# Risk factors of Multidrug Resistant Tuberculosis in central Nepal: A pilot study

Marahatta SB[1], Kaewkungwal J[2], Ramasoota P[3], Singhasivanon P[4]

[1] Ph.D Student, Department of Tropical Hygiene,

[2,4]Department of Tropical Hygiene,

[3]Department of Social and Environmental Medicine,

Faculty of Tropical Medicine Mahidol University, Thailand

**Corresponding Author**

Dr Pratap Singhasivanon

Department of Tropical Hygiene

Faculty of Tropical Medicine

Mahidol University

Thailand

Email.

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## ABSTRACT

**Introduction**

Tuberculosis is the most widespread infectious disease in Nepal and poses a serious threat to the health and development of the country. Incidences of drug resistant tuberculosis in Nepal are increasing and this tuberculosisis a major threat to successfully controlling tuberculosis .

**Objective**

The general objective of the study was to assess the risk factors of multi-drug resistant tuberculosis among the patients attending the National Tuberculosis Centre, Bhaktpur Nepal.

**Methods**

An observational study/ case-control study with a Atotal number of 55 multi-drug resistant tuberculosis cases and 55 controls. The study was conducted among the patient attending in the National Tuberculosis Centre , Bhaktpur Nepal for six months, between May–October 2010. sImulti-drug resistant tuberculosis wasThe collected data was analysed in SPSS 11.5 version. The association between categorical variables were analysed by chi-square tests, OR and their 95% CI were measured.

**Results**

The total number of patients used for the study was 110, of which among them 55 were cases and 55 were controls . Our study revealed that there were significant associations between history of prior TB MDR-TB OR =2.799 (95 % CI 1.159 to 6.667) (p=0.020); smoking habit OR =2.350 and (95%CI 1.071 to 5.159) (p=0.032); social stigma social stigma OR 2.655 (95%CI r 1.071 to 5.159) (p=0.013); knowledge on MDR-TB OR =9.643 (95% CI 3.339 to 27.846) (p < 0.001)and knowledge on DOTS Plus OR=16.714 (95% CI is ranging from 4.656 to 60.008) (p< 0.001). However, there was no association found between alcohol drinking habits and ventilation in the room.

**Conclusion**

Our study revealed that there were significant associations between history of prior tuberculosis, smoking habit social stigma social stigma, knowledge on multi-drug resistant tuberculosis and knowledge on DOTS Plus with multi-drug resistant tuberculosis However there was no association between alcohol drinking habit and ventilation in room with multi-drug resistant tuberculosis.

## Key Words

*directly observed treatment short course-plus, multidrug-resistant tuberculosis, risk factors*

## INTRODUCTION

Although progress has been made to reduce global incidences of drug-susceptible tuberculosis, the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis during the past decade threatens to undermine these advances. Globally, in 2008 alone, 440,000 cases of MDR tuberculosis are said to have occurred.[1] Multi-drug resistant TB (MDR TB) in Nepal is a major threat for successful TB control. The NTP has carried out four sentinel site surveillance of drug resistance in new tuberculosis patients since 1996 as part of the World Health Organization (WHO) and International Union Against Tuberculosis and Lung Disease (IUATLD) global network for surveillance of drug resistant tuberculosis. Levels of drug resistance are high, with nearly 14.7% of new patients resistant to at least one drug. Levels of MDR TB are low (2.9% among new cases) and 11.7% amongst previously treated cases. However, the pattern of drug resistance in new patients indicates the levels of resistance when they were infected, which may have been several years previously. Rifampicin resistance is low at 2.9% while higher primary resistance is to isoniazid (8.4%) and streptomycin (10.7%).[2] Many risk factors of MDR TB have been identified in recent publications: previous TB treatment; irregular treatment; gender; non-permanent residents; urban migration; urban residences; frequent travel; age; hygiene and sanitation; alcoholism; and smoking.[3] Despite all these risk factors, few or inadequate studies have been conducted on the occurrence of MDR TB, particularly in Nepal. The purpose of this study is therefore, focused solely on indentifying the risk factors of MDR TB in central Nepal.

## METHODS

This study was conducted among the patients attending National Tuberculosis Centre, Bhaktpur Nepal. We conducted an unmatched, questionnaire-based case control study amongst MDR-TB cases and Non-MDR TB controls those attending the National Tuberculosis Centre (NTC) between May 2010 to October 2010. The possible risk factors amongst MDR-TB cases and Non-MDR TB-cases were studied.

### Selection of cases and control

### Definition of case

Any tuberculosis case with resistance to both of the two major anti-tuberculosis drugs, Isoniazid and Rifampicin is classified as an MDR-TB case as per the finding of a drug sensitivity test and culture method following the protocol of NTP of Nepal.

### Identification of Cases

Identification of the cases were carried out through culture and drug sensitivity tests. Culture and sensitivity testing was carried out at the GENETUP laboratory. Before processing, the specimens were kept in a refrigerator at 4°c. After centrifugation and washing, the sediment was inculcated in tubes of LJ medium and incubated at 37°c for nine weeks or until colonies were observed (whichever showed the earliest signs). The drug resistance tests were performed by using the proportional method. Resistance tests to Rifampicin, Isoniazid, Streptomycin and Ethambutol were carried out. Resistance was expressed as a certain percentage of colonies that grew on critical concentrations of the drugs. Interpretation was carried out according to the usual criteria for resistance.

### Source of the cases

The cases chosen were from diagnosed MDR cases recorded at any of the three DOTS Plus centres from May 2010 up to October 2010 (at the National Tuberculosis Centre) and under their treatment. The risk factors associated with the cases were studied.

### Definition of Control

Sputum positive tuberculosis cases undergoing DOTS treatment for at least five months with negative finding on sputum microscopy.

### Identification of Control

Identification of control was conducted by using ZN staining for the identification of Acid fast bacilli (AFB) in laboratory.

The source of control constitutes hospital controls that were free from MDR tuberculosis i.e. sputum positive tuberculosis patients who had undergone DOTS treatment for at least five months with negative findings on sputum microscopy. The controls were selected from the same centre diagnosed during the same time frame as MDR-TB cases.

## MEASUREMENT OF RISK FACTORS

Information on the risk factors was assembled in precisely the same manner for cases and control. Information was collected from cases and control on a wide range of potential host related, environmental and health service factors for MDR TB. These include many potential risk factors. Standardised questionnaires were used to study subjects by field assistant using colloquial language after checking the accuracy of translation with the interviewers.

Data was entered in SPSS 11.5 version for analysis. Then the associations between categorical variable was assessed

by Chi-square testing. Means and proportions were calculated as appropriate. Unadjusted odds ratios (OR) and their 95% confidence intervals (CI) was estimated with MDR TB as an outcome. Univariate analysis was performed to measure the effect of each variable of interest in risk of MDR TB.

## RESULTS

Fifty-five patients with MDR TB and 55 Non-MDR TB patients made up the control group were included in the study. The mean age was 34.13 years in the MDR group and 32.09 years in e control group. Among the patients in the case group 36 (65.5%) were male and 19 (34.5%) were female. Amongst the control 41 (74.5%) were male and 14 (25.5%) were female. The analyses of the sex-wise distribution was divided by: geographic distribution, ethnicity, family type, economic status and occupation are shown in Table 1. Table 2 below shows the association between having a history of prior TB and the risk of MDR TB. The finding revealed that there is a strong association between having a history of prior TB with having MDR TB. The OR is found to be 2.799 (95 % CI 1.159 to 6.667) (p=0.020). The association between a smoking habit is significantly high amongst MDR-TB cases OR 2.350 and (95% CI 1.071 to 5.159) (p=0.032). Table 7 below shows the association between having an alcohol drinking habit and having MDR TB. The association between both is not significantly high with OR 0.554 and p=0.126). Table 7 below shows the association between social stigma and having MDR TB. The association between them is significantly high with OR 2.655 (95% CIr 1.071 to 5.159) (p=0.013). Table 7 below shows the association between having ventilation in the room and being at risk of MDR TB. The association between both is also not significant with OR 2.410 (95% CI ranging from 0.933-6.226) (p=0.065). Table 7 below shows the association between knowledge on transmission of TB and risk of MDR TB. The association between them is insignificantly high with OR 0.654 (p=0.647). The knowledge regarding MDR TB is strongly associated with OR is 9.643 (95% CI 3.339 to 27.846) (p<0.001). Likewise, the knowledge regarding DOTS Plus and having MDR TB is strongly associated. OR=16.714 (95% CI is ranging from 4.656 to 60.008) (p< 0.001).

Table 1. Characteristics of cases & controls

| **Sex** | Case | Control | Total |
|---|---|---|---|
| Female | 19 (34.5%) | 14 (25.5%) | 33 (30%) |
| Male | 36 (65.5%) | 41 (74.5%) | 77 (70%) |
| Address | | | |
| Mountain | 3(5.5%) | 1(1.8%) | 4(3.6%) |
| Hilly | 43(78.2%) | 50(90.9%) | 93(84.5%) |
| Terai | 9(16.4%) | 4(7.3%) | 13(11.8%) |
| Ethnicity | | | |
| Dalit | 4 (7.3%) | 1 (1.8%) | 5 (4.5%) |
| Disadvantaged Janjatis | 29(52.7%) | 20(36.4%) | 49 (44.5%) |
| Disadvantaged Non- Dalit Terai caste group | 1(1.8%) | 3 (5.5%) | 4 (3.6%) |
| Religious Minorities | 0 (0%) | 2 (3.6%) | 2(1.8%) |
| Relatively advantaged Janjatis | 5 (9.1%) | 17 (30.9%) | 22 (20.0%) |
| Upper caste Group | 16 (29.1%) | 12 (21.8%) | 28(25.5%) |
| Type of Family | | | |
| Nuclear | 46 (83.6%) | 35 (81%) | 81(73.6%) |
| Joint | 7 (12.7%) | 16(23%) | 23(20.9%) |
| Extended | 2 (3.6%) | 4 (6%) | 6(5.5%) |
| Occupation | | | |
| Unemployed | 7(12.7%) | 2 (3.6%) | 9(8.2%) |
| Freelance employment | 15(27.3%) | 18 (32.7) | 33(30.0%) |
| Farmer | 7(12.7%) | 3 (5.5%) | 10(9.1%) |
| Service | 7(12.7%) | 11 (20.0%) | 18(16.4) |
| Student | 9(16.4%) | 11 (20.0%) | 20(18.2%) |
| Housewife | 5 (9.1%) | 8(14.5%) | 13(11.8%) |
| Other | 5 (9.1%) | 2( 3.6%) | 7(6.4%) |

| | | | |
|---|---|---|---|
| Monthly Income of the Family | | | |
| < 5000 | 20(36.4%) | 10(18.2%) | 30(27.3%) |
| 5000-10000 | 11(20.0%) | 20(36.4%) | 31(28.2%) |
| 10000-15000 | 7(12.7%) | 9(16.4%) | 16(14.5%) |
| >15000 | 13(23.6%) | 10(18.2%) | 23(20.9%) |
| Don't Know | 4(7.3%) | 6(10.9%) | 10(9.1%) |

Table 2. Comparison of the characteristics of MDR-TB and Non-MDR TB

| Group | | MDR TB | Non MDR TB | OR(95% CI) | *p-value* |
|---|---|---|---|---|---|
| History of Prior Tuberculosis | Yes<br>No | 21 (38.2%)<br>3 (5.5%) | 10 (18.2%)<br>3 (3.6%) | 2.779 (1.159 to 6.667) | 0.020* |
| Smoking | Yes<br>No | 27 (49.1%)<br>28 (50.9%) | 16 (29.1%)<br>39 (70.9%) | 2.350 (1.071 to 5.159) | 0.032* |
| Alcoholic | Yes<br>No | 29 (52.7%)<br>26 (47.3%) | 21 (38.2%)<br>34 (61.8%) | 0.554(0.259 to 1.183) | 0.126 |
| Social Stigma | Yes<br>No | 34 (61.8%)<br>21(38.2%) | 19 (34.5%)<br>36 (65.5%) | 2.655 (1.223 to 5.765) | 0.013* |
| Ventilation in Room | Yes<br>No | 47 (85.5%)<br>8 (14.5%) | 39 (70.9%)<br>6 (29.1%) | 2.410 (0.933 to 6.226 ) | 0.065 |
| Knowledge on MDR TB | Yes<br>No | 27 (49.1%)<br>28 (50.9%) | 5 (9.1%)<br>50 (90.9%) | 9.643 (3.339 to 27.846 ) | <0.001* |
| Knowledge on DOTS PLUS | Yes<br>No | 27 (49.1%)<br>28 (50.9%) | 3 (5.5%)<br>52 (94.5%) | 16.714 (4.656 to 60.008 ) | <0.001* |

* p-value significant

## DISCUSSION

Drug resistance is major problem in tuberculosis treatment. In Nepal, levels of drug resistance are very high, with nearly 14.7% of new patients resistant to at least one drug[2] Previous treatment of tuberculosis has been consistently reported as the risk factor within various clinical conditions and populations.[4-10] The present study also revealed that previous treatment of tuberculosis was strongly associated with MDR TB OR =2.799 (95 % CI 1.159 to 6.667) (p=0.020).According to the National Tuberculosis Programme's Nepal National Survey in 2007, MDR among new cases of TB is 2.9% and MDR among previously treated cases is at 11% thereby giving a ratio of approximately 4:1 for prevalence of MDR in these groups,[2] this pattern holds true in our study too. Lomtadze et. al. determined previously administered TB treatment as an important risk factor for the development of drug resistance TB and reported that this situation increased development of drug resistance by five times on average.[11] A study by Faustine et.al. has shown that previous anti-TB treatment was the strongest determinant of MDR-TB in Europe. MDR-TB patients were more likely to have received previous tuberculosis treatment in 22 studies, with a pooled risk estimate of being 10 times higher for treated cases than for new patients.[12] Likewise, Mendoza et.al. reported that previous TB treatment for more than three months increased the risk of MDR TB.[13] Baghaei et. al. also reported that a positive history of previous anti-TB medication was significantly higher in the MDR-TB group compared to the non-MDR-TB controls (p=0.001).[14] Another study revealed that the risk of MDR in people previously given TB treatment was 10.54 times higher in those who were not given treatment.[15] Clark CM et. al. has shown that prior treatment of TB was independently associated with MDR-TB with OR=8.37 95% CI ranging between 3.92 to 17.89.[16] Likewise another study found that patients with MDR TB were more likely to have received previous treatment of tuberculosis compared to patients with non-MDR TB (58.3% vs. 16.2%, P=0.002).[17] A study carried out in China found that patients with a previous treatment history was more than five times likely to have an increased risk of MDR-TB (adjusted OR: 6.14, 95% CI: 4.61-8.17), compared with those previously who had not been treated.[17] A retrospective cohort study conducted in Spain revealed that previous treatment for tuberculosis as a risk factor for MDR TB with (OR: 3.44; 95% CI: 1.58-7.50; p = 0.003).[18] A prospective epidemiological case control study conducted in Europe found that previous tuberculosis treatment was found to be the most significant risk factor for MDR-TB.[19] Previous treatment for tuberculosis has been consistently associated with

MDR-TB.[20] It can also be concluded that prior treatment for tuberculosis is the most significant risk factor for MDR-TB. The strengthening of DOTS programme and close monitoring of tuberculosis patients seems to be the most promising endeavour to prevent the development of MDR TB.

Our study revealed that the association between having a history of smoking and MDR TB was significant with OR 2.350 and 95%CI ranging from 1.071 to 5.159 (p=0.032). A study done in western Nepal on the risk factors of MDR TB revealed that 74% of the MDR-TB patients had a history of smoking (past as well as present). [20] A study carried out in Pakistan revealed that MDR had shown strong associations with smoking (13%) as compared to non-smokers (5.6%) (p<0.05).[21] Also in another study, smoking appeared as one of the risk factors for MDR TB.[22] Smoking was found to be associated with isoniazid resistance but more evidence is needed to explain this association.[24] However, a study conducted in Korea amongst the military worker found no significant differences in terms of smoking history (P=0.658).[24] In North India, of the risk factors studied for MDR-TB, tobacco smoking had no relation to infection with MDR. [25] Whether or not smoking increases the chance of drug resistance in tuberculosis is yet to be unveiled.

Our finding infers that the association between having an alcohol drinking habit and having MDR TB is not significant OR=0.554 (p=0.126). Likewise in North India, of the risk factors studied for MDR-TB excessive alcohol intake, had no relation to infection with MDR.[25] The study done in Spain suggests that patients with alcohol abuse are less likely to have MDR-TB. This is an unexpected finding, since alcoholism has been associated with treatment default and poor treatment outcome among patients with TB in other countries, although some studies could not find a higher risk of MDR-TB in alcoholic patients.[18] Alcohol abuse/dependence was associated with an eight-fold increase in drug resistance (OR 8.58; 95% CI 2.09-35.32).[26] In a multivariable analysis, alcohol consumption during treatment was found to be the strongest predictors of poor treatment outcome for MDR TB.[39] In another study, alcoholism appeared as one of the risk factors for MDR TB.[22]

Social stigma and lack of scientific awareness about the disease and social commitments are stated reasons for interrupting and defaulting TB treatment. In our study, association between social stigma and having MDR TB is significant with OR 2.655 (95%CI 1.071 to 5.159) (p=0.013)

Our study revealed that the association between having ventilation in the room and the risk of MDR TB is found to be slightly insignificant OR 2.410 (95% CI ranging from 0.933-6.226) (p=0.065). Poor housing, overcrowding and homelessness are clear risk factors for MDR TB in the Terai region of Nepal.[27] Another study revealed that a lower number of rooms in the house can also be associated with MDR TB.[22]

Although a full knowledge of tuberculosis transmission and spectrum of disease are not crucial in finishing a course of medicine, it is a reflection of how well patients are being educated about their illness. Knowledge regarding MDR TB and DOTS Plus was significantly high amongst MDR TB patients. This reflects that the patients are well informed regarding MDR TB and DOTS Plus during their treatment.

The association between TB and poverty has been known for centuries, and this also applies to MDR-TB, a rather significant inverse association between MDR TB and family income.[22] Larger case control studies will be required to determine whether or not the socio-economic factors and poor knowledge leading to poor adherence to treatment thereby leading to the development of MDR-TB are proven.

## CONCLUSION

Many risk factors of MDR TB have been identified in recent publications. Our study revealed that there was a significant association between having a history of prior TB, a smoking habit, social stigma, knowledge of MDR TB and knowledge of DOTS Plus with MDR TB. However, there was no association between having an alcohol drinking habit and ventilation in the room. The strength and truthfulness of theses associations need to be examined with a multi-centre case-control study so that risk factors can be unveiled. Such studies can be designed on the basis of the findings of the present study. The findings of such studies could offer strong impetus to strengthen the DOTS Plus programme and may prove to be fruitful in reducing MDR TB burden in Nepal.

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