIV Testing and Counselling (HTC).⁽¹⁰⁾ The global evidence also shows that the stigma and discrimination among sex workers and people living with HIV are one of the factors for failure in seeking timely treatment.⁽¹¹⁻¹³⁾ However, there is very little quantitative information to understand the HIV vulnerability and sexual risk behaviour of the

Drayang girls in Bhutan. Therefore, this study will explore the underlying determinants that influence the sexual risk behaviour of the Drayang girls for HIV and STIs infection.

METHODOLOGY

Design and settings

This is a cross-sectional descriptive study conducted from May-July 2015 using structured questionnaires and taking blood samples. The major cities (Thimphu, Phuentsholing, and Paro) having more numbers of Drayangs were selected. The exact number of Drayang can be determined from the Bhutan Infocomm and Media Authority who issues the operational license for its establishment. As shown in Figure 1. The conceptual framework of Kembo J (2012) was adapted to guide the overall analysis.⁽¹⁴⁾ The original concept used in this model is to understand how the underlying determinants influence the proximate determinants for certain health outcomes. During the process of modification, the new variables (knowledge, alcohol, living arrangements, living city and work duration) were added to the framework without diminishing the original concept.

a. Study population and sampling

The study population includes the young girls and women working in the Drayangs. The convenient non-random sampling technique was used to recruit study respondents. Criteria were set to sample the target population: (a) respondents should be equal to or above 18 years of age, (b) be present in the selected Drayang; and (c) fulltime singer/dancer in the selected Drayang; and (d) provide consent to participate in the study without coercion. As shown in Figure 2. Out of 35 Drayangs in Bhutan located

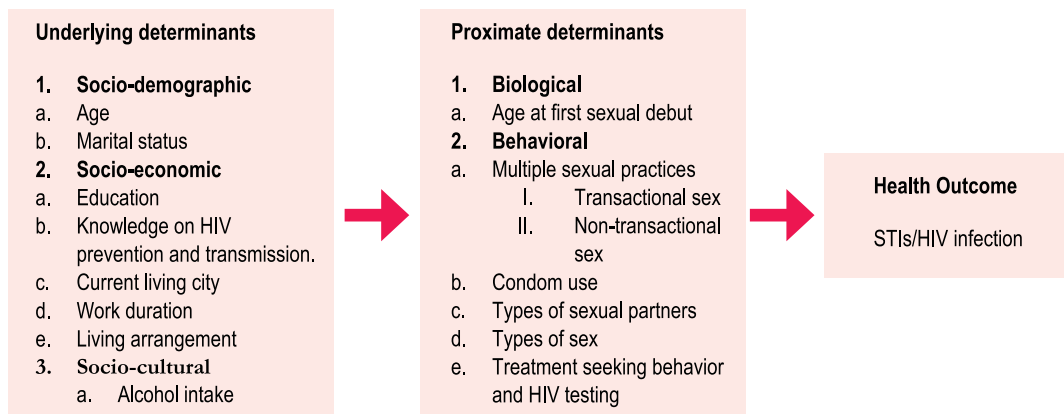


Figure 2. Conceptual framework for factors influencing the risk behavior of Drayang girls in acquisition and transmission of HIV/STIs infection in Bhutan. Source: Adapted from Kembo J (2012).

in seven districts, we have selected three major cities of Bhutan where 80% of the total Drayang girls are located. Out of 308 registered Drayang girls in 28 Drayangs, 245 were selected who met the selection criteria.

The research team collaborated with the Health Information and Service Centre (HISC) counsellors working with the Drayang girls on the preventions of HIV and STIs. The HISC counsellors coordinated with the respective Drayang owners/managers and discussed the participation of Drayang girls. Accordingly, the respective Drayang owners/managers and the HISC counsellors recruited the girls for a general briefing. All respondents were briefed about the study objectives and recruited into study only after obtaining consent.

b. Data collection tool

A structured questionnaire consisting of 39 variables was used to collect the information on the socio-demographic, economic, cultural, biological and sexual behaviour of the Drayang girls. The interval scale questions were used instead of dichotomous questions to overcome the sensitivity of the subject. Further, the questions pertaining to past sexual history was limited to one month prior to the survey to allow the participants recall accurately. We have developed questionnaires by keeping the general issues at the beginning and sensitive topics towards the end.

c. Data processing and analysis

The data collected was double entered, cleaned and checked for validity. HIV test was carried out using rapid diagnostic test kits with the final confirmatory test using enzyme-linked immune sorbent assay (ELISA). Syphilis test was conducted using TPHA while rapid test kits were used for hepatitis B testing. Descriptive statistics were analyzed using Epi Data software and association between variables were tested using Chi-square Test. The Fisher Exact Test was done using the online program.³⁹

d. Ethical considerations

The approval from the Research Ethics Board, Ministry of Health, Bhutan were obtained. Informed consent was sought from the respondents and data collected were secured under lock and key. Confidentiality of HIV test results was maintained by protecting the client's identity using code numbers and giving result in person by the HISC counsellors.

e. Quality assurance

The trained VCT counsellors and the certified Laboratory Technicians from Royal Centre for Disease Control (RCDC), MoH were trained on the research protocol, data collection tools, and data management before the conduct of the study. The data collection tools were pretested among the similar population in Thimphu and change incorporated.

RESULTS

The findings from the survey were presented based on the conceptual framework used in this study to see how underlying determinants influence the proximal determinants of the Drayang girls for HIV and STIs.

Underlying determinants

As mentioned under the study population and sampling, out of 308 Drayang girls, 245 of them have been included in the study with the mean age of 22 years. The socio-demographic characteristics of the Drayang girls showed that majority 71.4% (n=175) of the respondent falls within the age bracket of 18-24 years and 43.7% (n=107) are married, 29.8% (n=73) divorced while 26.5% (n=65) were unmarried. Some 42.4% (n=104) had middle-secondary education, 31% (n=76) with no-education and 22.1% (n=65) has completed primary education. The mean working duration in the Drayang by the girls is 8.4 months.

Table 1. Relationship between transactional sex by socio-demographic, economic and cultural factors of the Drayang girls in three cities* of Bhutan, 2015.

Demographic Characteristics	Transactional Sex			Chi-Square (<i>P-Values</i>)
	Total (N=245)	Yes (n=69)	No (n=176)	
	N	%	%	
Age group				
18-24 years	175	28.6	71.4	0.823
25-34 years	70	27.1	72.9	
Marital status				
Married	107	11.2	88.8	0.000
Unmarried	65	40.0	60.0	
Divorced	73	42.5	57.5	
Economic Characteristics				
Education				
No education	76	26.3	73.7	0.177
Primary	65	36.9	63.1	
Middle secondary	104	24.0	76.0	
Place of work				
Thimphu	116	25.0	75.0	0.014
Paro	51	17.6	82.4	
Phuntsholing	78	39.7	60.3	
Work Duration				
<=8 Months	161	29.2	70.8	0.620
>8 Months	84	26.2	73.8	
Living arrangement				
Self	44	40.9	59.1	0.001
Relatives	41	36.6	63.4	
Friends	66	33.3	66.7	
Hostel	23	30.4	69.6	
others	71	9.9	90.1	
Cultural characteristics				
Alcohol intake				
Yes	127	35.4	64.6	0.009
No	118	20.3	79.7	

Key:*Thimphu, Paro and Phuentsholing

Table 1 shows socio-demographic, socioeconomic and socio-cultural characteristics of the respondents and their association with transactional sex. The divorced women are significantly more likely ($p=0.00$) to engage in transactional sex as compared to unmarried and married (42.5% vs 40% and 11.2%). Girls working in bigger cities like Thimphu (39%) and Phuentsholing (25%) are more likely ($p=0.014$) to engage in transactional

sex compared to those working in smaller towns like Paro (17%). Girls who managed their own accommodation (40.9%) were most likely to engage in transactional sex as compared to their counterparts who lived with their relatives (36.6%), friends (33.3%), hostels (30.4%), and others (9.9%). Apparently, girls who consumed alcohol (35.4%) are most likely to engage in transactional sex than those who remained sober (20.3%).

Table 2. Biological & behavioral characteristics of Drayang girls in three cities* of Bhutan, 2015.								
Behavioral Characteristics	City							
	Thimphu		Paro		P/ling**		Total	
	n	%	n	%	n	%	N	%
Age at first sexual experiences (N=245)								
10-15 years	18	15.5	7	13.7	10	12.8	35	14.3
16-20 years	87	75.0	31	60.8	61	78.2	179	73.1
21-25 years	11	9.5	13	25.5	7	9.0	31	12.7
Total	116	100.0	51	100.0	78	100.0	245	100.0
Mean Age 17								
No. of transactional sex in last 30 days (n=69)								
<=3 times	14	48.3	3	33.3	13	41.9	30	43.5
>3 times	15	51.7	6	66.7	18	58.1	39	56.5
Total	29	100.0	9	100.0	31	100.0	69	100.0
No. of no- transactional sex in last 30 days (n=176)								
<=3 times	35	40.2	16	38.1	23	48.9	74	42.0
>3 times	52	59.8	26	61.9	24	51.1	102	58.0
Total	87	100.0	42	100.0	47	100.0	176	100.0
Condom use during transactional sex in last 30 days (n=69)								
All of the time	14	48.3	1	11.1	10	32.3	25	36.2
Some of the time	5	17.2	2	22.2	8	25.8	15	21.7
Not Used	10	34.5	6	66.7	13	41.9	29	42.0
Total	29	100.0	9	100.0	31	100.0	69	100.0
Condom use during no-transactional sex in last 30 days (n=176)								
All of the time	21	24.1	5	11.9	12	23.9	38	21.1
Some of the time	22	25.3	15	35.7	12	26.1	49	28.0
Not used	44	50.6	22	52.4	23	50.0	89	50.9
Total	87	100.0	42	100.0	47	100.0	176	100.0
Frequency of alcohol drinking per week in last month (n=127)								
>=3 times/week	11	16.4	5	25.0	13	32.5	29	22.8
<3 times/week	56	83.6	15	75.0	27	67.5	98	77.2
Total	67	100.0	20	100.0	40	100.0	127	100.0
Sex under alcohol intoxication (n=127)								
Yes	31	46.3	9	45.0	17	42.5	57	44.9
No	36	53.7	11	55.0	23	57.5	70	55.1
Total	67	100.0	20	100.0	40	100.0	127	100.0
Condom use during sexual intercourse under alcohol intoxication (n=57)								
Yes	7	22.6	2	22.2	3	17.7	12	21.1
No	24	77.4	7	77.8	14	82.4	45	78.9
Total	31	100.0	9	100.0	17	100.0	57	100.0

Key: *Thimphu, Paro and Phuentsholing, ** Phuentsholing.

Proximal determinants

Table 2 shows the biological and behavioural characteristics of the respondents. The mean age for the first sexual debut was 17 years and 73.1% of them had first sexual experience between the ages of 16-20 years whereas 14.3% have experienced first sexual intercourse between 10-15 years. Out of 245 sexually active females, 28.2 % (n=69) reported to having engaged in transactional sex (sexual intercourse between men and women, where exchange of money or materials goods takes place) and 71.8% (n=176)

non-transactional sex (marital, non-marital and extramarital sex without the exchange of money or materials good) during the last thirty days. However, both categories of girls had more than three sexual partners with transactional sexual category comprising 56.5% and non-transactional sexual category reporting 58.0%. The condom uses among those engaging in transactional sex and those not engaging in transactional sex was 36.2% and 21.1% respectively. Fifty-Seven of the respondents reported having engaged in sex under the influence of alcohol and their condom use was 21.1%.

Table 3. Prevalence of HIV and STIs among Drayang girls in three cities*, Bhutan, 2015.								
Indicators	Name of City							
	Thimphu (n=115)		Paro (n=51)		P/ling** (n=78)		Total (N=245)	
	n	%	n	%	n	%	N	%
A. Result from the onsite testing								
HIV								
Positive	1	0.9	0	0	1	1.28	2	0.82
Negative	114	99.1	54	100	77	98.7	243	99.2
Hepatitis B								
Positive	8	7.0	4	8	5	6.41	17	6.94
Negative	107	93.0	47	92	69	88.5	238	91.9
Syphilis								
Positive	2	0.9	0	0	6	7.69	7.0	2.86
Negative	113	98.3	51	100	72	92.3	238	97.1
B. Result from the survey questionnaires								
Any STIs in last 12 months								
Yes	31	27	7	13.7	7	8.97	45	18.4
No	84	73	44	86.3	71	91.0	200	81.2
Bad abnormal discharge in last 12 months (n=45)								
Yes	25	80.7	7	100	4	57.1	36	80.0
2 No	6	19.4	0	0	3	42.9	9	20.0
Sore or ulcer infection near vagina/anus (n=45)								
Yes	6	19.4	4	57.1	1	14.3	11	24.4
No	25	80.7	3	42.9	6	85.7	34	75.6

Key: *Thimphu, Paro and Phuentsholing, **Phuentsholing

Health outcome (HIV and STIs vulnerability)

Table 3 illustrates the HIV and STIs prevalence. The point prevalence of 0.82% was determined for HIV, 6.94% and 2.86% for hepatitis B and Syphilis respectively. However, when asked about any STIs in last twelve months 18.4% (n=45) of them

reported having experienced at least one form of STIs. Out of 45 who experienced STIs in last 12 months, 36 of them reported having experienced abnormal discharge from their vagina and 11 told that they had developed sore or ulcer in genital region.

DISCUSSION

This quantitative study is among the first of its kind to examine the underlying factors that increase the vulnerability of the Drayang girls for HIV and STI including the determination of point prevalence of HIV and STIs. The modified conceptual framework of Kembo J, 2012, guided the analysis of underlying factors influencing the proximal determinants of HIV and STIs infection. Although the authors have decided to publish the manuscript after one year and eight months from the date of conduct of the study, the findings are, still relevant, as no other researchers have conducted such studies so far. Moreover, the growth of Drayang in Bhutan has remained stagnant over the period but there was a slight increase in the number of Drayang girls (370 in 2015 to 400 in 2017). Concerning the situation of HIV in Bhutan, the number of cases has increased from 460 in 2015 to 570 in 2017 with no cases reported from the Drayang girls.⁽¹⁾ The major route of transmission is predominated heterosexual route of transmission.

One of the interesting findings that the study revealed was the low prevalence of transactional sex as compared to non-transactional sex. Therefore, the assumption that all Drayang girls would engage in transactional sex was not supported as evident from the findings, though the answers were self-reported. Nevertheless, the prevalence of 28.2% transactional sex with low condom use (36.2%) indicates an existence of risky sexual behaviors among the Drayang girls. Our finding was consistent with findings of the qualitative study by R. Lorway (2011), SBNS (2011), FA (2015) among the Drayang and other bar girls where some of the respondents mentioned about their engagement in transactional sex.^(4,5,16) Further, the BSS (2008) also found that 32.5% of 77 bars girls consisting of waitresses and singers in Thimphu and 52.0% of 25 of them in Phuentsholing had engaged in transactional sex one month prior to the survey. In both the case, the consistent condom use was 44.4% and 38.5% respectively. This shows the high possibility of some Drayang girls engaging in transactional sex owing to some similarity in their work.

The findings also depict multiple sexual partners among the Drayang girls with non-transactional sex group. For example, 42% of the Drayang girls had

engaged in multiple sexual partners with more than three partners within a month and the consistent condom use was 21.1%. When comparing the findings with GPS (2006) in Bhutan it was found that out of 788 urban females only 1.6% have engaged in multiple sexual partners in last 6 months prior to the survey and the consistent condom use was just 23.3%.⁽²⁾ This illustrates higher multiple sexual partners with low condom use among the Drayang girls as compared to the general urban females thus making them more vulnerable to HIV and STIs. The studies from different settings also showed that those women who are in multiple sexual relationships are more likely to face several risk factors for HIV and STIs like early sexual debut, longer duration of sexual activity, remaining with a promiscuous partner, concurrent partnership, and sexual harassment.⁽¹⁷⁻²²⁾ Therefore, introducing Behaviour Change Communication (BCC) programs can be one important aspect to enhance the condom negotiation skills of the Drayang girls.^(23,24) However, this study has limitations to understand the underlying factors for low condom use by the Drayang girls thus deserves further research.

In terms of socio-demographic characteristics, the divorced and unmarried women are engaged more in transactional sex as compared to married women. The result is consistent with the findings from the qualitative study by R. Lorway (2011) where the majority of those who engaged in transactional sex was from the divorced and unmarried categories of respondents.⁽⁴⁾ We do not know the specific reason for their engagement in transactional sex but we speculate that it may be due to their financial hardship as a single bread earner. In general, the global studies in different settings also showed that the divorced and unmarried women are more likely to face social challenges related to poverty, income and gender inequality thus exposing them to various risk including HIV and STIs.^(20,25-27) However, we cannot generalize these findings for other divorced women in Bhutan who are not working in Drayangs with same sexual behaviour as the study was confined to women who were working in the Drayang, and from them a small subset was divorced. Therefore, an in-depth study is required to understand the prevalence of transactional sex among Bhutanese women in general for an appropriate public health action.

Respondent's age was not associated with the engagement in transactional sex. The studies conducted by Singh and colleagues also found that no association between age and transactional sex among the women in Zambia.⁽¹⁸⁾ This shows that age is not only the sole factor for their engagement in transactional but it may also depend on other factors. Therefore, despite the differences in their age all of them are equally vulnerable to risky sexual behaviours.

Under the socioeconomic factors, the living arrangements and city in which the respondent lived was significantly associated with engagement in transactional sex. This may indicate that those Drayang girls who lived in bigger cities and have to pay their own house rent are more engaged in transactional sex as compared to those staying in hostels (free accommodations provided by Drayang owners) and with others (husband, parents, and relatives) who do not have to pay the house rents and other expenses. The R. Lorway's qualitative study among the Drayang girls also cited that the financial hardship and difficulty in paying the soaring house rents in the urban cities as one of the reasons for engaging in transactional sex.⁽⁴⁾ The other reason could be due to greater demand for sex in the entertainment sectors where alcohol was available. The study by Dunkle and Aral also revealed that economic stresses and low wages, unemployment, and poverty as some reasons for transactional sex by divorced and unmarried women.^(27,28) Therefore, the economic hardship can be one factor that is likely to increase the risky sexual behavior of Drayang girls in relation to HIV and STIs infection. As a result, the provision of free accommodation like hostels by the Drayang owners would ease their financial hardship and can contribute meaningfully to the overall growth of the Drayang business while preventing them from risky sexual behaviour.

Intake of alcohol was significantly associated with engagement in transactional sex. These findings are consistent with the results of R. Lorway's study, where it mentioned that both the Drayang girls and their bar patrons drink alcohol to socialize and subsequently connects with the potential sexual partners.⁽⁴⁾ The nationally representative survey in South Africa also shows that alcohol-drinking women are two times likely to report transactional sex.⁽²⁹⁾ The study in Vietnam among the youths and

another study by Cherish MF also established a correlation between alcohol intake and unsafe sex.^(30, 31) Therefore, the chances of alcohol influencing the risky sexual behaviour of the Drayang girls are high. However, there is a limitation to this finding because the study could not confirm whether these girls are drinking alcohol while at work or after their work. Therefore, understanding how occupational and work environment influence alcohol drinking and sexual behaviour of Drayang girl is important.

The point prevalence of HIV is low among the Drayang girls. One of the reasons for low HIV prevalence among the Drayang girls may be due to the current low adult HIV prevalence in the general population, which is 0.21%.⁽³²⁾ Other reason could be due to their shorter stay in Drayang as a worker may have protected them from HIV infection but this needs further validation.

This study has some limitations. First, the mixed methods would have suited well for a sensitive topic instead of just relying on quantitative method. The purposeful or response-driven sampling would be more appropriate than convenient sampling for sensitive topics. The use of convenient sampling method may have caused sampling bias despite the high response rate (80%) and we cannot generalize the results. The conceptual framework was not used to develop the study questionnaire rather it has been used only to analyze the results. Therefore, important variables like monthly income, sexual concurrency, and intergenerational sex were not included. The study mostly relied on structured and close-ended questions. All questions related to 'transactional sex' were phrased as 'commercial sex'; and 'sex under alcohol influence' as 'sex after alcohol'. All these may have resulted in information and consequences bias.

CONCLUSION

This study, focusing on Drayang girls shows a low prevalence of HIV and STIs. However, the presence of high-risk behaviour with low condom use still makes them vulnerable to HIV and STIs. The study recommended putting more effort to the current HIV/STIs interventions by increasing awareness of HIV and STI, targeted interventions like Behaviour Change Communications (BCC), condom promotion, condom negotiation skills and access for testing and treatment of HIV and STI among the Drayang girls.

CONFLICT OF INTEREST

None

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TUBERCULOSIS IN NEPAL: SITUATION, CHALLENGES AND WAYS FORWARD

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ABSTRACT

Introduction: Globally, tuberculosis is a major public health problem. Moreover, the emergence of drug resistant forms of TB has threatened TB prevention and treatment efforts. Despite the long history of tuberculosis prevention efforts, tuberculosis still ranks among the top ten causes of deaths in Nepal. Furthermore, Nepal being land locked with two high TB burden countries i.e. India and China, it has added difficulties to National Tuberculosis program. Hence this study aims to review the situation of National Tuberculosis Program in Nepal and explore the possible challenges and ways forward for NTP to strengthen the TB diagnostics and treatment services in Nepal.

Methods: This study is based on the review of available literatures and data sources related to tuberculosis prevention, care and control. Secondary data published by National Tuberculosis Program in the annual report for the year 2015, 2016 and 2017 were considered for the situation analysis of tuberculosis in Nepal. We used different platforms like Google scholar, PubMed to search relevant literatures.

Results: This has been a huge gap between WHO TB estimates and TB cases notification by the national system. It was 22% in 2015, 27% in 2016 and 29% in 2017. However National Tuberculosis Program has maintained treatment success rate consistently above 90%. Tuberculosis program has yet not achieved universal HIV testing, although HIV testing among TB patients has increased rapidly. Similarly, only 75%, 1994 received DST out of 2601 retreatment TB cases have received DST in 2017 despite guideline suggest mandatory drug susceptibility testing for retreatment TB cases.

Conclusion: Case notification has reduced gradually. It is difficult to achieve the target envisioned by NSP 2016-21 if the current case notification trend persists. NTP needs to expand service sites ensuring minimum quality standards as well as scale up targeted intervention addressing human right issues to identify the missing TB cases. NTP needs to regulate the quality of diagnosis and treatment TB services offered by private sector.

Key words: Tuberculosis, TB, Situation, Challenges, Nepal

INTRODUCTION

Globally, tuberculosis is a major public health Problem. There were an estimated 10 million new TB cases around the world and have caused an estimated 1.3 million deaths in 2017.¹ TB usually

affects all the countries and all the ages; however, least developed countries bear the burden of TB the most.² Poverty and malnutrition aggravates the burden of TB.^{3,4} Often, TB is cited as the poor man's disease. Globally South-East Asia region (44%) and African region (25%) contribute around 70% of the global TB burden. Furthermore, India (27%), China (9%), Indonesia (8%), Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South-Africa (3%) alone share the two-thirds of global burden.^{1,5} Nepal is landlocked between two high TB burden countries, India and China. Moreover, Nepal shares open-border

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relationship with India. At this context, identifying, enrolling, treating TB patients and tracking them till the treatment duration and minimizing the risk of transmission to healthy population have been a difficult task to National Tuberculosis Program (NTP). Besides, the development of resistant strains by mycobacteria and comorbid conditions with other diseases like HIV and diabetes have intensified the difficulties.^{6,7} Hence this article aims to assess the situation of tuberculosis in Nepal, explore the challenges and opportunities for action to NTP to achieve the targets envisioned by National Strategic Plan (NSP) for Tuberculosis Prevention, Care and Control (2016-21) and End TB Strategy (2016-35).^{8,9}

METHODS

This study is based on the review of available literatures and data sources related to tuberculosis prevention, care and control. Both published as well as unpublished studies and reports were used. Secondary data published by National Tuberculosis Program in their annual reports for the year 2015, 2016 and 2017 were used for the situation analysis of TB program in Nepal.^{10,11,12} Besides, we used different search engines like Google, Google Scholar and PubMed database to retrieve articles highlighting the prevention, care and control strategies, interventions and challenges for TB program around the world. Abstract of the relevant articles were reviewed and screened for relevancy prior retrieving the full articles. Besides, references of the selected articles were also reviewed to explore additional useful articles.

RESULTS AND DISCUSSION

Gap between estimated and TB case notification

There has been a wide gap between WHO TB estimates for Nepal and TB cases notification by the national system. The gap has increased gradually; it was 22% (9,888 TB Patients, 44000 estimated vs. 34112 notified) in 2015, 27% (11,944 TB patients, 44000 estimated vs. 32056 notified) in 2016 and 29% (13236 TB patients, 45000 estimated vs. 31764 notified) in 2017.^{10,11,12} At this context, finding missing TB cases, especially the childhood TB cases, is major challenge for the NTP.¹³ These patients could have either undiagnosed or have diagnosed and not reported in the national system.

Barriers to appropriate diagnosis as well as poor linkages between the treatment and diagnosis has been identified as major obstacle which NTP needs to address.¹⁴ Besides, intervention like contact tracing of index TB patients, sputum courier at hard to reach areas, DST among retreatment TB cases need to be implemented at scale.¹⁵

Decreasing diagnosis of clinically confirmed TB cases

Furthermore, trend analysis shows diagnosis of clinically confirmed, pulmonary TB cases (PCD) has declined rapidly in comparison to bacteriologically confirmed, pulmonary TB cases (PBC) and extra-pulmonary TB cases (EP). PCD cases notification had contributed 20% (6677 out of 34112 notified TB cases) of total TB cases notification in 2015 and has been decreasing thereafter (17%; 5850 out of 32056 notified TB cases in 2016, 15%; 5216 out of 31764 notified TB cases) in 2017).^{10,11,12} National data shows the gradual reduction in the number of clinically confirmed TB cases with the expansion of GeneXpert sites. However, it needs further studies to validate the association. But, studies from Nepal, Uganda and Cambodia found that clinicians werenot preferring clinical judgement for the diagnosis of TB, especially among childhood TB cases.^{16,17,18} Hence the focus of NTP should be placed on rational use of GeneXpert machines as well as capacity building of clinicians for clinical diagnosis of TB cases.

Significant proportion of TB deaths and Lost to follow-up

In Nepal, 9 out of 10 newly registered (new and relapse) TB patients are successfully treated.^{10,11,12} NTP has maintained treatment success rate consistently above 90% which is above the global average.¹ It was 92% in 2015, 90% in 2016 and 91% in 2017.^{10,11,12} However, among retreatment TB cases, it is still below 90%; the best figure was 88% in 2017 in comparison to 72% in 2015, 86% in 2016. Despite, decreasing TB cases notification and high treatment success rate, TB mortality rate is consistently at around 3% which is unacceptably high given that TB deaths are prevented if it is diagnosed on time, treated with prescribed regimen till the end of treatment duration.¹² Moreover, mortality due to TB is disproportionately high among male than female.^{10,11,12} Besides there are significant number

of TB patients who are lost to follow-up from DOTS services. Proportion of lost to follow up TB patients in 2015 was 2% (785 out of 36050 registered TB cases).¹⁰ It has increased gradually thereafter. It was 2% (781 out of 34112 registered TB cases) in 2016, 3% (827 out of 32056 registered TB cases) in 2017.^{11,12} Their treatment status and treatment outcome are unknown. Lost to follow-up cases can serve as source for disease transmission in the community and aggravate the TB prevention efforts through the development of drug resistant forms of TB.^{19,20,21} Patient counselling, education and development of patient tracking mechanism to track and re-enroll such cases back into the treatment would enhance treatment adherence, reduce the risk of TB transmission.²¹ NTP needs to invest on the expansion as well as strengthening its existing online NTP application like eTB, DR TB patient tracking and laboratory system.

Case holding by private sectors

The contribution of private sector in the referral and/or diagnosis of TB patients was 19% (6552 out of 34112 notified cases) in 2015, 18% (5969 out of 32056 notified cases) in 2016 and 23% in 2017 (7227 out of 31764 notified cases).^{10,11,12} It includes all TB cases referred either for diagnosis, treatment or both from private hospitals, polyclinics or pharmacies. However, true figure regarding the case holding by the private sectors in Nepal is yet unknown. Report on census of private hospitals published by CBS on 2013 shows 214 registered hospitals across the country. Majority of them were in central region (143 hospitals) followed by eastern (68 hospitals), western (59 hospitals), mid-western (21 hospitals) and far-western (10 hospitals) region respectively.²² It could have increased in the recent years. Few studies conducted in Nepal have shown patients receiving diagnostics and treatment services from the private sector irrespective of cost incurred, quality of prescribed regimen, skill of private practitioners.^{23,24} Moreover, majority of the private sector hospitals are out of national reporting mechanism.¹² As a result, there is dearth of information regarding the TB case holding by the private sectors. Hence quality and quantity of TB diagnostic and treatment services provided by the private sector should be monitored and reported in the national system. Delivery of TB services through private sector should be guided by the policy documents like PPM strategy for TB prevention and care.²⁴

TB diagnostic services and their quality

In Nepal, sputum microscopy, chest x-ray, GeneXpert MTB/RIF machine, culture/DST and LPA methods are the diagnostic options for TB suspects.¹² NTP depends largely on the quality of these diagnostic services. Sample collection and its processing methods as well as capacity of technicians are vital to ensure the diagnostic quality.²⁵ Based on the number of service delivery points, presumptive TB patients have comparatively greater access to sputum microscopy (604 microscopy centers) than other diagnostic services (31 GeneXpert sites, 2 culture/DST laboratories).¹² However, national trend shows false positive (+ve) and false negative (-ve) rate among the slides re-examined at regional level quality control centers is consistently high. Among the participating (72%, 432 out of 604) microscopy centers (MCs) in 2017, 19 MCs (4%) had >5% false negative results and 10 (2%) MCs had >5% false positive results.^{10,11,12} Although the participation of MC in quality control has increased from 60% (345 out of 576 MCs) in 2016 to 72% in 2017, still a significant proportion of MCs are out of quality assurance mechanism.^{11,12} Similarly, error, invalid and no results account around 7% (1684 out of 23818 tests in 2016, 1480 out of 21077 tests in 2017) of the total tests in GeneXpert machine.^{11,12} Although the MTB (sensitive and resistant cases) detection rate has increased gradually from 19% (4555 out of 23818 tests) in 2016 to 24% (5162 out of 21077 tests) in 2017, yield is very low in comparison to its cost inputs and test sensitivity.^{11,12} Hence, greater access to and low sensitivity of microscopy have been found as major diagnostic concern.²⁶ Expansion of diagnostic services with high sensitivity (like Culture, GeneXpert) are inevitable to reduce the number of false positive and false negative test result. But still, adequate financing, skilled human resources and addressing bio-safety issues pose additional challenges for NTP which needs to be addressed.²⁷

Poverty, malnutrition and TB HIV Diabetes Co-infection

Tuberculosis has strong relationship with social determinants like wealth quintile, smoking and alcohol habits, housing standards, occupations.^{3,4} In Nepal, still one forth of the total population (25.16%) are under the poverty line.²⁸ Similarly, thirty-six

percent of children under age 5 are stunted, 10% are wasted, 27% are underweight.²⁹ Evidence has shown malnutrition as a strong predictor of TB among half of the all active TB cases.^{30,31} Similarly, HIV and diabetes co-infection with TB has placed an immense burden to the TB prevention and treatment efforts. It has nourished the development of active TB among the immune-compromised and has intensified TB deaths.^{32,33} Despite the huge efforts, HIV testing among TB patients has increased rapidly (7% (2408 out of 34112) in 2015, 18% (5722 out of 32056) in 2016 and 54% (17164 out of 31764) in 2017) but it is still far below the goal of universal HIV testing.^{10,11,12} Hence, NTP needs to initiate as well as intensify targeted interventions to address HIV and diabetes coinfection among TB patients. Besides, NTP needs to extend coordination and coordination with different ministries, divisions and centers, government and non-government organizations, stakeholders and communities to address the social determinants to fight against TB.

Burden of multi-drug resistant (MDR) TB

Nationwide, the proportion of new cases with multidrug-resistant TB (MDR-TB) was 2.2% among new cases and 15.4% among retreatment cases based on DRS survey carried out in 2011/12.¹² However, the diagnosis of MDR TB cases in Nepal has declined gradually (379 MDR, 71 XDR TB cases in 2015, 309 MDR, 77 Pre-XDR, 17 XDR TB cases in 2016 and 343 MDR, 19 XDR TB cases in 2017).^{10,11,12} While treatment success is stagnant around 70% among MDR TB cases and 35% among XDR TB cases.¹² Studies have shown that Retreatment TB cases are comparatively more at the risk of development of drug resistant forms of TB.³⁵ Even, TB treatment guideline developed by NTP has envisioned mandatory DST for all the retreatment TB cases. However, DST among retreatment TB cases is low. Only 75%, 1994 received DST out of 2601 retreatment TB cases have received DST in 2017.¹²

Adequate financing for NTP

There were 581 microscopy centers across the country in 2015.¹⁰ It has increased gradually thereafter to 576 centers in 2016 and 604 centers in 2017.^{11,12} Similarly, GeneXpert sites were also expanded gradually during this period, from 26 GeneXpert sites in 2015 to 30 sites in 2016 and 31

sites in 2017 respectively.^{10,11,12} But still, there is gap between TB diagnostic sites versus TB treatment sites in terms of their number.¹² Expansion of service sites with quality is inevitable to achieve global and national milestones and targets on TB. Increasing coverage with quality needs adequate investment.³⁶ However, NSP 2016-21 has already projected a funding gap of 45.8 million US dollar during its implementation.⁸ It would create huge challenge for Government of Nepal/NTP to achieve the targets envisioned amid the funding gap. Often quality is compromised first with funding gap. So NTP should advocate with ministry of health and finance on time and explore other funding agencies like Global Fund.

Human right issues on TB

TB is still a stigmatizing disease. Often, TB patients face stigma and discriminatory behaviour which has resulted in delay access to needed TB diagnostics and treatment services.³⁷ Studies have identified tuberculosis related stigma as a barrier for active case finding interventions like sputum courier, contact tracing.^{37,38} Although NTP has initiated targeted intervention among vulnerable population like refugees, migrants, internally displaced population, prisoners, slums, malnourished children and ANC mothers, it still lacks mechanism to track and address the human right violation issues faced by TB patients.³⁹ Hence NTP as a governing body should implement interventions like empowerment activities for people with TB, training to health workers on right based approaches in TB diagnosis and treatment, sensitize law makers, policy makers and law enforcement agencies on TB as well as should advocate to reform any laws and regulations that hinders TB rights and services.

CONCLUSION

TB case notification has reduced gradually in Nepal. Finding missing TB cases is one of the major challenge for NTP. At this context, it is difficult for NTP to achieve the targets set by NSP 2016-21 as well as milestones and targets of End TB strategy 2016-35. Hence, NTP needs to expand service delivery sites ensuring the minimum quality standards as well as build the capacity and confidence of health workers in the diagnosis and treatment of TB patients. Besides,

NTP should develop mechanism to regulate and monitor the quality and quantity of TB services provided by private sector. Targeted interventions addressing the human rights issues faced by TB patients support in the identification of hidden TB cases in the community. Likewise, NTP needs to explore donors and other funding agencies to reduce the funding gap.

CONFLICT OF INTEREST

None

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EPIDEMIOLOGY OF DRUG RESISTANT TUBERCULOSIS IN SAMTSE GENERAL HOSPITAL, BHUTAN: A RETROSPECTIVE STUDY

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ABSTRACT

Introduction: Multidrug resistant tuberculosis (MDR-TB) is defined as a case of tuberculosis resistant to rifampicin and isoniazid which are the first line anti tuberculosis drugs. Globally emergences of MDR-TB possess a challenge to TB control. In Bhutan, the proportion of MDR-TB is high at par with the global level. This study will explore the predictors of MDR-TB and the trend at Samtse General Hospital which has high burden of tuberculosis.

Methods: This was a retrospective cross sectional study. The data was extracted from TB treatment cards maintained at TB unit of Samtse General Hospital TB from January 2012 to June 2018.

Results: The study showed the prevalence of drug resistant to at least one drug at 21% and MDR-TB prevalence at 16%. The patients with previous treatments (AOR: 4.59; 95% CI .03-.18) and patients under the age of 30 years (AOR: 2.7; 95% CI 1.01- 7.42) were significantly associated with MDR-TB.

Conclusion: This study shows high prevalence of MDR-TB in Samtse. Better strategies and concrete actions need to be developed to combat the increase of MDR-TB.

Key words: MDR, Gene Xpert, Primary MDR-TB, drug resistant, TB, Bhutan

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* and is one of the top ten killers in the world second after HIV (human immunodeficiency virus).¹

Commendable success has been made in reducing the TB burden through implementation of Directly Observed Treatment Short course (DOTS). However, the fight against TB has been hampered by emergence of multi-drug resistant tuberculosis (MDR-TB) and HIV.² MDR-TB is defined as type of mycobacterium tuberculosis strain that is resistant to the two main first line anti tuberculosis drugs - rifampicin and isoniazid.³ MDR-TB has been declared as public health problem by World Health Organisation (WHO) in 2013. MDR-TB similar to

drug sensitive TB, spreads via respiratory aerosols and poses a risk for outbreaks⁴. MDR-TB can occur either due to infection with drug resistant strain (known as primary MDR-TB) or develop in those patients who were previously treated (known as secondary MDR-TB)³.

Globally in 2017, there were an estimated 0.558 million cases of MDR/RR-TB with 82% of them MDR-TB. Of these, 3.5% were among the new cases and 18% among the previously treated TB.¹ Moreover of the total MDR-TB cases, 8.5% of them developed extensively drug resistant TB cases. Almost half of the cases of MDR-TB were from the three countries of India, China and Russia¹. South East Asia region accounted for one third of global burden of MDR-TB in 2015.⁵ In Bhutan, the incidence rate of MDR/RR-TB was 22 per 100,000 population in 2017.⁴ Of this, 13% were among the new cases and 33% among retreated cases.¹⁸

In Bhutan, the National Tuberculosis Control Programme (NTCP) under the Ministry of Health is responsible for implementation of TB related preventive and promotive health activities. It initially started with short course chemotherapy followed by

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implementation of DOTS in 1997.⁶ The objectives of NTCP has been to increase the case notification and treatment success rate above 90% among prevalent TB cases and improve the MDR TB case detection and success rate above 75%.⁷ Bhutan has also ratified the sustainable development goals (SDG) of reducing the TB deaths by 90% and TB incidence by 80% compared to 2015 by 2030.⁸

Until 2010, there was no culture and drug sensitivity testing for TB in Bhutan. Patients were treated as a suspected case of MDR-TB based on clinical judgement. Since then, Lowenstein Jensen (LJ) medium has been used for the diagnosis of MDR-TB. This was followed by introduction of *Mycobacteria Growth Indicator Tube* (MGIT) in 2012 and line probe assay in 2014. Due to increasing number of MDR/RR cases, the GeneXpert testing has introduced in three Regional Hospitals and two hospitals of Phuntsholing and Samdrup Jongkhar since 2017⁹ and in Samtse General Hospital in 2019.

The treatment success of MDR-TB remains low at 55% compared to 82% in drug sensitive TB¹. The MDR-TB requires a treatment for at least 24 months while drug sensitive TB is treated for 6-8 months. In addition, while the drug sensitive TB costs around USD 2000 for the full course of treatment, MDR-TB requires almost 25 times that of drug sensitive TB.¹⁰

Although, the number of MDR-TB cases has been increasing in Bhutan, there are no published studies to assess the predictors of MDR-TB at the hospital level. The objective of this study is to assess the prevalence, type of drug resistant TB and predictors of MDR-TB. The findings from this study will help to determine strategies to be taken in high burden areas like Samtse.

METHODS

Study setting

Samtse District is one of the most populated district located 275 kilometres from the capital Thimphu bordering the Indian State of West Bengal. Samtse district has a population of 62590 as of 2017. It has 2 hospitals and 2 Basic Health Unit (BHU) Grade 1 and 10 BHUs. The Samtse General Hospital serves as the referral point for all hospitals and BHU due to the availability of specialist care and

diagnostic facilities. Samtse General Hospital is a 40 bedded district hospital with TB wards constructed exclusively for tuberculosis patients. Samtse has one of the highest tuberculosis burden in Bhutan.⁸

All patients who present to the hospital with clinical signs suggestive of TB (cough for more than two weeks with fever, chest pain, haemoptysis and weight loss) undergo sputum examination for TB by Ziehl-Neelsen stain and a chest x-ray. One early morning sputum sample and two spot sputum samples are collected in a sterile uricol container. Once the patient is diagnosed to have smear positive TB, they are admitted in the TB ward to break the chain of transmission of the disease.

The newly diagnosed patients on category one are admitted till they become smear negative while those on category two treatment (treatment failure and relapse) are kept for two months. All the TB patients who are admitted or transferred in from other health centres are given treatment card and a copy is retained at the hospital for future references. The TB card has patient information on age, sex, type of TB, treatment regime, weight and outcome of the treatment.

Drug sensitivity testing

The smear positive sputum samples are tested for drug resistance by GeneXpert MTB/RIF in the hospital. The sample processing and testing are performed as per the Standard Operating Procedures (SOP) of the Global Laboratory Initiative of the Stop TB Partnership.¹¹ An additional sputum sample is shipped in cold chain to the Royal Centre for Disease Control (RCDC, National reference laboratory) for culture and drug testing using Lowenstein Jensen (LJ) medium. The reports are updated on TB/ISS (Tuberculosis Information and Surveillance System) which is a web based recording and reporting of TB.

Study design and data collection

This was a retrospective cross sectional study conducted using the data extracted from the TB treatment cards maintained in the TB unit of the Samtse General Hospital. All the patients registered from 1st January 2012 to 30th June 2018 were included for the study. The information on age, sex, type of TB, treatment regime, weight and

outcome of the treatment were obtained from the patients treatment card. Information on laboratory diagnosis were obtained from the *TBISS* website of RCDC.

Ethical Clearance

The ethical clearance was taken from the Research Ethical Clearance Board of Health (*Ref. No.REBH/Approval/2018/037*) under the Ministry of Health, Bhutan. Since this was a retrospective study with no direct contact with the patients, the informed consent was not found to be necessary. The names of the patients were coded for sake of confidentiality.

Data management and analysis

The data was entered and in IBM SPSS version 20 (SPSS Inc. Chicago. 2007) and analysed using STATA software. The data was double checked to ensure that they were no mistakes and discrepancy in data. Descriptive analysis was presented in frequency and percentages. The continuous variables like age and weight was converted into a categorical variable and compared using Chi square test and Fisher test to test if there is any associations with the dependent variable. Multiple logistic regressions with backward elimination were used to check for any associations between the variables. The p-value less than 0.05 were taken as the significant.

RESULTS

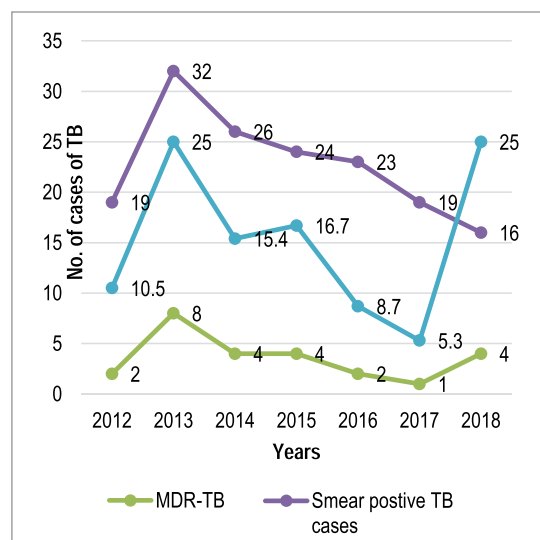
During the study period from January 1st 2012 to June 30 2018, a total of 341 patients were registered in the TB unit of Samtse General Hospital for the treatment. Of this 159 (46.6%) were smear positive TB, 42 (12.3%) were smear negative TB and 140 (41.1%) were extra pulmonary tuberculosis (EPTB).

Table 1: Characteristic of tuberculosis patients

	Characteristic	N=159 (%)
1	Sex	
	Male	91 (57.2)
	Female	68 (42.8)
2	Age group (years)	
	<=14	3 (1.9)

	15-28	86 (54.1)
	29-42	27 (17)
	43-56	17 (10.7)
	>=57	26 (16.4)
3	Weight (kg) (n=146)	
	< 30	1 (0.7)
	30-59	134 (91.8)
	60-90	11 (7.5)
4	Treatment category	
	category 1	136 (85.5)
	category 2	23 (14.5)
5	Treatment outcome	
	Cured	104 (65.4)
	Completed	6 (3.8)
	Treatment failure	28 (17.6)
	Defaulted	1 (0.4)
	Unknown	1 (.63)
	Died	7 (4.4)
	Ongoing treatment	13 (8.2)

Out of 159 smear positive TB cases, 91 (57.2%) were male patients. Of total sputum positive cases, 104 (65.41%) were declared cured, 6 (3.77%) completed treatment and 13 (8.18%) were still undergoing treatment at the time of study (Table 1). The majority of the cases (71%) were seen in the age group between 15-42 years with mean age of 33.7 years. However, 28 patients (17.61%) defaulted or had treatment failure and 7(4.4%) patients died while the status of one patient (0.63%) was unknown.



Trend of MDR-TB

Of the 159 patients, at least 33 (21%) patients had resistant to at least one of the anti-tuberculosis drugs. The total number of MDR TB cases reported ranged from 1-8 cases with total of 25 cases in last six and half years (Figure 1). The annual prevalence of MDR-TB ranged from 5.3% to 25%. The overall prevalence of MDR-TB was 16 % (25 cases) out of 159 cases. The prevalence of MDR-TB among retreatment cases was 35 % (n=8) while it was 13 % (n=17) among the new cases. During the same period, eight newly diagnosed tuberculosis patients developed mono-resistant to isoniazid.

Age	Non-MDR	MDR	Total	p-value
< 30 years	72 (53.7%)	18 (72%)	90 (56.6%)	0.124
>30 years	62 (46.3%)	7 (28%)	69 (43.4%)	
Sex				
Male	80 (59.7%)	11 (44%)	91 (57.2%)	0.187
Female	54 (40.3%)	14 (56%)	68 (42.8%)	
Weight (n=195)				
<50 kg	80 (59.7%)	15 (60%)	95 (59.8%)	1
>=50 kg	54 (40.3%)	10 (40%)	64 (40.3%)	
Treatment category				
category 1	119 (88.8%)	17 (68%)	136 (85.5%)	0.007
category 2	15 (11.2%)	8 (32%)	23 (14.5%)	

Factors associated with MDR-TB

There was a significant difference in MDR-TB among those on category 1 and category 2 TB patients (p-value=0.007) (Table 2). While male sex suffered more from pulmonary TB, females constituted for 56% of total MDR-TB cases. However, there was no significant differences between male and female (p-value=0.187).

During multiple regression, patients with previous treatments were significantly associated with MDR-TB with adjusted odds ratio 4.59 (95% CI .03-.18) adjusting for the age. The patients under the age of 30 years were also 2.7 times more likely to develop MDR-TB (95% CI 1.01- 7.42) (Table 3).

Characteristic	AOR	p-value	95% CI
Age < 30 years	2.7	0.046	1.01- 7.42
Category 2 treatment	4.59	0.005	.03-.18

DISCUSSION AND CONCLUSION

In this study, the mean prevalence rate of MDR-TB over last six and half years was 16%. The prevalence of primary MDR-TB was 13% while secondary MDR-TB was 35%. The correlates for MDR-TB in Samtse were age less than 30 years and patients in category 2.

There are reports on the national prevalence of MDR-TB in Bhutan but no data at the hospital level. The prevalence of primary MDR-TB and secondary MDR-TB in this study is comparable to the national prevalence, where primary MDR-TB was 13% and secondary MDR-TB at 33% in 2017.¹ The burden of primary MDR-TB and secondary MDR-TB is higher in Bhutan than other South East Asia countries (Primary MDR-TB at 2.7% and secondary MDR-TB at 13%) and globally (Primary MDR-TB (3.5%) and secondary MDR-TB (18%)).¹ It is not known why Bhutan has high prevalence rate of MDR-TB. This calls for further investigation in development of MDR-TB in Bhutan. However, Bhutan is expected to see increased detection of MDR-TB cases due to recent introduction of GeneXpert in all regional hospital and three district hospitals.

Patients previously treated for TB is strongly associated with MDR-TB. This has been seen in other studies done in other countries.¹²⁻¹⁶ Drug resistance is known to occur due to inappropriate use of anti-tuberculosis drugs.² Younger people are more likely to develop drug resistant TB.² Young being more active members of the community, increases their contact with MDR-TB patients thus increasing the probability of acquiring TB¹⁴⁻¹⁷ as well as their reluctance and irregular intake of drugs.¹³

It is a concern to see an increase in the number of MDR-TB cases in Bhutan as MDR-TB is associated with low treatment success, higher drug reactions and is comparatively more expensive. Multiple factors are responsible for development of MDR-TB like poor drug adherence, low income, young age,

alcohol consumption, low educational status.^{17,19} The treatment of MDR-TB is usually associated with poorer outcome (global treatment success rate for MDR-TB is 54% compared to 83% in drug sensitive TB), more drug toxicity, longer duration of treatment and more financial burden compared to drug sensitive tuberculosis.²⁰ The increase in MDR-TB could also lead to development of extremely drug resistant TB. The country status of MDR-TB cases indirectly shows the performance of the national tuberculosis control programme.

In Bhutan, the drug sensitivity for extra-pulmonary tuberculosis is not done on routine basis. Studies from India showed the drug resistant among extra pulmonary patients to be as high as 19%.²¹ The increase in number of primary MDR-TB is one of the concern for tuberculosis program as it shows that transmission of MDR-TB is taking place in the community. Although, the diagnosed MDR-TB patients are admitted and treated in the hospitals to break the chain of transmission, there are still undiagnosed cases in the community which serves as the sources of transmission. So, active surveillance and further research needs to be undertaken to explore the means for development of primary MDR-TB in Bhutan.

LIMITATIONS OF THE STUDY

This study has several limitations to be considered. The study population is not representative of TB patients in Bhutan as it involved only one district hospital. Due to the retrospective nature of the study, patients risk behaviours like alcohol intake, smoking and drug adherence which are the risk factors for MDR-TB were not available

CONFLICT OF INTEREST

None

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Case Study

CASE SERIES OF POTT'S SPINE DIAGNOSED BY ZN STAIN AND BACTEC MGIT IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Introduction: Pott's spine is a destructive form of tuberculosis and accounts for approximately half of all cases of musculoskeletal tuberculosis. Spinal Tuberculosis is most often missed due to inadequate sample and lack of clinical history. Most of the Extrapulmonary tuberculosis (EPTB) can be diagnosed by Ziehl Nelson stain (ZN) only, when clinically suspected samples are adequate and optimally stained. We are reporting four case series of spinal tuberculosis diagnosed by ZN stain and confirmed by Bactec MGIT Culture.

Material & Methods: These four clinically suspected spinal biopsis were received for ZN stain and MTB culture by MGIT.

Results: All the four spinal biopsies were found positive by ZN stain as well as by BacTec MGIT. All the four cases were HIV negative. ESR and CRP of all four cases were raised.

Discussion & Conclusion: Spinal tuberculosis can be easily diagnosed by ZN stain in resource constraint lab. Despite its common occurrence and the high frequency of long-term morbidity, there are no straight forward guidelines for the diagnosis and treatment of spinal tuberculosis. Early diagnosis and prompt treatment is necessary to prevent permanent neurological disability and to minimize spinal deformity.

INTRODUCTION

Pott's spine is a destructive form of tuberculosis and accounts for approximately half of all cases of musculoskeletal tuberculosis. Spinal Tuberculosis is, most often missed due to inadequate sample and lack of clinical history. Many of the (Extra pulmonary tuberculosis) EPTB can be diagnosed by Ziehl Nelson stain (ZN) only, when clinically suspected samples are adequate and optimally stained. The risk of developing tuberculosis is estimated to be 20–37 times greater in people co-infected with HIV than among those without HIV infection.¹We are reporting four case series of spinal tuberculosis diagnosed by ZN stain and confirmed by Bactec MGIT Culture.

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CASE HISTORY

A series of four cases with similar complaints of significant low back pain were admitted in our tertiary hospital.

	Case1	Case 2	Case 3	Case 4
Age	50 yrs	61 yrs	40yrs	30yrs
Sex	Male	Male	Female	Female
Co morbid condition	Hypertension	Type2 Diabetes mellitus	Nil	Nil
Site of Lesion	Lumbar (L1-L3)	D8-D9	D9-10	D11-D12

MATERIAL MEHTODS

All four cases were investigated radiologically and by our laboratory services to find out the etiology.

Biopsy of all cases were taken after all aseptic

precautions from different site of lesion for Histopathology, ZN staining and Bactec MGIT Culture.

ZN stain was done with a positive control as per standard guidelines.

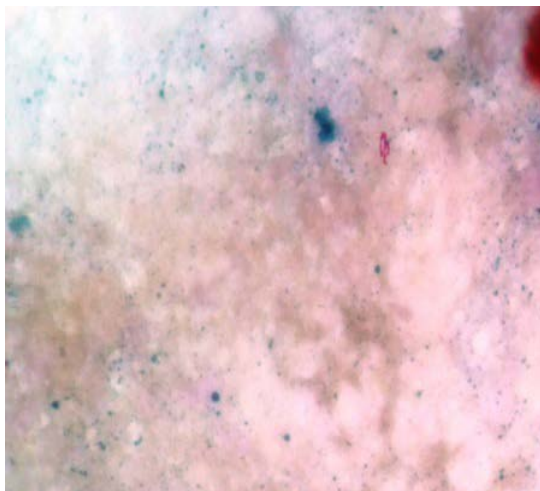
Complete investigations with different parameters were done to diagnose the cause of spinal tuberculosis.(Table-1).

Parameters	Case1	Case2	Case3	Case4
Total Count	13100	11900	13200	16900
ESR	70MM 1hr	80MM 1hr	72mm 1hr	18mm 1hr
CRP	148.7	88.4	43.30	17.07
Hemoglobin(g m/dl)	8.4	8.8	8.5	10
ELISA (Viral markers)	Negative	Negative	Negative	Negative
Procalcitonin		2.69		
ZN Stain	18-20 AFB/100 Oil Immersion Field	20-22 AFB/100 Oil Immersion Field	15-20 AFB/100 Oil Immersion Field	5-10 AFB/100 Oil Immersion Field
Bactec MGIT	Positive	Positive	Positive	Positive

RESULTS

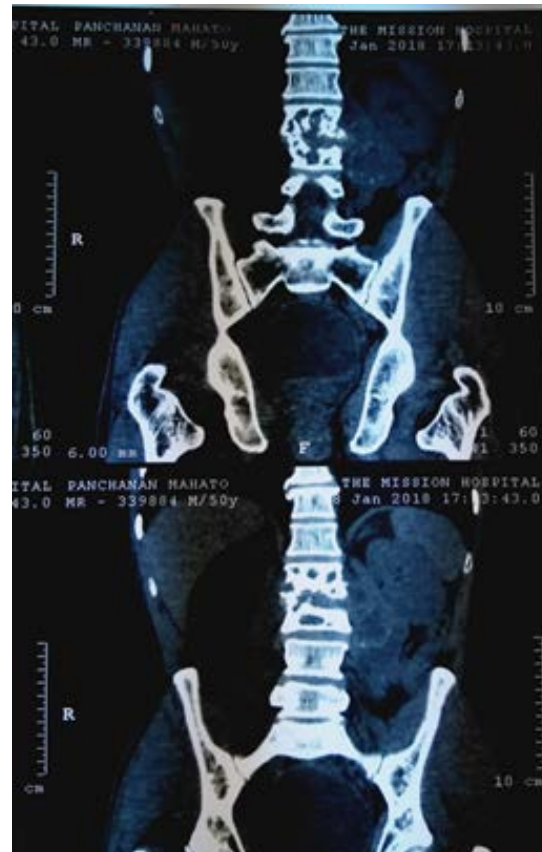
Case1

The ZN stain of spinal tissues shows plenty of neutrophils with 18-20 AFB/100 Oil Immersion Field (OIF) (Fig-1).



TB culture by Bactec MGIT was found to be positive. Histopathological findings showed granulomatous lesion suggestive of tuberculous origin and was negative for malignancy.

Radiological Findings: MRI Spine shows spondylodiscitis at L1-L3 level with introsseous abscess formation with extension of abscess in the ventral epidural space of spinal canal causing spinal canal stenosis along with Right psoas myositis and left psoas muscle abscess (46.7x28.4x53.3mm).It also showed degenerative changes at L5-S1 level. (Fig-2)



Case2

Biopsy from D8 –D9 was taken for Histopathology, ZN staining and Bactec MGIT Culture .The ZN stain of spinal tissues showed many neutrophils with 20-22 AFB/100 OIF.TB culture with Bactec MGIT was positive for TB. Histopathological findings showed areas of necrosis, few epithelioid granulomas and many entrapped necrotic bony trabeculae. No malignancy was seen.

MRI dorsal Spine showed spondylodiscitis at D9-D10 level with spondylitis involving D8, D9 &D10 vertebral bodies. Paravertible and extradural collection behind D9 and D9-D10 disc with resultant spinal cord compression. Tuberculosis etiology was suspected due to calcified bodies in paravertible collection.

CT scan of dorsal spine showed lytic destruction of D9 vertebrae with associated mild paraspinal collection and calcification. Narrowing of left D8-D9 neural foramina.

All lab reports were within normal range except ESR (80MM 1hr), Total count (11900), Hb (8.8), CRP(88.4), procalcitonin (2.69), CA 125(44.4) .

Case3

After all aseptic precaution, biopsy from D9-D10 were taken for Histopathology, ZN staining and Bactec MGIT Culture (Table-2).The ZN stain of spinal tissues shows plenty of neutrophil with 10 AFB/100 OIF .TB culture with Bactec MGIT was positive for MTB .Histopathological findings showed granulomatous lesion suggestive of tuberculous origin and it was negative for malignancy.

All lab reports were within normal range except ESR (72MM 1hr), Total count (13200), Hb (8.5), CRP (43.30) .

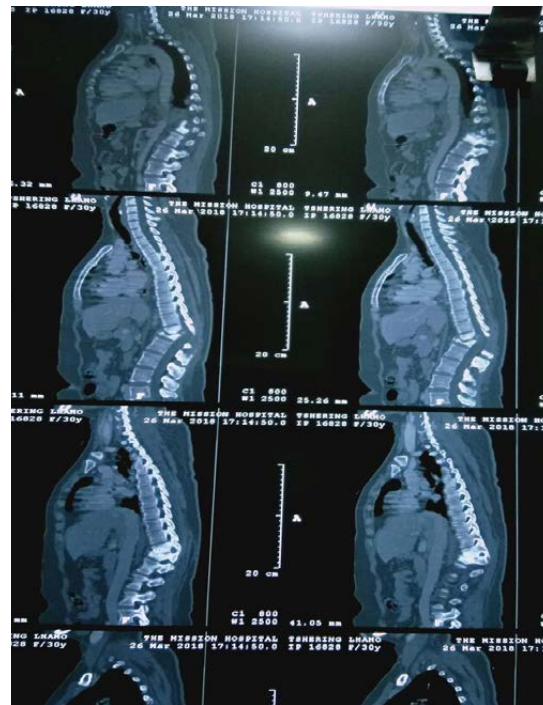
MRI dorsal Spine showed infective spondylitis at D9-D10 level with destruction of intervertebral disc and adjacent vertebral end plates seen.D9 vertebra was completely destroyed. Spondylitis was seen at D6, D7, D8 and D11.Abscess was seen at D9-D10 disc at endplate level with extension of abscess in the pre and para vertebral region, in the ventral epidural space and at neural foraminae. Pre and para vertebral abscess was seen from the level of superior end plate of D6 vertebra to D10 level. Intraosseous extension of collection seen in D7,D8 vertebral body with erosion of anterior cortex. Ventral epidural collection was seen posterior to D9 and D10 vertebral body.AtD7 level paravertebral collection was extending into adjacent pleural space and lung with consolidation.

Case4

Biopsy was taken from D11-D12 for Histopathology, ZN staining and Bactec MGIT Culture (Table-2). Plenty of neutrophil with 05 AFB/100 OIF was seen by ZN stain of spinal tissues.TB culture with Bactec MGIT was positive for MTB.On Histopathological examination showed areas of necrosis, few epithelioid granulomas and many entrapped necrotic bony trabeculae.

All lab reports were within normal range except ESR (18 mm 1hr), Total count (16900), Hb (10), CRP (17.07).

MRI of dorsolumbar spine: Spondylodiscitis noted at the level of D11-D12 causing kyphotic deformity and narrowing of spinal canal to approximately 6.4mm.Stretching of spinal cord at this level with altered signal intensity within suggestive of myelopathic changes.Pravertebral abscess noted along D11-D12 vertebra tracking along right ileopsoas muscle and forming a collection within right quadrates lumborum muscle at the level of L2 L3 vertebra measuring approximately 38x45x21 mm. (Fig-3)



DISCUSSION AND CONCLUSION

Extrapulmonary TB (EPTB) constitutes about 15%–20% of all cases of TB.^(2,3) The diagnosis of Pott's spine is difficult due to the paucibacillary nature of sample, difficulty in obtaining specimens from deep-seated organs and inability to get an additional specimen. As an outcome, failure to diagnose and treat affected patients leading to increased morbidity and mortality, development of secondary resistance (including extensively drug-resistant TB) and ongoing transmission of disease⁽⁴⁾

In our case series, thoracic region is predominantly involved for spinal tuberculosis.

The prognosis for spinal tuberculosis can be improved by early diagnosis and rapid intervention. Spinal tuberculosis can be easily diagnosed by ZN stain in resource constraint lab with only little effort.

Early diagnosis and prompt treatment is necessary to prevent permanent neurological disability and to minimize spinal deformity. All four patients were started with Anti tuberculosis treatment and they are doing extremely well.

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