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 outbreaks[4]. 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 Russia[1]. 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 2017[9] and in Samtse General Hospital in 2019.

The treatment success of MDR-TB remains low at 55% compared to 82% in drug sensitive TB[1]. 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 access 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 *TBISS* (Tuberculosis Information and Surveillance System) which is a web based recording and reporting of TB.

Study design and data collection

This was aretrospectivecross 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 patents 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 SamtseGeneral 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 malepatients. 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.
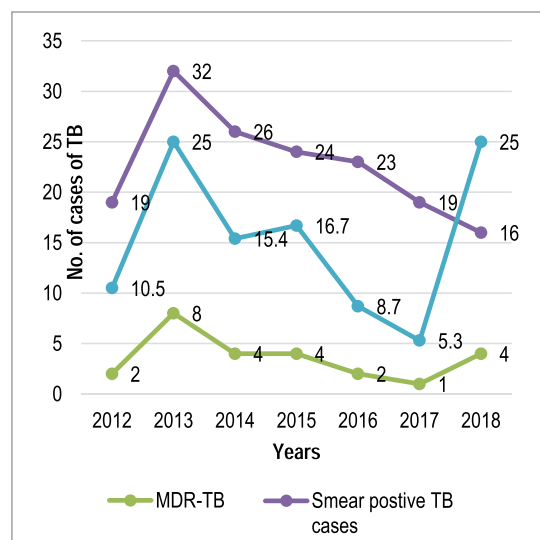
Trend of MDR-TB

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.

Table 2: Risk factors for MDR-TB patients

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).

Table 3: Adjusted Odds ratio for risk factors for MDR-TB

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-TBwas13% and secondary MDR-TBat 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 TB[14-17] 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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