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Determinants of Multi-Drug Resistant Tuberculosis among Tuberculosis Patients in Southern Ethiopia: A Case Control Study

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ABSTRACT

Background: Multi-drug resistance tuberculosis (MDR) have been a hazardous concern both in developed and developing countries. Little information is available regarding the determinants of MDR-TB in Ethiopia, and hence, We assessed the probable determinants of MDR-TB in Southern Ethiopia.

Methods: A case-control study was conducted. Cases were TB patients with simultaneous resistance to at least rifampicin (RMP) and isoniazid (INH) and controls were TB patients who were susceptible to first line TB drugs and registered as cure or treatment completed from March 2016 to March 2018. We used simple random sampling method to select cases and controls. Data were collected using semi-structured questionnaire with face to face interview and patients' clinical record review. Bivariate and multivariate logistic regression analysis was done to determine determinants of MDR-TB. Significance level was adjusted at p-value <0.05.

Results: A total 102 cases together with 102 controls participated in the study. The mean age for cases and controls were 35.6 years (SD± 13.6) and 31.2 years (SD ±15.4) respectively. Factors that independently predicted MDR-TB were: time to reach health facility taking more than three hours (AOR 2, 95%CI=0.10-0.45), history of contact with known MDR-TB patients (AOR 6, 95%CI=1.8-19.7), patients with no formal education (AOR 4.40, 95%CI=1.7-13.3), patients who didn't get counseling (AOR 5, 95% CI=1.8-14) and patients who didn't hear about MDR-TB (AOR 6.8, 95% CI=2.99-15.3).

***Conclusion*:** Multiple factors predicted MDR-TB. Patients: at distant location, with known contact history of MDR-TB patients, with low level of literacy, who lack information on MDR-TB and who didn't get counseling deserve special attention.

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Introduction

Tuberculosis (TB), with an estimated 9.6 million new TB cases and 1.5 million TB related deaths, is the main cause of morbidity and ninth leading cause of death worldwide, (1). From the total global TB cases, an estimated 5% of TB cases develop MDR-TB (3.3% from new cases and 20% from re-treated) (1), thus making TB control programs challengeable (2). MDR-TB is a form of tuberculosis infection caused by the resistance to treatment to at least two more potent anti-TB drugs (isoniazid and rifampicin) (3). During anti-TB treatment, there is selection pressure on a population of *Mycobacterium tuberculosis* resulting in the occurrence of spontaneous resistance causing mutations in a number of susceptible TB cells, which then gradually multiply to become the dominant sub-population (4).

Drug resistance among previously treated TB patients, refers to resistance in patients who have been treated for TB for period lasting more than one month (5). WHO estimated that 5825 MDR-TB cases existed in Ethiopia in the year 2010 as a result the country has planned to treat >8500 MDR-TB patients (6). Patients infected with MDR strains are less likely to be cured from TB, particularly if they are co-infected with HIV or suffer from other immune suppressive diseases (7). Although, TB is curable, MDR-TB is more difficult to treat than drug susceptible TB because it requires the use of less effective second line anti-TB drugs, which are often associated with major side effects (8). MDR-TB is associated with a two to four-fold period of treatment, psychological problems, economic wastage, and poor treatment adherence and consequently treatment failure, it is also associated with higher case fatality rates (50- 80%) because of drug toxicity (9). Most of MDR-TB cases are due to poor adherence with TB medications, irregular use of drugs, interrupted drug supplies, physician error and accessibility of drug without prescription (10). MDR-TB is associated with higher rates of failure (11) and may develop XDR-TB (Extreme drug resistant TB), a condition of resistance to rifampicin, isoniazid, and quinolones and at least one of the three injectable second line drugs (kanamycin, capreomycin or amikacin) which its recent increasing prevalence is alarming (12). Despite the lack of comprehensive surveillance data from Africa, MDR-TB has been recognized as an emerging public health concern (13-15). The emergence of MDR-TB tend to reverse earlier gains in TB control programs in resource limited settings, especially in Sub-Saharan Africa. In populations with high TB prevalence, the expected negative impact is so diverse, thus important for the description of epidemiology of MDR-TB. In Ethiopia, the low socioeconomic status of the population, high prevalence of infectious diseases, unfavourable treatment outcomes, longer treatment period (about two years), higher treatment costs, and many more complications make MDR-TB a more complex disease than TB (16, 17).

Based on a WHO report, Ethiopia ranked 15th among 27 countries with high drug resistant TB with an estimated 5200 cases occurring each year (18, 19). Although MDR-TB is a growing concern in resource limited countries like Ethiopia, it is largely under-reported, compromising control efforts. Information concerning the true extent of the problem of MDR-TB in the African region is limited. Since, there are significant gaps in surveillance, and lack of standards for methodology, data sharing and coordination. The overall epidemiology of drug resistant TB is not well understood in Ethiopia (20). Ethiopia is among the 30 of high TB, HIV, and MDR TB burden countries that accountable for 80% of all estimated TB cases worldwide, with annual estimated TB incidence 207/100,000 population and death rate of 33/100,000 for 2014 (21) The national drug resistant TB sentinels report in 2013 shows the MDR prevalence of 2.3% among new TB cases 17.8 among previously treated TB cases (22). To reduce the

burden of MDR-TB, The government of Ethiopia has designed a strategy to provide bacterial culture and drug susceptibility testing (DST) at least to all MDR-TB suspected cases (23). In a study conducted in Ethiopia, some independent determinants' for MDR-TB were contact history with known TB patient, previous history of treatment history of hospitalization, sputum smear positive and social stigma [24]. Information available on some of these issues is limited and controversial. For instance, high prevalence levels of drug resistance have been found among HIV patients. However, other studies have found no association between HIV and drug resistance (25). Many new cases of MDR-TB have emerged due to error in TB management such as the use of a single drug to treat the disease, the addition of a single drug to a failing regimen, the failure to identify pre-existing resistance, the initiation of an inadequate regimen using first line anti-TB drugs, variations in bioavailability of anti-TB drugs predispose the patient to the development of MDR-TB (26). Previous studies done in Ethiopia, reported that being male, prior exposure to anti-TB treatment, non-adherence for first line anti-TB treatment, drug side effects during first line treatment, treatment not directly observed by the health worker and interruption of treatment for at least a day were factors significantly associated with MDR-TB (27, 28). Hence, understanding the burden of the most prevailing infections like MDR-TB is urgently required to guide public health interventions that are both specific and effective and also it is known that epidemiologic information on risk factors of MDR-TB is important for prevention and control of the spread of the disease in countries where drug resistance is major threat. However, there is information scarcity in the study area and at large to our country. Thus, the aim of this study was to determine factors that determine MDR-TB in TB patients in southern part of Ethiopia.

Materials and Methods

Study setting, population and design

We conducted institutional based unmatched case-control study from March 14, 2016-March 13, 2018 in the south region of Ethiopia, one among the nine highest administrative units in Ethiopia located at 275 Km from the national capital city, Addis Ababa. Based on the 2007 Census conducted by the Central Statistical Agency of Ethiopia (CSA), the region has an estimated total population of 18 million which makes it the third most populous region in Ethiopia. Currently, MDR-TB diagnosis and treatment services are restricted to selected regional hospitals. Accordingly, only six hospitals render these services which are Jinka, Mizan Tepi University teaching, Yirgalem, Butajira, Arbaminch and Hosanna hospitals. Cases were all TB cases that have been diagnosed with molecular line probe assay (LiPA) or microbial culture to have developed MDR-TB (resistant to at least Isoniazid and Rifampin) in SNNPRS during the study period and controls were all TB cases who have been treated and declared to be cured in the same hospitals of SNNPRS where the cases are being treated during the study period. Patients who developed MDR-TB confirmed with molecular line probe assay or drug sensitivity test/culture during the study period were included in to the study as cases. Similarly, non MDR-TB patients who were susceptible to first line TB drugs and registered as cure or treatment completed during the study period were included into the study as controls. Patients whose residence was out of the region, or had completed the treatment 2 years before the data collection period, or had too severe illness to respond to the interview question, or being XDR patients, were excluded from the study.

Operational definitions

MDR-TB cases were defined as those patients who have been declared to be infected by *M. tuberculosis* strains which are resistant to at least two most effective TB drugs (isoniazid and rifampin). MDR-TB was confirmed by molecular techniques or culture media.

We defined drug susceptible TB cases as those who had been diagnosed having TB which are susceptible to first line anti-TB drugs, received by the selected clinics, completed the treatment and declared to be cured by laboratory confirmation as shown in the clinics' tuberculosis registers. History contact with MDR-TB cases was measured by asking the respondents if he/she has ever had contact with MDR-TB patients before. Irregularity of treatment was measured by asking the case or control if he/she had been treated before for TB and if he/she took the drug intermittently. If he/she reports that he/she had discontinued, number of such incidents will be asked, and number of irregularities will be analyzed if they have independent effects on the cases or controls.

Duration of the previous treatment was defined those respondents who reported to have previous treatment history was asked if they have completed the full regimen or discontinued before completion. Similarly, outcome of the previous treatment was assessed by asking respondents about previous treatment history and classified as defaulter (if discontinued before completing the treatment), failed (if treatment completed but no cure), completed (received full regimen but no laboratory confirmation for cure) or cure (completed the treatment and confirmed in sputum examinations). Previously treated patients the one that received a 1 month or more of anti-TB drugs in the past may have positive or negative bacteriology and may have disease at any anatomical sites. Relapse is declared when a patient declared as cured or treatment completed of any form of TB in the past, but who report back to health service and now found to be acid fast bacilli smear positive or culture positive. We defined treatment failure when a patient who is sputum smear or culture positive at 5 month or later during treatment and defaulter if, patients whose treatment was interrupted for 2 consecutive month or more.

Sample size

The sample size was calculated using StatCalc function of Epi-Info version 7 with the application of Fleiss sample size calculation formula for unmatched case control study. Assuming 80% power at 95% CI, precision of 5%, a case to control ratio of 1:1 with a proportion of TB retreated among controls 1.6%, proportion of TB retreated among cases 11.8%. Considering 10% non-response, final calculated sample size was 208 (102 cases and 102 controls).

Variables and measurement

The outcome variable of interest was MDR-TB status. Predictor variables recorded were socio-demographic variables: (age, sex, income, living condition, family size), behavioral factors: (Khat chewing, smoking and alcohol drinking history), TB-related previous (infection, treatment discontinuation, treatment irregularity, history of contact with MDR-TB cases, category of treatment, duration of the treatment, outcome of the treatment), and comorbidities (Presence of HIV, diabetic mellitus, lung diseases and cardiovascular diseases).

Data collection procedure

Data were collected from registers of TB clinics and interviews of the patients. Structured questionnaires, developed after review of various literatures, were used. The questionnaire was translated to local language (Amharic). Health officers and nurses who was trained about MDR-TB and working at TB treatment initiation center collected the data from registers and interview.

The data collection tool was pre-tested on 11 MDR-TB and drug-sensitive TB patients (5% of

the sample size) in Arbaminch hospital, which is not included in the study, before it is administered to the study participants. To select controls, first list of tuberculosis patients who were treated and declared to be cured or treatment completed within 2 years prior to data collection period from TB clinics of the selected hospitals was identified using registers. Then, using the serial numbers as sampling frame, the participants were selected randomly as per the proportion of sizes to the hospitals selected. A required data element was extracted from the corresponding records and 2 trained data collectors (nurses by profession) contacted them for interviews to get the remaining data elements. To select cases, individuals who were receiving MDR-TB treatments from the same hospitals as controls have been sampled will be selected randomly and the data will be extracted from the registers and through interviews. To avoid risk of infection, the interview was conducted by staff members who are working in the MDR-TB clinics of the selected hospitals.

Data quality assurance

The quality of data was assured through careful design, translation and retranslation, and pre-testing of the questionnaire, proper training of the interviewers and supervisors, supervision of the data collecting procedures, proper categorization and coding of the data. The principal investigators and the supervisors were check the accuracy and reliability of the data collection process. They gave clarifications when ambiguity occurred during data collection. Discussions were held among the principal investigators, supervisor, and data collectors, as necessary.

Data entry, processing and analysis

Data coding, entry, and cleaning was performed using Epi-Data version 3.1 and exported to SPSS version 21.0 for analysis. To determine predictors of MDR-TB two strategies are used. Primarily, predictor variables were entered into separate bivariate logistic regression model. Secondly, all variables from the bivariate models with p-value ≤0.25 were included in a final multivariate logistic regression models. Associations were examined at $p<0.5$ level of significance.

Ethical statement

Ethical clearance was obtained from the Research and Ethical Review Board of Jimma University. Furthermore; statement about the purpose of the study was read to each study participants and were interviewed privately. Unique identifiers were used to ensure confidentiality.

List of abbreviations: AFB- Acid Fast Bacilli, DOTS: Directly Observed Treatment Short Course, DST: Drug Sensitivity Test, FL-DST: Full first Line-DST, LiPA: Line probe Assay, MDR: Multidrug-Resistant, RR: Rifampicin Resistant, SLDs: Second-Line Drugs, SL-DST: Second Line DST, XDR-Extra Drug-Resistant.

Result

Socio-demographic characteristics of participants

A total of 204 participants, 102 participants who had MDR-TB (cases) and 102 subjects who had no MDR-TB (controls) were included in the study making a response rate of 96.22%. The mean age among cases and controls were 35.6 years (±13.6 SD) and 31.2 years (±15.4 SD) respectively. Regarding sex of the subjects, 69 (67.6%) of cases and 68 (66.7%) of controls were males and, the study showed 67 (65.7%) of cases and 64 (62.7%) of controls were married, and 22 (21.6%) of cases and 31(30.4%) of controls were single. For detail see (Table 1).

Table 1. Socio-demographic factors of MDR-TB among cases and controls patients in south region, Ethiopia, 2018(n=204).

Variables	Cases N (%)	Controls N (%)	COR (95%CI)	P-value
Sex				
Male	69(67.6)	68(66.7)	0.96(0.53-1.71)	0.881
Female	33(32.4)	34(33.3)	1	
Age				
<25	17(16)	32(31.4)	0.43(0.16-1.1)	0.08
26-45	70(68.6)	58(56.9)	0.97(0.42-2.2)	0.93
>45	15(14.7)	12(11.8)	1	
Religion				
Protestant	55(53.9)	50(49.0)	1	
Orthodox	25(24.5%)	35(34.3)	0.64(0.34-1.23)	0.286
Muslim	22(21.6%)	17(16.7)	1.18(0.56-2.46)	0.667
Marital status				
Married	67(65.7%)	64(62.7)	1	
Single	22(21.6%)	31(30.4)	0.56(0.21-1.50)	0.252
Divorced/widowed	13 (12.7%)	7(6.9)	0.38(0.13-1.11)	0.078
Occupational status				
Farmer	41(40.2)	27(26.5)	1	
House wife	23(22.5)	20(19.6)	1.89(0.47-7.71)	0.37
Merchant	7(6.9)	16(15.7)	1.44(0.34-6.09)	0.623
Government employee	27(26.5)	34(33.3)	0.99(0.24-4.06)	0.992
Other	4(3.9)	5(4.9)	0.55(0.11-2.67)	0.456
Ethnicity				
Gurage	23(22.5)	30(29.4)	1	
Hadiya	25(24.5)	24(23.5)	0.51(0.19-1.34)	0.274
Oromo	5(4.9	5(4.9)	0.69(0.26-1.84)	0.464
Sidama	29(28.4)	28(27.5)	0.67(1.52-2.91)	0.59
Amhara	5(4.9)	5(4.9)	0.69(0.27-1.79)	0.447
Other	15(14.7)	10(9.8)	0.67(0.15-2.91)	0.59
Educational status				
No formal education	56(54.9)	43(42.2)	2.8(1.4-5.7)	0.003
Primary school	29(28.4)	22(21.6)	2.86(1.3-6.4)	0.01
Secondary and above	17(16.7)	37(36.3)	1	
Residence				
Urban	28(27.5)	45(44.1)	2.08(1.16-3.74)	0.014
Rural	74(72.5)	57(55.9)		
Time to reach health facility				
≤3 Hour	67(65.7)	46(45.1)	1	
>3 hour	35(34.3)	56(54.9)	2.33(1.33-4.1)	0.003

Table 2. Previous TB related history and other TB related factors of MDR-TB among cases and controls in south region, Ethiopia, 2018(n=204)**.**

Variables	Case	Control	COR95%CI	p-value
	N (%)	N (%)		
Alcohol				
Yes	40(39.2)	26(25.5)	0.5 (0.29-0.96)	0.037
No	62(60.8)	76(74.5)	1	
Ever Smoke				
Yes	30(29.4)	12(11.8)	0.3(0.15-0.7)	0.002
No	72(70.6)	90(88.2)	1	
Ever khat chew				
Yes	31(30.4)	31(30.4)	0.4(0.21-0.84)	0.014
No	71(69.6)	86(84.3)	1	
Type of TB				
Smear positive TB	92(90.2)	59(57.8)	0.15(0.7-0.32)	0.001
Smear negative or extra pulmonary	10(9.8)	43(42.2)		
Living situation				
Individually	10(9.8%)	11(10.8%)		
With family	92(90.2%)	91(89.2%)	1.1(0.45-2.75)	0.818
Family size				
≥2	33(32.4%)	34(33.3%)	1.1(0.58-1.88)	0.88
<2	69(67.6%)	68(66.7%)	1	
Contact history				
Yes	19(18.6%)	11(10.8%)		
No	83(81.4%)	91(89.2%)	1.9(0.85-4.2)	0.118
Heard about MDR				
Yes	33(32.4%)	68(66.7%)		
No	69(67.6%)	34(33.3%)	4.18(2.3-7.5)	0.001
Site of disease				
Pulmonary TB	93(91.2%)	70(68.6%)	0.2(0.095-0.47)	0.001
Extra pulmonary	9(8.8)	32(30.4)	1	

Table 3. First line TB treatment related factors of MDR-TB among cases and controls in south Ethiopian region, 2018 (n=204).

Variables	Case N (%)	Control N (%)	COR 95% CI	p-value
History of TB before.				
Yes	74(72.5)	8(7.8)	0.03(0.01-0.75)	0.001
No	28(27.5)	94(92.2)	1	
Number of TB episodes				
<2	32(43.2)	7(90)		
≥2	42(56.8)	1(10.0)	9.2(1.4-98.07)	0.022
Treatment category				
Category I	36(48.6)	7(77.8)	1	
Non-category I	38(51.4)	1(22.2)	12.1(5.9-24.95)	0.001
Outcome of the treatment				
Cure/complete	18(22)	5(55.6)	1	
Default	21(28.8)	1(11.1)	0.85(0.4-4.4)	0.233
Failure+	35(50)	2(33.3)	0.2(0.3-6.9)	0.621
Adherence intensive phase				
Yes	15(20.5)	5(33.3)	0.14(0.45-32.48)	0.217
No	21(28.8)	1(11.1)	1	
Adherence continuation phase				
Yes	19(25.7)	5(66.7)	1	
No	55(74.3)	3(33.3)	22.2(2.56-192.5)	0.005
Ever counselled by health care worker about TB				
Yes	69(67.6)	92(90.2)	1	
No	43(21.1)	10(9.8)	4.4(2.03-9.53)	0.001
Had diabetes mellitus?				
Yes	8(7.8)	2(2)	0.24(0.05-1.14)	0.071
No	94(92.2)	100(98)	1	
Had cardiovascular diseases				
Yes	4(3.9)	3(2.9)	0.74(0.16-3.4)	0.701
No	98(96.1)	99(97.1)	1	
Had lung disease other than TB				
Yes	5(4.9)	3(2.9)	0.59(0.14-2.6)	0.475
No	97(95.1)	99(97.1)	1	
HIV sero- status				
Yes	4(3.9)	7(6.9)	1.8(0.5-6.4)	0.358
No	98(96.1)	95(93.1)	1	

Table 4. Multivariate logistic regression analysis of predictors of MDR-TB among cases and controls in south Ethiopian region, 2018.

Variables	Case N (%)	Control N (%)	COR(95% CI)	AOR(95% CI)
Educational status				
No formal education	56(54.9)	43(42.2)	2.8(1.4-5.7)	4.4(1.7-11.3)*
Primary school	29(28.4)	22(21.6)	2.86(1.3-6.4)	3.4(1.2- 9.8)*
Secondary and above	17(16.7)	37(36.3)	1	1
Time to reach health facility				
≤3 hr	67(65.7)	46(45.1)	1	1
>3 hr	35(34.3)	56(54.9)	2.33(1.33-4.1)	2 (0.10-0.45)*
Type of TB				
Smear positive TB	92(90.2)	59(57.8)	0.15(0.7-0.32)	22.5(7.8-64.8)*
smear negative or extra-pulmonary	10(9.8)	43(42.2)	1	1
Counselling status				
Yes	69(67.6)	92(90.2)	1	1
No	43(21.1)	10(9.8)	4.4(2.03-9.53)	6(1.79-19.7)*
Hear about MDR-TB				
Yes	33(32.4%)	68(66.7%)	1	1
No	69(67.6%)	34(33.3%)	4.18(2.3-7.5)	6.8(2.99-15.3)*
History of contact				
Yes	19(18.6%)	11(10.8%)	1	1
No	83(81.4%)	91(89.2%)	1.9(0.85-4.2)	6(1.8-19.72)*

* Significant at p-value< 0.05

Previous TB Related history among participants

The history of contact among cases was higher 19(18.6%) than controls 11 (10.8%). Similarly, the proportion of participants who heard about MDR-TB among cases 33 (32.4%) was lower than controls 68 (66.7%). From the study participants 93 (91.2%) cases and 70 (68.6%) controls had pulmonary TB (Table 2).

First line TB treatment related factors of MDR-TB

The proportion of previous TB infection was 74 (72.5%) among cases 8 (7.8%) among controls. Concerning participants' treatment category, 38 (51.4%) of cases and 22.2% of control were return after default, failure retreatment, or relapse (Table 3).

Predictors of MDR-TB

In multivariate logistic regression analysis, we identified six independent predictors of MDR-TB. These included, time to reach health facility taking more than three hours (AOR= 2, 95% CI (0.1-0.45), History of contact with known MDR-TB patients (AOR=6,95% CI (1.8-19.7), absence of formal education (AOR= 4.4, 95% C, (1.7-11.3), counseling status, (AOR=5, 95% CI (1.8-14) and hearing about MDR-TB previously

(AOR= 6.8, 95% CI (2.99-15.3) were significantly associated with risk of MDR-TB.

Discussion

TB drug resistance is a major public health problem that threatens not only the progresses in the treatment of TB, but also the control of this infectious disease, thus disproportionately affecting areas with weak TB control program (29). In this study factors independently associated with MDR-TB were the absence of formal education, time to reach health facility ≥3 hour, type of TB, absence of counseling during treatment visit, no contact history with known MDR patients and having no information about MDR-TB.

Among socio demographic factors, educational status is one of the predictors in this study. TB patients with no documented formal education and TB patients who attended their secondary education had high risk for MDR-TB compared to others. This finding is in line with a study conducted in China which revealed that high scholar and lower educational degree are risk factors for MDR-TB (30, 31). In this study sex and age were not predictor of MDR-TB in contrary to study done in Amhara region (32) and Addis Ababa (33). This variation could be explained from methodological variation across studies. In current study, time to reach health facility >3hr was risk for MDR-TB, which was consistent with a study done in China in which travelling distance to take >3hr to reach health facility predicted MDR-TB (31). In this study, smear positive TB patients developed MDR-TB. This finding was in line with studies conducted in Ethiopia (24, 34), in which smear positive pulmonary TB showed a strong associated with MDR-TB. (24).

In this study, history of contact with known MDR-TB patients was found predictor for MDR-TB. This finding is consistent with other studies (24, 31, 35) that contact history with known MDR patient as one of risk factor for MDR-TB.

In this study counseling during treatment visit was found as a strong predictor of MDR-TB. This is in line with a mixed study done in Japan which showed that two interventions appeared to improve treatment outcome for those receiving counseling combined support were great to those not receiving (36). In this study having no information about MDR-TB is associated with high risk of developing MDR-TB. A cross sectional study done in university of Lahore supported this finding in that the participants who did not have good knowledge and awareness about MDR and XDR-TB predicted MDR-TB (37). However, limitation of the study is the fact that using data with incomplete information might introduce bias.

Conclusion

Multiple factors predicted the development of MDR-TB. Lower educational status, type of TB, travel time more than 3 hours, lack of professional counseling, history of contact with MDR TB patient, knowledge about MDR before starting TB treatment were found to be strongly associated with MDR TB. To alleviate and strengthen MDR-TB control programs, strengthening TB infection control practices at health facilities, appropriate treatment of susceptible TB patients, strengthening DOTS program to enhance patient adherence and identification of high risk for MDR-TB and early investigation (DST) is highly recommended. Moreover, delivery of appropriate patient counseling service and decentralization of TB related services is also part of the recommendation.

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Conflict of interest

No potential conflicts of interest were disclosed.

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