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Field Epidemiology Training Program, Bureau of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625901734-5, Fax: +6625918581, Email: osireditor@osirjournal.net, http://www.osirjournal.net

Multidrug-resistant Tuberculosis Patients in Bhutan, August 2011 to July 2012

Jit Bahadur Darnal[1,*], Swaddiwudhipong W[2]

1 Mongar Regional Referral Hospital, Mongar, Bhutan

2 Department of Community and Social Medicine, Mae Sot General Hospital, Tak Province, Thailand

* Corresponding author, email address: jitb67@gmail.com

Abstract

This study aimed to describe the factors associated with multidrug-resistant tuberculosis (MDR-TB) in Bhutan. The study covered all MDR-TB patients admitted to Gidhakom Hospital, Thimphu from August 2011 to July 2012. Data were collected from MDR-TB registers, laboratory registers and inpatient records as well as from interview with patients about demographic characteristics, history of previous anti-TB treatment, compliance and contact history. There were total 19 MDR-TB patients. Majority of the patients were males (63%). Median age was 25 years for males and 30 years for females. Of the 19 cases, 47% and 37% had contacted with TB case and MDR-TB case in the same house respectively. About 74% reported previous history of anti-TB treatment. Among those with previous treatment, 79% did not comply with the directly observed treatment short-course (DOTS). It was found that 20% of new cases and 50% of previously treated persons were resistant to four first-line drugs. In conclusion, previous anti-TB treatment, non-compliance to DOTS and contact with MDR-TB were observed in majority of the cases. We highlighted the importance of early detection of MDR-TB, providing health education on prevention of disease transmission and strengthening DOTS policy. Investigation on household contacts should be given priority to identify and control the spread of TB.

Key words: tuberculosis, multidrug-resistant, directly observed treatment short-course, Bhutan

Introduction

The Bhutan Ministry of Health has made several advances in management of tuberculosis (TB) since 1986.[1] In order to address the TB problem in the country, the National Tuberculosis Control Program (NTCP) was established in 1976. One major strategy was the introduction of directly observed treatment short-course (DOTS) in 1994 and it was implemented nationwide in 2004.[1] In Bhutan, a person diagnosed with TB is usually admitted to a hospital for 1-2 weeks and asked to continue DOTS at home for the treatment. A DOTS provider could be a health worker, a family member or a community member who observed a TB patient taking the daily dose of anti-TB drugs. Treatment success rate for smear-positive TB had been maintained above 90% since 2005. However, the current challenge is the emergence of multidrug-resistant tuberculosis (MDR-TB).[2]

MDR-TB is defined as the infection with strains of *Mycobacterium tuberculosis* that are resistant to at least isoniazid and rifampicin, the two most efficacious first-line anti-TB drugs. Extensively drug-resistant tuberculosis (XDR-TB) is defined as MDR-TB plus resistance to fluoroquinolone and at least one second-line injectable agent of amikacin, kanamycin or capreomycin.[3]

There was no representative data on drug resistance TB in Bhutan. In 2010, the World Health Organization (WHO) estimated that MDR-TB prevalence in the country was around 1.7-2.5% among new TB cases and 17-18% among retreatment TB cases.[2] Since facilities that provided MDR-TB services had been limited in the country, all MDR-TB cases were referred to Gidhakom General Hospital which was located in Thimphu and the only center in the country providing the MDR-TB treatment. The public health laboratory attached to Jigme Dorji National Referral Hospital, Thimphu was the only laboratory in the country for TB drug sensitivity test.

In 2011, MDR-TB was isolated in five of 382 (1.3%) new patients with smear-positive TB and 14 out of 70 (20.0%) retreatment cases.[4] Though the number of MDR-TB cases was not high, emergence of such cases threatened the effort and effectiveness of NTCP in the country.[1] Since no study on MDR-TB was conducted in the past, this study was initiated to describe epidemiological characteristics of MDR-TB

patients, treatment compliance and factors associated with MDR-TB patients. The study results would be useful to the NTCP for MDR-TB control in the country.

Methods

In 2011, total 215 health facilities, including 31 hospitals, were serving 695,822 people in Bhutan. All health services in Bhutan are provided free of charge. Most people can normally access to health care services and facilities when they are sick. Gidhakom Hospital with 60 beds (20 beds for MDR-TB patients) was the only hospital equipped to provide health care to MDR-TB cases. All MDR-TB cases were admitted to this hospital for six months and referred back to health facilities in their villages for follow-up.

We conducted a descriptive study among all MDR-TB patients admitted to Gidhakom Hospital from August 2011 to July 2012. MDR-TB was defined as infection with strains of *M. tuberculosis* that were resistant to at least isoniazid and rifampicin. Inclusion criterion for this study was restricted to MDR-TB patients admitted during the same period of the study. Patients who were unwilling to participate in the study were excluded. Ethical approval was obtained from the Research Ethics Board of Health in Bhutan.

Data collection was conducted by reviewing medical records including MDR-TB registers, laboratory registers and inpatient records for information on previous anti-TB treatment, treatment outcomes and laboratory results. In addition, we interviewed patients using a semi-structured questionnaire for demographic characteristics, clinical symptoms, previous anti-TB treatment, history of contact with TB cases and their knowledge on TB. The data were analyzed using Epi Info (version 3.5.3).[5] Fisher's exact test and chi-square test were used. P-value of 0.05 was considered as statistical significance.

Results

There were total 19 MDR-TB patients identified, with 63% were males. The most common symptoms experienced by MDR-TB patients were cough (91%), chest pain (86%), weight loss (71%), breathlessness (65%), fever (62%) and hemoptysis (62%). Median age was 25 years for males (range 14-65 years) and 30 years for females (range 22-41 years). More males (83.3%) were literate compared to females (42.9%), with p-value of 0.19. Median household income of males was higher than that of females (Table 1).

Of the 19 MDR-TB cases, 14 (73.7%) reported previous history of anti-TB treatment (Table 2). Of

Table 1. Demographic characteristics of MDR-TB patients by gender in Bhutan, August 2011 to July 2012

Characteristic	Male (n=12)		Female (n=7)		Total (n=19)	
	Number	Percent	Number	Percent	Number	Percent
Age (year)						
Median (range)	25 (14-65) years		30 (22-41) years		27 (14-65) years	
≤15	1	8.3	0	0	1	5.3
16-25	4	33.3	1	14.3	5	26.3
26-45	6	50.0	5	71.4	11	57.9
>45	1	8.3	1	14.3	2	10.5
Marital status						
Married	8	66.7	6	85.7	14	73.7
Single	4	33.3	1	14.3	5	26.3
Literacy						
Literate	10	83.3	3	42.9	13	68.4
Illiterate	2	16.7	4	57.1	6	31.6
Occupation						
Employee	8	66.7	1	14.3	9	47.4
Business	2	16.7	1	14.3	3	15.8
Student	1	8.3	1	14.3	2	10.5
Others*	1	8.3	4	57.1	5	26.3
Median household income (Ngultrum)**/month	15,000 (5,000-20,000)		10,000 (5,000-20,000)		10,000 (5,000-20,000)	

* *Including farmers, housewives and monks*

** *50 Ngultrum = 1 USD*

Table 2. Previous anti-TB treatment and underlying diseases in MDR-TB patients by gender in Bhutan, August 2011 to July 2012

Previous anti-TB treatment	Male (n=12)		Female (n=7)		Total (n=19)	
	Number	Percent	Number	Percent	Number	Percent
Previously treated case	10	83.3	4	57.1	14	73.7
Did not follow DOTS treatment*	9	90.0	2	50.0	11	78.6
Missed anti-TB drugs ≥7 days*	4	40.0	1	25.0	5	35.7
Median duration on previous anti-TB treatment* (range)	12 (5-18) months		8 (8-12) months		8 (5-18) months	
Treatment outcome before MDR-TB						
Failure*	5	50.0	1	25.0	6	42.9
Relapse*	4	40.0	3	75.0	7	50.0
Default*	1	10.0	0	-	1	7.1
Drinking alcohol during anti-TB treatment*	6	60.0	1	25.0	7	50.0
Contact history						
Contact with TB case in the same house	6	50.0	3	42.9	9	47.4
Contact with MDR-TB case in the same house	5	41.7	2	28.6	7	36.8
Other underlying diseases including bronchial asthma and diabetes	3	25.0	4	57.1	7	36.8

** With previous anti-TB treatment*

those with previous treatment, 78.6% did not comply with DOTS. In addition, 35.7% of them reported of missing prescribed anti-TB drugs for seven or more days while treatment failure and relapse occurred in 42.9% and 50.0% respectively. Half of them (50.0%) also reported drinking alcohol during the past anti-TB treatments, with most of them were males.

Of the 19 cases, 47.4% and 36.8% reported contact with TB case and MDR-TB case in the same house respectively. During MDR-TB treatment, 83% of the male and 71% of the female cases were aware that TB could be transmitted through droplets and face mask should be used to reduce the chance of transmitting TB to other close contacts. Similarly, 75% of the male and 86% of the female patients knew that MDR-TB could be cured by taking prescribed medicines.

A review of TB data from the same period showed that among 70 retreatment TB cases, there were 10 with treatment failure, 55 relapsed and five defaulted cases. Sixty percent (6/10) of those with treatment failure who developed MDR-TB compared to 13% (7/55) of relapsed and 20% (1/5) of defaulted cases (p-value = 0.004). Overall, 20% (14/70) of these retreatment cases developed MDR-TB during the study period.

Drug sensitivity test of the 19 MDR-TB cases (five new and 14 retreatment cases) showed that 20% of the new cases and 50% of the previously treated patients were resistant to four first-line drugs: isoniazid, rifampicin, streptomycin and ethambutol (Table 3). No patients met the case definition of XDR-TB in this study.

Discussion

This was the first study on MDR-TB conducted in Bhutan. We found that majority of MDR-TB cases were males, having history of previous anti-TB treatment and contact with TB or MDR-TB patients. These findings were compatible with the global tuberculosis report on surveillance and response of WHO.[2]

Table 3. Drug resistant patterns of MDR-TB patients by types of patient in Bhutan, August 2011 to July 2012

Drug resistant pattern	New cases (n=5)		Retreatment cases (n=14)		Total (n=19)	
	Number	Percent	Number	Percent	Number	Percent
2 drugs (isoniazid, rifampicin)	1	20.0	5	35.7	6	31.6
3 drugs (isoniazid, rifampicin, streptomycin)	3	60.0	2	14.3	5	26.3
4 drugs (isoniazid, rifampicin, streptomycin, ethambutol)	1	20.0	7	50.0	8	42.1

P-value = 0.19

Similar studies conducted in Nepal[6], India[7] and Bangladesh[8] reported that majority of MDR-TB cases were males as well. In addition, these studies hypothesized that women were more compliant with treatment and therefore, less likely to develop MDR-TB strains compared to men. This might be true in Bhutan as well since our results showed that MDR-TB women had better treatment compliance than MDR-TB men. The finding of young age group among MDR-TB cases might emphasize on importance of this newly emerging problem in the country. However, lack of laboratory facilities for diagnosing MDR-TB in the past could have missed the cases in the previous years.

Three-forth of our study population had history of anti-TB treatment before they developed MDR-TB, with nearly half of those cases had treatment failure. This finding was consistent with the other reports since previous anti-TB treatment had been widely recognized as a predictor of MDR-TB by different studies.[6-8] Reports from the WHO identified that retreatment was strongly associated with MDR-TB.[9]

Though Bhutan had achieved more than 90% of treatment success rate during past seven years[2] and proportion of previously treated cases who developed MDR-TB was in line with the WHO estimation of 20%, it was still a burden for the country. The poor outcomes from previous treatment could have been caused by poor adherence and non-compliance of DOTS, indicating the problems in implementing DOTS and monitoring effectively in the country. Poor drug adherence could have increased the chance of drug resistance. Studies on DOTS versus self-administered therapy (SAT) for TB patients found that higher cure rate and better sputum conversion rate were achieved among patients on DOTS compared with those on SAT. These studies provided evidences that even in the best SAT, results were inferior to those achieved through DOTS.[9-11]

We found higher percentage of the isolates resistant to the four first-line anti-TB drugs compared to the findings of other studies,[12-14] except in Bangladesh where 65% were resistant to all four first-line drugs.[8] Increasing incidence of resistance to isoniazid and rifampicin has become alarming because these are the most potent bactericidal and sterilizing drugs in the TB control program, and are used in fixed-dose combination of short-course therapy for TB. Therefore, resistance to these drugs could lead to failure of the TB program.

Another finding in this study was the high number of contact with MDR-TB cases before they developed MDR-TB. The studies conducted in other countries found that the household contacts constituted a high risk group for TB.[15-16] Higher rates of MDR-TB among contacts indicated that drug resistant strains were circulating and being transmitted from person to person. Therefore, active case finding among household contacts of MDR-TB patients is important to identify the secondary spread.

Limitations

As the number of cases was small, it might limit the interpretation of detailed analyses. When the participants were asked to recall their behavior, it could subject to recall bias due to difficulty in remembering the past events and their treatment adherence from several years ago, particularly for chronic cases. In addition, drug quality was not explored in this study.

Public Health Actions and Recommendations

Association between MDR-TB and prior exposure to anti-TB treatment necessitates closer monitoring on treatment outcomes of individual patients as well as follow-up for drug resistance. We highlighted the importance of early detection of MDR-TB cases, providing health education on household protection, strengthening DOTS policy and monitoring the management of DOTS at all levels. Investigation on household contacts should be given priority in order to identify and control the spread of TB. Lack of diagnostic facilities for MDR-TB in Bhutan coupled with remoteness and poor transportation system implied that MDR-TB cases could be grossly under-diagnosed. Extension of such facilities to regional hospitals would be helpful for better treatment to reduce the burden of TB and MDR-TB, and also for better estimation of the MDR-TB burden and pattern of anti-TB drug resistance,.

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Suggested Citation

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