# Analysis of the Factors Leading to Causation of Multidrug Resistant Tuberculosis among Cases Registered under Revised National Tuberculosis Control Programme in East Sikkim – A Case Control Study

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**ABSTRACT**

**BACKGROUND**

Tuberculosis (TB) is a curable and preventable disease. Emergence of multi drug resistance TB (MDR TB) threatens to undo the progress made towards control of TB. While treatment is available for MDR TB, it is of a long duration and is also more expensive and toxic. Understanding the various factors that are associated with MDR TB may help to formulate and implement effective preventive practices for control of MDR TB. We wanted to assess the various epidemiological factors among MDR TB cases registered under Revised National Tuberculosis Control Programme (RNTCP) in East Sikkim and study the current & past TB treatment including adverse drug reactions.

**METHODS**

A community-based case control study was conducted over 4 months in the eastern district of Sikkim. MDR TB cases registered under Revised National Tuberculosis Control Programme (RNTCP) in the first two quarters of 2019 were compared with matched healthy controls. Data was collected by a door to door survey using a pre-designed and pre-tested questionnaire and analysed on Statistical Package for the Social Sciences (SPSS) 20.

**RESULTS**

A total of 62 cases (14 non-respondents) of MDR TB were identified and were matched with 63 controls. 30.5 % cases were young adults in the age group 15 to 25 years, 66 % of the cases reported being currently unemployed, 16 % were homemakers, 11 % of cases fell below poverty line. A higher proportion of cases as compared to controls reported a habit of skipping a meal, poor housing conditions and comorbidities than controls. A known history of contact with a case of tuberculosis was given by 11.3 % cases; 18 % cases gave a previous history of TB; about 51 % cases reported a delay in diagnosis which delayed treatment initiation.

**CONCLUSIONS**

Previous history of TB with history of relapse / failure, contact of MDR TB emerged as the most significant risk factors and presence of comorbid conditions like diabetes & hypertension can be used to indicate higher risks of drug resistance.

**KEYWORDS**

Multi Drug Resistant Tuberculosis, MDR TB, Case control, Revised National Tuberculosis Control Programme, Sikkim

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## BACKGROUND

Tuberculosis (TB) has been a part of human life for a long time and has been traced back thousands of years, even in India. The causative agent of this dreaded disease (*Mycobacterium tuberculosis*) was discovered by Robert Koch in 1882 and Johann Schonlein coined the term "tuberculosis" in 1834. Before this, it went by many names like "consumption", the "white plague" and even "captain of all these men of death". These names from a time before modern medicine and our current understanding of TB, tell us of the devastation this disease left in its wake.[1]

Today, while TB is curable and preventable it is still one of the top 10 causes of death worldwide.[2] From not understanding the scientific basis of TB to finding its causative agent and eventually the effective medicines that gave a new lease of life to patients, we have come a long way. This progress, however, has been threatened in the past decade due to the emergence of multi drug resistance TB (MDR TB). It is caused by *Mycobacterium tuberculosis* that is resistant to both isoniazid and rifampicin with or without resistance to other drugs. These two drugs are among the first line treatment of TB.[2]

Drug resistance surveillance data show that 3.9 % of new and 21 % of previously treated TB cases were estimated to have had rifampicin or multidrug-resistant tuberculosis (MDR / RR - TB) in 2015.[3] In Sikkim, multi-drug-resistant TB cases were found amongst 11 % of the new tuberculosis cases & 30 % of the retreatment cases which is much higher than the national statistics even though Sikkim has a small population.[4] While MDR-TB is treatable and curable by using second-line drugs, treatment options are limited and require extensive chemotherapy (up to 2 years of treatment) with medicines that are expensive and toxic. As reported by the World Health Organisation (WHO) only 56 % of patients of MDR TB make a full recovery worldwide.[2] In India, 56 % of the estimated MDR patients were undiagnosed and 64 % of the estimated MDR patients were untreated.[5] The emergence of MDR TB presents a pressing public health challenge more so for India as we report the highest burden of both drug sensitive (27 %) and MDR TB (27 %).[2,6] Therefore, understanding the various factors that are associated with MDR TB may help in better understanding the epidemiology of the disease. This information can be used to improve and implement effective preventive practices for control of MDR TB.

We wanted to determine the various epidemiological factors among MDR TB cases compared with matched controls registered and assess the current & past TB treatment history including adverse drug reactions of the MDR TB cases registered under RNTCP in East Sikkim.

## METHODS

A community-based case control study was conducted over a duration of 4 months in the east district of Sikkim. Cases and their matched controls were selected for this purpose. For selection of cases, total enumeration of all the MDR TB cases registered under Revised National Tuberculosis Control Programme (RNTCP) in east district of Sikkim in the first & second quarter of 2019 was done. Cases were compared with more than equal number of matched healthy controls taken from the same age group, geographical area (urban or rural), gender and ethnicity but not from the same family members.

The protocol for the study was presented to the IRPEC and independent ethics committee (IEC) of Sikkim Manipal Institute of Medical Sciences (SMIMS) for approval following which approval was sought from the Government of Sikkim. After obtaining all the required approvals, a list of all the MDR TB cases including their addresses were obtained from State TB Cell Sikkim and suitable matched healthy controls were recruited. For collection of data, door to door survey was carried out to collect information from all the MDR-TB cases. The study subjects were explained about the purpose of the study and written informed consent was obtained assuring strict confidentiality. The cases and controls were interviewed with the help of a pre-designed and pre-tested questionnaire. All of the information was noted down in an interview schedule and medical examination record forms. Data was checked for completeness, entered on Microsoft Excel sheet and was analysed using SPSS version 20. Data was categorised and presented in proportions. Odds ratio with 95 % confidence intervals has been calculated for determining strength of association.

## RESULTS

A total of 62 cases of MDR TB were identified and were matched with 63 controls. There were a total of 14 non respondents among the cases. Most of the cases (30.5 %) were young adults in the age group 15 to 25 years. Half of them were hindus (50 %) and belonged to the other backward caste (33.9 %) (OBC of Sikkim State). Almost half of the cases (45 %) were married and 70 % lived in nuclear families. It can be observed from table 1 that the cases and controls were matched for socio-demographic factors.

Table 2 compares the socio-economic aspects of cases and controls. As compared to the cases, a higher proportion of controls had better education status. While almost half of the controls reported were currently unemployed, 66 % of the cases reported were currently unemployed, only 48 % of them reported were unemployed even before they developed MDR TB. Most of the cases were unemployed (19.3 %), homemakers (16 %), skilled workers (12.8 %) or students (11.2 %). About 11 % of cases fell below poverty line which is much higher than 1.5 % controls who were below poverty line. Most of the cases and controls were non-migrants, but 13 % of cases and 23.8 % of controls were migrants mostly from within the country. A lower proportion of the cases (72.5 %) as compared to controls (82.5 %) reported had a mixed / non-vegetarian diet. A higher proportion of cases as compared to controls reported a habit of skipping a meal, almost 39 % cases missed their breakfast while only 16 % controls reported skipping breakfast, 33 % cases and 13 % controls missed their lunch, 25 % cases and 9.55 % controls reported skipping dinner.

| Demographic Variable | | Sex: Male Cases (%) | Male Controls (%) | Female Cases (%) | Female Controls (%) | Total Cases (%) | Total Controls (%) |
|---|---|---|---|---|---|---|---|
| Age in Years | 15 - 25 | 6 (9.6) | 8 (12.6) | 13 (20.9) | 13 (20.6) | 19 (30.5) | 21 (33.32) |
| | 26 - 35 | 5 (8.0) | 7 (11.1) | 11 (17.7) | 9 (14.3) | 16 (25.7) | 16 (36.9) |
| | 36 - 45 | 5 (8.0) | 7 (11.1) | 8 (12.9) | 8 (12.6) | 13 (20.9) | 15 (32.1) |
| | 46 - 55 | 4 (6.4) | 6 (9.5) | 3 (4.8) | 2 (3.1) | 7 (11.3) | 8 (20.8) |
| | 56 - 65 | 2 (3.2) | 2 (3.1) | 2 (3.2) | - | 4 (6.4) | 2 (3.2) |
| | 66 - 75 | 2 (3.2) | - | - | 1 (1.5) | 2 (3.2) | 1 (1.6) |
| | 76 - 85 | - | - | 1 (1.6) | - | 1 (1.6) | - |
| Religion | Hindu | 13 (20.9) | 21 (33.3) | 18 (29.0) | 22 (34.9) | 31 (50.0) | 43 (68.3) |
| | Buddhist | 7 (11.2) | 5 (7.9) | 13 (21.0) | 9 (14.2) | 20 (32.3) | 14 (22.2) |
| | Christian | 2 (3.2) | 2 (3.1) | 7 (11.3) | 2 (3.1) | 9 (14.5) | 4 (6.4) |
| | Muslim | 2 (3.2) | 1 (1.5) | - | 1(1.5) | 2 (3.2) | 2 (3.2) |
| Caste | Scheduled caste | 2 (3.2) | 3 (4.7) | 2 (3.2) | 1 (1.5) | 4 (6.4) | 4 (6.4) |
| | Scheduled tribe | 2 (3.2) | 3 (4.7) | 11(17.7) | 10 (15.8) | 13 (21) | 13 (20.6) |
| | Other backward classes | 9 (14.5) | 11 (17.4) | 12 (19.4) | 10 (15.8) | 21 (33.9) | 21 (33.3) |
| | General category | 4 (6.4) | 12 (19.0) | 5 (8.0) | 13 (20.6) | 9 (14.5) | 25 (39.7) |
| | Others | 1 (1.6) | - | - | - | 1 (1.6) | - |
| | Unknown (non-respondent) | 6 (9.6) | - | 8 (13.0) | - | 14 (22.6) | - |
| Marital Status | Married | 11(17.7) | 16 (25.3) | 17 (27.4) | 10 (15.8) | 28 (45.1) | 26 (41.1) |
| | Unmarried | 7 (11.2) | 13 (20.6) | 12 (19.4) | 21 (33.3) | 19 (30.6) | 34 (53.9) |
| | Widow / widower | - | - | - | 2 (3.1) | - | 2 (3.1) |
| | Separated / divorced | - | - | 1 (1.6) | 1 (1.5) | 1 (1.6) | 1 (1.5) |
| | Unknown (non-respondent) | 6 (9.6) | - | 8 (13.0) | - | 14 (22.6) | - |
| Type of Family | Nuclear | 17 (27.4) | 25 (39.6) | 27 (43.5) | 26 (41.2) | 44 (70.9) | 51 (80.8) |
| | Joint | 1 (1.6) | 4 (6.3) | 3 (4.8) | 7 (11.1) | 4 (6.4) | 11 (17.4) |
| | Three Generation | - | - | - | 1 (1.5) | - | 1 (1.5) |
| | (non-respondent) | 6 (9.6) | - | 8 (13.0) | - | 14 (22.6) | - |

***Table 1. Distribution of Study Participants (Cases & Controls) According to Sociodemographic Profile (N = 125)***

| Socioeconomic Variables | | Sex: Male Cases (%) | Male Controls (%) | Female Cases (%) | Female Controls (%) | Total Cases (%) | Total Controls (%) |
|---|---|---|---|---|---|---|---|
| Education | Illiterate | 2 (3.2) | - | 2 (3.2) | - | 4 (6.4) | - |
| | Primary 0 - 3 | 2 (3.2) | 5 (7.9) | 6 (9.6) | 2 (3.1) | 8 (12.8) | 7 (11) |
| | Middle 4 - 7 | 1 (1.61) | - | 6 (9.6) | - | 7 (11.2) | - |
| | Secondary 10+ | 6 (9.6) | 5 (7.9) | 9 (14.5) | 4 (6.3) | 15 (24.1) | 9 (14.2) |
| | Higher secondary 12 | 2 (3.2) | 5 (7.9) | 2 (3.2) | 9 (14.2) | 4 (6.4) | 14 (22.1) |
| | Diploma | - | - | - | 1 (1.5) | - | 1 (1.5) |
| | Graduate | 3 (4.8) | 7 (11.1) | 1 (1.61) | 10 (15.8) | 4 (6.4) | 17 (26.9) |
| | Post graduate | 2 (3.2) | 7 (11.1) | 3 (4.8) | 8 (12.6) | 5 (8) | 15 (23.7) |
| | Unknown (non-respondent) | 6 (9.6) | - | 8 (13.0) | - | 14 (22.6) | - |
| Occupation | Unskilled worker | - | - | - | - | - | |
| | Semiskilled worker | 1 (1.61) | - | - | 3 (4.7) | 1 (1.61) | 3 (4.7) |
| | Skilled worker | 6 (9.6) | 3 (4.7) | 2 (3.2) | 5 (7.9) | 8 (12.8) | 8 (12.6) |
| | Clerical / shop / farm owner | 1 (1.61) | 12 (19.0) | 3 (4.8) | 14 (22.2) | 4 (6.4) | 26 (41.2) |
| | Semi-professional | 4 (6.4) | 1 (1.5) | - | - | 4 (6.4) | 1 (1.5) |
| | Professional | - | 7 (11.1) | 1 (1.61) | 8 (12.6) | 1 (1.61) | 15 (12.7) |
| | Home maker | - | - | 10 (16.1) | - | 10 (16.1) | - |
| | Student | 3 (4.8) | 1 (1.5) | 4 (6.4) | 1 (1.5) | 7 (11.2) | 2 (3.0) |
| | Unemployed | 3 (4.8) | 3 (4.7) | 9 (14.5) | 1 (1.5) | 12 (19.3) | 4 (6.2) |
| | Unknown (non-respondent) | 6 (9.6) | - | 8 (13.0) | - | 14 (22.6) | - |
| Present employment status | Employed | 6 (9.6) | 19 (30.1) | 1 (1.5) | 14 (22.2) | 7 (11.2) | 33 (52.3) |
| | Unemployed | 12 (19.3) | 10 (15.8) | 29 (46.7) | 20 (31.7) | 41 (66) | 30 (47.5) |
| | Occasionally going for work | - | - | - | - | - | - |
| | Student | - | - | - | - | - | - |
| | Unknown (non-respondent) | 6 (9.6) | - | 8 (13.0) | - | 14 (22.6) | - |
| Past employment status | Employed | 11 (17.7) | NA | 6 (9.6) | NA | 17 (27.3) | NA |
| | Unemployed | 7 (11.2) | NA | 23 (37.0) | NA | 30 (48.2) | NA |
| | Occasionally going for work | - | NA | 1 (1.5) | NA | 1 (1.5) | NA |
| | Student | - | NA | - | NA | - | NA |
| | Unknown (non-respondent) | 6 (9.6) | - | 8 (13.0) | - | 14 (22.6) | - |
| Below poverty line | Yes | 3 (4.8) | 1 (1.5) | 4 (6.4) | - | 7 (11.2) | 1 (1.5) |
| | No | 15 (24.1) | 28 (44.4) | 26 (41.9) | 34 (53.9) | 41 (66) | 62 (98.3) |
| | Non respondent | 6 (9.6) | - | 8 (13.0) | - | 14 (22.6) | - |

***Table 2. Distribution of Study Participants According to Socioeconomic Profile (N =125)***

| Comorbidities | | Sex: Male Cases (%) | Male Controls (%) | Female Cases (%) | Female Controls (%) | Total Cases (%) | Total Controls (%) | Odds Ratio (95 % CI), P Value |
|---|---|---|---|---|---|---|---|---|
| Diabetes mellitus | Present | 4 (6.4) | 1 (1.6) | 5 (8.0) | 0 | 9 (14.5) | 1 (1.6) | 14.308 (1.743 - 117.42) |
| | Absent | 14 (22.5) | 28 (44.4) | 25 (40.3) | 34 (53.9) | 39 (62.9) | 62 (98.4) | P = 0.0022 |
| Hypertension | Present | 0 | 1 (1.6) | 2 (3.2) | 0 | 2 (3.2) | 1 (1.6) | 2.696 (0.237 – 30.655) |
| | Absent | 18 (29.0) | 28 (44.4) | 28 (45.1) | 34 (53.9) | 46 (74.1) | 62 (98.4) | P = 0.8107 |
| Thyroid disease | Present | 0 | 0 | 4 (6.4) | 0 | 4 (6.4) | 0 | 12.843 (0.6739 - 244.76) |
| | Absent | 18 (29.0) | 29 (46.0) | 6 (9.6) | 34 (53.9) | 44 (70.9) | 63 (100) | P = 0.0325* |
| HIV | Present | 1 (1.61) | 0 | 0 | 0 | 1 (1.61) | 0 | 4.011 (0.1597 – 100.72) |
| | Absent | 17 (27.4) | 29 (46.0) | 30 (48.3) | 34 (53.9) | 47 (75.8) | 63 (100) | P = 0.4324* |
| Other disease | Present | 0 | 0 | 1 (1.61) | 0 | 1 (1.61) | 0 | 4.011 (0.1597 – 100.72) |
| | Absent | 18 (29.0) | 29 (46.0) | 29 (46.7) | 34 (53.9) | 47 (75.8) | 63 (100) | P = 0.4324* |

***Table 3. Distribution of Study Participants as per the Presence of Comorbidities***

*Fisher's exact test used

More cases reported comorbidities than controls, diabetes mellitus was reported by 14.5 % of cases and 1.6 % of the controls followed by hypertension reported by 3.2 % cases and 1.6 % controls. Cases were more likely to have a co-existent morbidity than control, especially diabetes mellitus (OR 14.308 CI - 1.743 - 117.42) and disorders of thyroid (OR 12.843 CI 0.6739 - 244.76). None of the females in control group had any comorbidities.

| Housing Environment | | Cases (%) | Controls (%) | Odds Ratio (95 % CI), P-Value |
|---|---|---|---|---|
| Housing | Pucca | 42 (67.7) | 55 (87.3) | 1.018 (0.3281 – 3.160) P = 1.000* |
| | Katcha | 3 (4.8) | 5 (7.9) | |
| | Mixed | 3 (4.8) | 3 (4.8) | |
| | Unknown | 14 (22.6) | - | |
| Overcrowding | Present | 6 (9.7) | 2 (3.2) | 4.357 (0.8382 – 22.648) P = 0.0744* |
| | Absent | 42 (67.7) | 61 (96.8) | |
| | Unknown | 14 (22.6) | - | |
| Ventilation | Adequate | 44 (71.0) | 63 (100) | 12.843 (0.6739 – 244.76) P = 0.0325* |
| | Inadequate | 4 (6.4) | 0 | |
| | Unknown | 14 (22.6) | - | |
| Indoor air pollution | Present | 1 (1.61) | 0 | 4.011 (0.159 – 100.72) P = 0.432* |
| | Absent | 47 (75.8) | 63 (100) | |
| | Unknown | 14 (22.6) | - | |

***Table 4. Distribution of Study Participants According to Housing Environment***

*Fisher's exact test used

On assessing the housing standards, it was found that more cases than controls lived in katcha houses and houses with overcrowding, inadequate ventilation and indoor air pollution. Cases were more likely to be living in houses with poor ventilation (OR - 12.843 CI - 0.6739 – 244.76 P = 0.0325). A known history of contact with a case of tuberculosis was given by 11.3 % MDR TB cases.

### Past TB Treatment History of Cases

While almost 60 % of cases gave no history of TB in the past, 12.9 % gave a history of pulmonary TB, 3.2 % had bone TB and 1.6 % had TB of the lymph nodes. Most of these episodes had been diagnosed in government hospitals and directly observed therapy short course (DOTS) centres. Adverse effects were reported by 11.3 % of cases among which nausea was most frequently reported (6.4 %) followed by joint pains (4.8 %), gastrointestinal upset (1.6 %) and dizziness (1.6 %). A history of skipped doses was given by 14.5 % of the cases. While 14.5 % cases reported having completed their treatment in the past, 3.2 % reported not completing treatment in the past.

### History of Present Episode of TB

Most of the cases reported with symptoms of cough and fever (12.9 %) and 17.7 % reported cough, fever and weight loss. Most (54 %) of the current cases of MDR TB were diagnosed in tertiary care hospitals, while 11.3 % were diagnosed in District Tuberculosis Centres. While 24.2 % of cases were able to start treatment immediately, 51.5 % of the cases reported a delay in diagnosis which led to a lag in initiation of treatment.

## DISCUSSION

This study found that most of the cases of MDR TB in Sikkim were young adults (15 to 25 years) who were slightly younger than the cases reported in other studies from South Asia like Atre et al. in Mumbai, and Rifat et al. in Bangladesh and Africa by Blackson et al. and Elduma et al.[7,8,9,10] TB is notorious for infecting mostly adults in their most productive years.[2] The cases had lower education levels, were mostly unemployed and had a high proportion who fell below poverty line, similar findings were observed and reported by Atre et al., Rifat et al. and Desissa et al.[7.8,11] Thus, poverty and unemployment might leave a person vulnerable to MDR TB.

While studies report higher proportion of cases being employed in services which may be considered as "lower services" this study reports that most of the cases were employed in skilled jobs or were students some of this difference may be attributed to a difference in categorisation, however nearly 16 % of the cases were housewives and similar finding was reported by Atre et al., thus this becomes a matter of concern with regards to women's health especially in India.[7] It was observed in the present study that more cases than controls lived in katcha houses and houses with overcrowding, inadequate ventilation and indoor air pollution which corroborates with findings reported by Atre et al.[7]

About 13 % of the cases were migrants, while this is lesser than that reported by Atre et al. (more than 50 % of cases were migrants), Edulma et al. reported that migrants are significantly associated with having MDR TB.[7,10] The adverse living conditions and the financial burdens faced by migrants may be attributed to this finding. Skipping of meals was reported by cases in the present study. Since poor nutrition is a known risk factor for development of TB, this could have compromised the nutritional status of cases making them vulnerable to infection.[2]

Diabetes mellitus was the commonest comorbidity reported by the cases in this study, about 14 % cases were known cases of diabetes. Diabetes is known to pose a serious risk for development of TB, and it has been reported that it may even increase the risk of drug resistance among those already infected with TB.[12] Studies conducted in various parts of the world have established that a past history of treatment for TB is an important risk factor for developing drug resistance, here it was observed that 18 % of cases reported a history of TB treatment in the past.[9,10,11] However, it must be noted that almost 60 % had no such history which raises concerns of primary drug resistant TB. More than half of the cases reported were diagnosed in a tertiary care level and more than half reported a delay in starting treatment. Htun et al. also reported a delay in beginning the treatment by almost 51 % cases in their study. The delay may be caused due to many factors but most importantly by a delay in the diagnosis itself.[13] Since MDR TB has poorer outcomes in comparison to drug sensitive TB this delay can adversely impact the outcome.

## CONCLUSIONS

Previous history of TB with history of relapse / failure, contact of MDR TB emerged as the most significant risk factors. This study shows that presence of comorbid conditions like diabetes & hypertension can be used to indicate higher risks of drug resistance in this setting. Information was obtained on why Sikkim being a small State with very less population and a good per capita expenditure in health has the highest proportion of MDR-TB in India.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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