ADDIS ABABA UNIVERSITY SCHOOL OF PUBLIC HEALTH

RISK FACTORS FOR MULTI DRUG_RESISTANT TUBERCULOSIS AMONG NEWLY DIAGNOSED MDR-TB PATIENTS OF ALL AFRICA LEPROSY, TUBERCULOSIS AND REHABILITATION TRAINING CENTRE (ALERT) HOSPITALS, ADDIS ABABA, ETHIOPIA 2020, A FACILITY BASED CASE CONTROL STUDY

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A RESEARCH PAPER (THESIS) TO BE SUBMITTED TO AAU,COLLEGE OF HEALTH SCIENCE, DEPARTMENT OF PUBLIC HEALTH IN THE PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTERS IN PUBLIC HEALTH

Addis Ababa

April, 2021

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ACRONYMS /ABBREVIATIONS

AA	Addis Ababa
ALERT	All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre
AOR	Adjusted Odds Ratio
CI	Confidence Interval
DST	Drug Susceptibility Testing
EDHS	Ethiopian Demographic and Health Survey
EHNRI	Ethiopia Health and Nutrition Research Institute
MDR-TB	Multi-Drug-Resistant Tuberculosis
M. tuberculosis	Mycobacterium Tuberculosis
SPSS	Software Packages for Social Sciences
WHO	World Health Organization

ABSTRACT

Background: Multi drug resistant tuberculosis (MDR-TB) is an emerging challenge for TB control programs globally. **Ethiopia** is among the 30 High TB, HIV and MDR-TB Burden Countries in the world. Development of drug resistance is hugely man-made problems resulting inadequate treatment due to suboptimal adherence, and continued transmission of resistant strains in the community. Updated knowledge of the associated factors of MDR-TB is so substantial to allocate resources, and to address prevention and control measures. Therefore, the objective of this study was to identify associated factors of multi-drug-resistant tuberculosis in among newly diagnosed patients and treated at ALERT Hospitals Addis Ababa, Ethiopia, between August 1 2020 and September 30 2020.

Method: A health facility based case-control study was conducted to assess socio demographic, behavioral and clinical risk factors using a structured questionnaire and clinical record reviewing. Analysis were performed using SPPS software and to identify association between dependent and explanatory variables logistic regression analysis were performed and statistically significant associations were described using odds ratio at 95%CI and P- value of < 0.05.

Result: A total of 120 respondents' (40 newly diagnosed MDR-TB cases and 80 drug susceptible pulmonary TB patients, control) were enrolled in this study. Number of rooms per household (AOR=3.61, 95% CI=1.2-10.6), history of previous treatment (AOR=12.77, 95% CI=4.2-38.6) and TB contact history (any type of TB) (AOR=7.62, 95% CI=2.3-25.4) was significantly associated with MDR TB infection.

Conclusion: This study revealed that having history of previous anti-TB treatment exposure, living in only one room house hold and having previous TB contact history were identified to be the determinants of MDR-TB infection.

In light of these findings, the strategies in controlling MDR-TB should come up with emphasize on peoples or patients having history of previous TB treatment, TB contact history and those living in houses with only one room (crowded places). Moreover, Implementation of adequate TB infection control practices at health facilities is importance.

1. INTRODUCTION

1.1 Background

Multi drug resistance tuberculosis (MDR-TB) is the TB strain with drug resistance to first line or second line TB drugs which is diagnosed with Drug-susceptibility testing(DST)(1). Detection of MDR/RR-TB requires bacteriological confirmation of TB and testing for drug resistance using rapid molecular tests, culture methods or sequencing technologies(2). Individuals with presumptive or confirmed diagnosis of Tuberculosis should be evaluated for risk of contracting drug resistant form of Tuberculosis. Every patient diagnosed to have tuberculosis should have susceptibility information at least for Rifampicin and preferably for isoniazid, using rapid molecular techniques such as X-pert test(3). In the interim, priority of screening using rapid DST tests should be given for those patients who carry medium to high risk for drug resistant TB acquiring. High risk group are patients with treatment failure of second course of TB treatment, treatment failure of New TB patient and TB patients who develop active TB following history of contact with a DR-TB patient. Medium risk group are TB patients in whom Tuberculosis is diagnosed after prior history of successful TB treatment (TB relapse), TB patient whose smear remains positive after two months of full TB treatment and TB patient who discontinued TB treatment for eight consecutive weeks after receiving for one or more months(4).

Isoniazid-resistant TB (Hr-TB) refers to Mycobacterium tuberculosis strains in which resistance to isoniazid and susceptibility to rifampicin. Rifampicin-resistant TB (RR-TB) strains are considered not to be susceptible to rifampicin on the basis of DST and, as a result, are eligible for treatment with MDR-TB regimens(5). Rifampicin-resistant TB strains may be susceptible or resistant to isoniazid (i.e. MDR-TB), or resistant to other first-line TB medicines (poly resistant) or second-line TB medicines (e.g. extensively drug-resistant [XDR]-TB). So MDR-TB and RR-TB cases are often grouped together as MDR/RR-TB(4).

Tuberculosis (TB) strains with drug resistance (DR-TB) are more difficult to treat than drug-susceptible ones, and threaten global progress towards the targets set by the End TB Strategy of the World Health Organization (WHO)(6). Treatment requires a course of second-line drugs for at least 9 months and up to 20 months, supported by counseling and monitoring for adverse events(7). There is thus a critical need for evidence-based policy recommendations on the treatment and care of patients with DR-TB, based on the most recent and comprehensive evidence available. A second-line TB medicine (or drug)is an agent reserved for the treatment of drug-resistant TB while First-line

TB medicines used to treat drug-susceptible TB. MDR-TB treatment with second line drug may have an intensive (injectable) phase, longer MDR-TB regimens and shorter MDR-TB regimen(5).

1.2 Statement of the problem

Tuberculosis (TB) still continues to be a big public health problem worldwide. It is the second leading cause of death from all infectious diseases globally. Tuberculosis kills an estimate of 1.3 million people every year worldwide (8). Multi-drug resistant tuberculosis (MDR-TB) has been framed by the World Health Organization as a pressing, global public health problem (9). Patients who suffer from TB that is resistant to at least rifampicin and isoniazid, two of the most important standard anti-TB drugs, are defined as MDR-TB patients (10). They have only a 60% chance of cure (11).

Global MDR-TB caused an estimated 600,000 new TB cases and 240,000 deaths in 2016 and MDR-TB accounts for 4.1% of all new TB cases and 19% of previously treated cases worldwide (12). The highest burden of MDR-TB has been reported to be in China, India, Russia, and South Africa, and those countries have > 60% of all cases worldwide (13). Furthermore, the MDR-TB prevalence has soaked up 47% of the expense for the response to anti-TB programs globally (14), and strained local health resources (15). These alarming data showed the urgent need for MDR-TB control.

In Africa, there was a report of 69,000 MDR-TB cases(16).The emergence of MDR-TB is linked to weak TB control programs and sub-optimal TB case management (17). This realization is more pronounced in Sub-Sahara Africa, due to its limited resources and shortage of trained TB health work force (18). Indeed, by 2016 only 18 out of the 46 Sub-Sahara Africa countries reported ever conducting a national MDR-TB survey, a major constraint to proper planning and to achieving the End TB Strategy targets (19).

MDR TB is also one of the most serious public health challenges in Ethiopia (20). Ethiopia is one of the 27 high MDR-TB countries; it is ranked 15th with more than 5000 estimated MDR-TB patients each year (3). The main new barrier that challenges the control of TB is high burden of multidrug-resistant TB (MDR-TB) (8). Furthermore, MDR-TB is mostly man-made, resistant TB strains can be acquired or new resistant TB strains can emerge due to different factors: previous, inadequate use of anti-TB drugs (15), inappropriate TB treatment (21), and poor adherence to anti-TB drugs, long-lasting illnesses, and previous TB treatment (22). Very recently, WHO concluded that people living with HIV are facing the emerging threats of drug resistant TB (23). Thus, MDR-TB can be minimized by making tight identification of its predictors (8). Therefore, it is quite important to identify the risk factors for the newly diagnosis of MDR-TB in ALERT Hospital.

1.3 Significance of the study

The aim of this case control study was to identify determinants for MDR-TB in a cohort of patients who has newly developed MDR-TB & on follow up in ALERT Hospital. so that the management of patients was also be strengthened through preventing these factors, alongside patient treatment which was a positive impact on successful treatment outcome, and decrease the burden of the disease as a whole, and also to explore further information related to risk factors associated with microbiologic confirmation of MDR-TB disease among newly diagnosis patients of having MDR TB and finally to suggest possible preventive measures.. More over researchers and academician was use this study for reference.

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2. LITERATURE REVIEW

2.1 Burden of MDR TB

In 2018, globally there were about half a million new cases of rifampicin-resistant TB (of which 78% had multi drug resistant TB). The three countries with the largest share of the global burden were India (27%), China (14%) and the Russian Federation (9%)(24). Globally, 4.1% of new TB cases and 19% of previously treated cases had multi drug resistant TB or rifampicin-resistant TB (MDR/RR-TB), with the highest proportions (>50% in previously treated cases) in countries of the former Soviet Union(25).There was some progress in testing, detection and treatment of MDR/RR-TB between 2017 and 2018. Globally in 2018, 51% of people with bacteriologically confirmed TB were tested for rifampicin resistance, up from 41% in 2017. A global total of 186 772 cases of MDR/RR-TB were detected and notified in 2018, up from 160 684 in 2017, and 156 071 cases were enrolled in treatment, up from 139 114 in 2017. Despite these improvements, the number of people enrolled in treatment in 2018 was equivalent to only one in three of the approximately half a million people who developed MDR/RR-TB in 2018. Closing this wide gap requires one or more of the following to be increased: detection of TB cases, the proportion of TB cases bacteriologically confirmed, coverage of testing for drug resistance among bacteriologically confirmed cases and coverage of treatment for those diagnosed with MDR/ RR-TB(25). The latest treatment outcome data for people with MDR/RR-TB show a global treatment success rate of 56%. Examples of high MDR-TB burden countries with better treatment success rates (>70%) are Bangladesh, Ethiopia, Kazakhstan and Myanmar(26).

Ethiopia is among the high TB, MDR-TB, and TB/HIV burden countries with an estimated 151 and 1.4 TB and MDR-TB cases per 100,000populationsrespectively. Based on the WHO 2019 global TB report, 0.71% of new TB cases and 16% of retreatment TB cases in Ethiopia were estimated to have MDR/RR-TB (WHO, 2019). In the same year, three XDR-TB cases were also reported(27).

The country's has expressed its commitment to accelerate the fight to end TB epidemic by 2035 by endorsing the new post-2015 Global "END TB strategy" and has already aligned the National TB Strategic Plan within the framework of National Health Sector Transformation Plan. The National End TB strategy aims to end the TB epidemic by reducing TB related deaths by 95% and by cutting incident TB cases by 90% between 2015 and 2035; and to ensure that no family is burdened with catastrophic expenses due to TB. Additional resistance to core second line drugs, i.e. fluoroquinolones and/or injectable, has been a recent phenomenon in Ethiopia requiring treatment with the newly introduced novel and repurposed TB drugs though estimation of the actual prevalence is not yet well known. In the face of lack of national capacity to perform universal DST

for all incident TB cases, the country is underperforming in ensuring early diagnosis and administering appropriate therapy(3). But currently, most WHO regions and many high TB burden countries including Ethiopia are not on track to reach milestones of the End TB Strategy(28).

A cross-sectional study was conducted in West Armachiho and Metema districts of Ethiopia in 2014 shows that the prevalence of confirmed TB resistant to Rifampicin and Isoniazid were (5.7 %). The overall prevalence of MDR-TB was 5.7 % (2.3 % among new cases and 13.9 % among previously treated cases). History of previous treatment (OR=7, P=0.025) was significantly associated risk factor for MDR-TB(29). The overall prevalence of MDR TB in all TB cases was estimated to be 1.4% as the study conducted in Ethiopia Addis Ababa showed(30).Also other systematic review of the literatures on prevalence of MDR-TB showed 0-46.3% and previous exposure to anti tuberculosis treatment was also the most common risk factor for MDR-TB in Ethiopia(31).

2.2. Determinants of MDR TB

2.1.1. Socio-demographic factors

Different studies at different places have showed an association with socio demographic variables and MDR TB. These variables are Age category, sex, educational status and number of rooms in residency. An age was ≤30 years were seven times more likely to have MDR-TB compared to those whose age was >30 years. [adjusted odds ratio [AOR]=7, 95% confidence interval [CI]: 2.4–21.07] as the study conducted in Addis Ababa(32). A study conducted in Ethiopia reveals that those respondents who have male sex have two times more at high risk of having MDR - TB than female (AOR: 2.7;95% CI: 1.1-6.5)(30,32)A study conducted in Ethiopia reveals that those respondents education above 10^{th} grade have (AOR: 3.7; 95% CI: 1.1- 12.1)(33).

Number of rooms in residence: A study conducted in Ethiopia , St petter hospital and Nekemte hospital reveal that those respondents living in a household with only one room were five times at higher risk of having MDR-TB than patients living in a household with two or more rooms (AOR=5.07, 95% CI:1.68–15.38) (32,34)

2.1.2. Behavioral factors

Behavior related factor like smoking alcohol drinking habit and History of imprisonment have showed association. A study conducted in Belarius and Sudan reveal that those respondents with history of smoking have significant association with MDR – TB with (OR: 1.5; 95% CI: 1.1–2.0), history of imprisonment (OR: 1.5; 95% CI: 1.1–2.0) and history of alcohol abuse (OR: 1.3; 95% CI: 1.0–1.8) showed association.(34, 35)**.**

2.1.3. Clinical risk factors

Clinical factors of the study participant like previous treatment exposure to anti TB, history of contact to TB patient, history of hospitalization, HIV status, Smear result at the time of diagnosis, Disclosure statue of the patient and Diabetes mellitus status of the patient. Study conducted in Addis Ababa reveal that Contact history with a known TB patient (adjusted odds ratio [AOR]: 1.9, 95% CI: 1.1–3.3)(36). HIV has been reported as a major factor, creating a fertile ground for the TB disease. Study conducted in Ethiopia, 2017, show that respondents who had HIV infection were three times more likely to have MDR-TB when compared to respondents who had no HIV infection (AOR=3.1, 95% CI: 1.02–9.40)(34,37)**.** A study conducted in Addis Ababa, in 2017 patients who had been hospitalized for TB management were 4 times more likely to have MDR-TB than drug susceptible TB (AOR: 4.4; 95% CI: 2.2–7.8).(36)

Smear result at the time of diagnosis shows that Sputum-smear positivity (AOR: 1.9, 95% CI: 1.1–3.4)**,** Patients who had co-morbid with diabetes were less likely to have MDR-TB than DS-TB (AOR: 0.2; 95% CI: 0.05–0.8) and patients who have social stigma have risk of developing MDR-TB (AOR: 5.2; 95% CI: 1.8–14.4)(32,34).Respondents who had previous history of treatment for TB were 21 times more likely to develop MDR-TB compared to those who had no previous history of TB treatment (AOR=21; 95% CI: 17.80–28.80) and most study have identified this variables as significant risk factors of MDR TB(3,28,31,33–37).

2.1.4 Conceptual framework

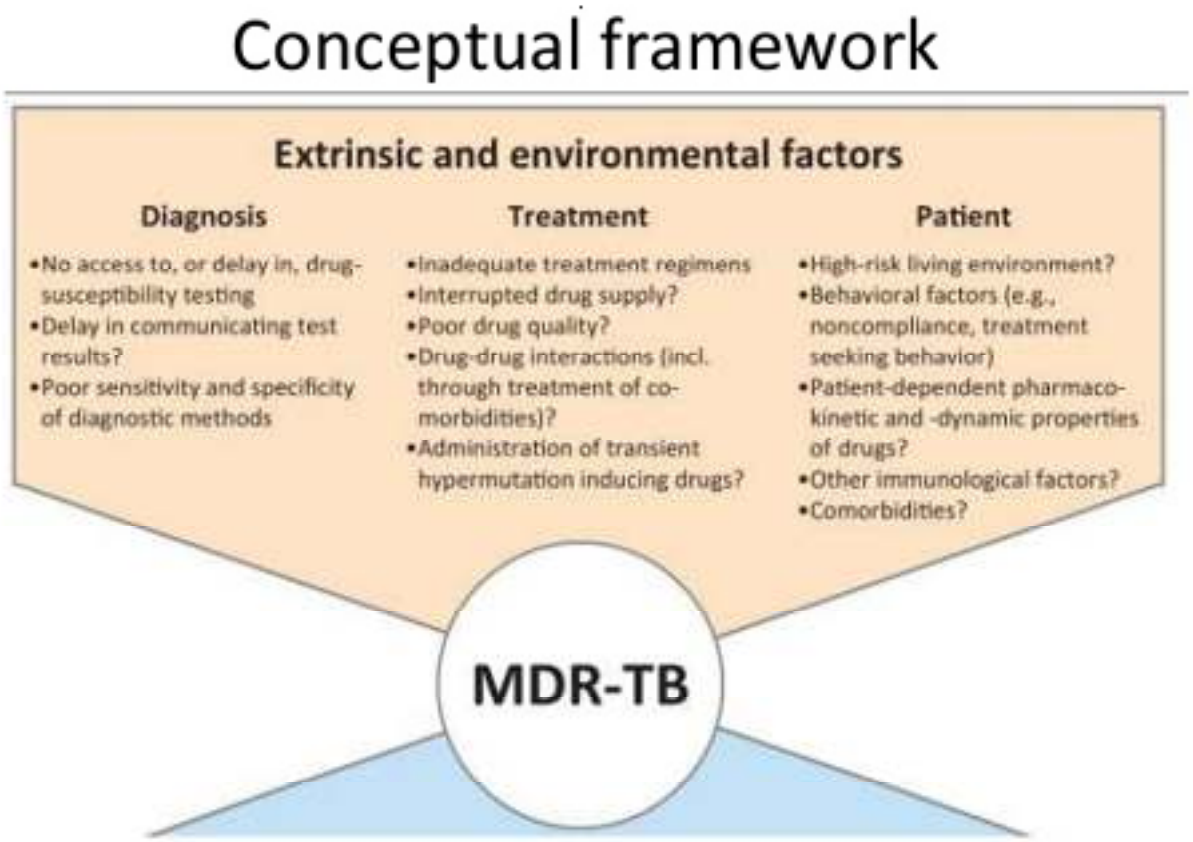

Figure 1 conceptual frame work for proximal risk factors of MDR TB (38)

3. OBJECTIVE

3.1 General Objective

The objective of this study was to identify factors associated for Multi-Drug resistant (MDR-TB) in ALERT Hospitals, Addis Ababa city, Ethiopia.

3.2 Specific objective

- To identify factors associated for newly diagnosis MDR TB patients among MDR TB patient in ALERT Hospitals, Addis Ababa city, Ethiopia.

4. METHODS AND MATERIALS

4.1. Study area and period

This health institution–based case control study was conducted in ALERT Hospital, Addis Ababa, Ethiopia, which is one of the only two MDR TB centers in Addis Ababa, mandated to provide second-line anti-TB treatment. The estimated population size of Addis Ababa is around 3.6million (Ethiopia Population 2019 (Demography, Maps and Graphs) World Population Review) www.world population review.com. Administratively, the city is divided into 10 sub-cities and further classified in to 117woreda (lowest government administrative unit).The study period of this study was from August to September 2020.

4.2. Study setting

Case were selected from ALERT Hospital, one of the two MDR-TB patient treatment centers in Addis Ababa, and control were selected from Akaki H/C, Ledeta/Beletshachew H/C, Kotebe H/C, Addis ketema H/C and Nefaseselke health centre.

4.3. Study design

Institution based case control.

4.4. Population

4.4.1. Source population

All MDR TB patients who were newly diagnosed to have resistant TB and who are on treatment during the study period were source of population for cases, while for controls were all Susceptible TB /pulmonary TB/ patients who have had an outcome of cure after treatment algorithm one.

4.4.2. Study population

This study considered sampled cases and controls as study population. Cases were newly diagnosed resistant MDR TB patients with culture positive Mycobacterium tuberculosis, resistant to at least isoniazid and rifampicin and have on treatment during the study period. Controls were all consecutive new pulmonary TB patients whose last first-line anti TB treatment outcome was cure or treatment completed but not resistant within the last six month prior to this study period.

4.4.3. Inclusion criteria

All new MDR-TB patients diagnosed by culture and DST at the EHNRI and who were on treatment at ALERT Hospital during the study period were consider as cases and included in the study. The control were a new pulmonary TB patient who was completed first line anti-TB treatment and declare cure or treatment completed using the WHO criteria and adopted by FMOH of treatment

outcomes(39). They were selected from 5 randomly selected health facilities in Addis Ababa from where MDR-TB cases were diagnosed and which are referral catchments to ALERT hospital for the second-line treatment centers. Controls were a patient who was finished first line TB treatment and their treatment outcomes was cure, but not resistant.

4.4.4. Exclusion criteria

MDR TB cases, for control patient who are transfer to other health unit, unknown treatment out comeand who were absent on call were excluded from this study. Children aged <5 years old, and patients whose permanent residence was out of Addis Ababa were also excluded from the study.

4.5. Sample size and sampling technique

4.5.1. Sample size determination

Sample size was calculated using Epi-info version 7 for sample size determination of unmatched case control study with the assumption of CI =95%, Power = 80%, Control to case ratio =2:1. Taking proportions of different variables from literature it was determined as follows,

Table 1: sample size determination of the study

Variable	Proportion of control exposed	AOR	Estimated sample size	Reference
HIV infection	40	3.1	120	St peter hospital Ethiopia(28)
Living in 1 room	38	5	66	
Age category ≤ 30 Compared to > 30	42	7	52	
Smoking history	45	7.4	54	Study in Nekemte hospital(36)

Finally sample size required for this study was 120 of which 80 are controls and 40 cases.

4.4.2. Sampling technique

All cases and controls randomly, fulfilling the inclusion criteria was included during the study period until the proposed sample size is achieved.

4.5. Data collection procedures

4.5.1. Study Variables

Dependent variable: Presence MDR-TB

Independent variables: includes

- **Socio-demographic factors:** Age, Sex, Religion, Educational status, marital status, Number of rooms in Residence, Monthly income, Family size, Occupation.
- **Behavioral factors:** History of imprisonment, Smoking habit, and Alcohol drinking habit
- **Clinical risk factors:** Known TB contact history, previous TB treatment history, history of hospitalization, Smear result at the time of diagnosis, HIV status of the patient, diabetes mellitus status of the patient, disclosure statue of the patient, previous history of use of anti-microbial drug- lower- than recommended doses, history of obstructive pulmonary disease(COPD), and history of psychiatric disorders.

4.5.2. Data collection

Data collection was performed by interviewer administered using semi-structured and pretested questionnaire adapted from different relevant literatures. Data collection tool prepared in English and translated in to local language Amharic for data collection and back to English to check its consistency. Seven nurses' data collectors and two BSc nurses supervisors were assigned to collect data. The questionnaire encompasses variables to assess socio demographic factors, behavioral factors, and clinical factors.

4.6. Operational definitions

Multidrug-resistant TB /MDR-TB: resistance to at least both isoniazid and rifampicin.

Resistance among new patients: resistance in patients who have never undergone anti-tuberculosis treatment or have taken anti-TB drugs for less than 1 month. These patients have been infected by other persons with resistant strains, Primary MDR-TB.

Resistance among retreated patients: resistance in patients who have undergone anti-tuberculosis treatment for ≥1 month. This generally includes treatment failures, relapses or patients who return to treatment after being lost to follow-up (LTFU). These patients may have developed resistant bacilli during treatment, or may have been primarily infected or re-infected by other persons with resistant bacilli.

Isoniazid-resistant TB (Hr-TB): Mycobacterium tuberculosis strains in which resistance to isoniazid and susceptibility to rifampicin.

Rifampicin-resistant TB (RR-TB): strains are considered not to be susceptible to rifampicin on the basis of DST and, as a result, are eligible for treatment with MDR-TB regimens.

Cases: Culture confirmed new MDR-TB patients referred from all locations of Addis Ababa and registered at All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre (ALERT) Hospitals.

Control: New pulmonary TB patients whose last first-line anti-TB treatment outcome was cured or treatment completed.

Cured: A pulmonary TB patient with bacteriological confirmed TB at the beginning of treatment who was smear- or culture- negative in the last month of treatment and on at least one previous occasion.

4.7. Data quality control

Training was given to the data collectors & supervisors on the objectives of the study, data collection process, data collection tool and interviewing approach. Before the actual data collection, Pre-test was performed on 5% of the total sample size in a health facility not included in the study and necessary corrections was taken accordingly. Finally the collected data was checked for completeness, consistency, accuracy and clarity on daily basis.

4.8. Data analysis procedure

The collected data was checked for completeness, coded and entered into a computer using Epi data version 7 and transferred to Statistical software for social sciences (SPSS) version 25 for analysis. Descriptive statistics like frequencies, percentage and proportion were computed. Bivariate and multivariable binary logistic regressions were carried out to identify determinant factors of MDR TB. Bivariate logistic regression was done and all explanatory variables with p value less than 0.2 in bivariate analysis were included into the final multivariate logistic regression model to identify the final associated variables. Then Variables with a p-value < 0.05 with 95% CI were considered to be statistically significant and taken as showing association described with Adjusted Odds Ratio (AOR). Data was presented by numbers, frequencies, tables, percentages for different variables.

4.9. Ethical considerations

Ethical clearance was obtained from Addis Ababa University School of Public Health Research Ethics Review Committee, Addis Ababa Health Bureau public health research and emergency management directorate and ALERT Hospital Research Ethics Review Committee. A formal letter was also submitted to all concerned bodies in the study area to obtain their co-operation in facilitating the study. The interviewers were explained the objective of the study to the study

participants and got informed consent prior to data collection. The respondents were told that they have the right to refuse or decline at any time of the interview without any form of prejudice if they desire so. The study participants were also explained that the confidentiality was assured and the information they give us will not be used for any other purpose than to the purpose mentioned in this study.

4.10. Result dissemination

The final report will be submitted to Addis Ababa University, School of Public Health campus graduate student program. The findings of the study will also be communicated to the study hospital and other relevant concerned bodies who are directly or indirectly working to improve the prevention and control strategies. An attempt would also be made to publish the study findings on a reputable journal.

5. RESULT

Socio demographic characteristics of respondents

A total of 120 respondents' (40 cases and 80 controls) were recruited in to this study of which all of them are the residents of Addis Ababa city (urban). Male sex accounts 77(64.2%) of total respondents, 53(66.3%) among controls and 24(60%) among cases. The minimum and maximum ages were 7 and 75 years respectively with mean age of 32.48(SD-12.5) years. The mean age among controls and cases were 32.3(SD-13.5) and 32.7(SD-10.1) respectively. The age category below 30 years accounts 69(57.5%) of total respondents, 47(58.8%) of controls and 22(55%) of cases. From total respondents private business occupation accounts 47 (39.2%) followed by 23 (19.2%) government employee. About 63(52.5%) from total respondents and 25(62.5%) among cases and 38(47.5%) among control live in houses with only one room (table 2).

Table 2 socio-demographic characteristics of respondents by study group, Addis Ababa, Ethiopia 2020

Variables	categories of variables	participant		Total
		Cases	controls	
Sex	Male	24(60.0)	53(66.3)	77(64.2)
	Female	16(40.0)	27(33.80	43(35.8)
age category	below 30 years	22(55.0)	47(58.8)	69(57.5)
	30 years and above	18(45.0)	33(41.3)	51(42.5)
Education	No schooling	4(10.0)	13(16.3)	17(14.2)
	Primary School	10(25.0)	11(13.8)	21(17.5)
	Secondary school	14(35.0)	23(28.8)	37(30.8)
	College and above	12(30.0)	33(41.3)	45(37.5)
Occupation	Daily Labourer	5(12.5)	15(18.8)	20(16.7)
	House Wife	3(7.5)	9(11.3)	12(10.0)
	Private business	18(45.0)	29(36.3)	47(39.2)
	Government employee	7(17.5)	16(20.0)	23(19.2)
	Others	7(17.5)	11(13.8)	18(15.0)
current marital status	married	21(52.5)	37(46.30	58(48.3)
	Other	19(47.5)	43(53.8)	62(51.7)
monthly income of the family	below 500	2(5.0)	3(3.8)	5(4.2)
	501 -1000 birr	6(15.0)	9(11.3)	15(12.5)
	above 1001 birr	32(80.0)	68(85.0)	100(83.3)
Room number	1 room only	25(62.5)	38(47.5)	63(52.5)
	2 and above room	15(37.5)	42(52.5)	57(47.5)
family size	1-3	28(70.0)	60(75.0)	88(73.3)
	Above 3	12(30.0)	20(25.0)	32(26.7)

Behavioral Characteristics of Respondents

From the total respondents about 25(20.8%), 12(30%) among cases and 13 (16.3%) among controls have smoking behavior of which about 22(88%) of them had smoked for five years and above. The prevalence of alcohol drinking behavior was 64 (53.3%) among total respondents, 19(47.5%) among cases and 45(56.3%) among controls. Only 9 (7.5%) respondents have had history of being in prison (Table 3).

Table 3 description of behavioral characteristics of respondents by study group, Addis Ababa, Ethiopia 2020

Variables	Category of variables	Participant		Total	Chi-square test
		Case	Control		
Smoking	Yes	12(30)	13(16.3)	25(20.8)	0.08
	N0	28(70)	67(83.8)	95(79.2	
Smoking duration	<= 5 years	5(41.7)	8(61.5)	13(52)	0.27
	6-10 years	4(33.3)	1(7.7)	5(20)	
	> 10 years	3(25)	4(30.8)	7(28)	
alcohol	Yes	19(47.5)	45(56.3)	64(53.3)	0.36
	No	21(52.5)	35(43.8)	56(46.7)	
Drinking habit	Occasionally	9(47.4)	25(55.6)	34(53.1)	1
	Every week	4(21.1)	10(22.2)	14(21.9)	
	Every day	3(15.8)	9(20)	12(18.8)	
	Stopped	3(15.8)	1(2.2)	4(6.3)	
Have you ever imprisoned	Yes	3(7.5)	6(7.5)	9(7.5)	1
	No	37(92.5)	74(92.5)	111(92.5)	

Description of clinical Characteristics of Respondents

The normal BMI of respondents is 34(85%) among cases, 60 (75%) among controls and 94(78.3%) among total while about 5(12.5%) are underweight among cases, 19(23.8%) among controls and 24(20%) among controls. About 26(65%) of cases have history of use of anti TB drugs for less than one month in the past and 12(15%) of controls have history of use of microbial drugs in the past. The

prevalence of HIV infection and diabetes mellitus among cases and controls are 4(10%), 15(18.8%) and 1(2.5%) and 2(2.5%) respectively (table 4).

Table 4 description of clinical characteristics of respondents by study group, Addis Ababa, Ethiopia 2020

Variables	categories of variable	participant		Total	Ch-square test
		case	control		
BMI	Over weight (25-29.9)	1(2.5)	1(1.3)	2(1.7)	0.32
	Normal (18.5-24.9	34(85.0)	60(75.0)	94(78.3)	
	Under weight (<18.5)	5(12.5)	19(23.8)	24(20.0)	
Previous history of use of microbial drug	Yes	26(65.0)	12(15.0)	38(31.7)	0.000
	No	14(35.0)	68(85.0)	82(68.3)	
HIV infection status	Reactive	4(10.0)	15(18.8)	19(15.8)	0.43
	Non-reactive	35(87.5)	64(80.0)	99(82.3)	
	Unknown	1(2.5)	1(1.3)	2(1.7)	
Diabetes mellitus status	Yes	1(2.5)	2(2.5)	3(2.5)	0.32
	No	10(25.0)	31(38.8)	41(34.2)	
	Unknown	29(72.5)	47(58.8)	76(63.3)	
TB contact history	Yes	15(37.5)	14(17.5)	29(24.2)	0.018
	No	25(62.5)	66(82.5)	91(75.8)	
Hospitalization history	Yes	9(22.5)	7(8.8)	16(13.3)	0.043
	No	31(77.5)	73(91.3)	104(86.7)	
TB sputum smear result	Negative	0	1(1.3)	1(0.8)	0.47
	Positive	40(100)	79(98.8)	119(99.2)	
Disclosure status	Disclosed	36(90.0)	72(90.0)	108(90.0)	1
	Did not disclose	4(10.0)	8(10.0)	12(10.0)	
COPD status	Yes	15(37.5)	21(26.3)	36(30.0)	0.20
	No	25(62.5)	59(73.8)	84(70.0)	
Psychiatric disorders status	Yes	5(12.5)	6(7.5)	11(9.2)	0.37
	No	35(87.5)	74(92.5)	109(90.8)	

Determinants of MDR TB

Determinants of MDR TB are presented in table 5 below. Those variables with P-value < =0.2 on Bivariate analysis and some important variables were entered to the multivariate Analysis. Multivariate logistic regression was done to identify their associations with MDR TB infection after

adjusted for socio-demographic and other related variables. Then those variables with P-value < =0.05 on multivariate analysis were considered as to be determinant factors for MDR TB infections (table 5). Variables like room number, educational status, TB contact history, antibiotic treatment history, smoking, hospitalization and presence of COPD were significant during binary logistic regression at p value 0.2. So they were included in multivariate analysis for final identification of determinant factors of MDR TB.

Table 5; Determinant factors of MDR TB infection at ALERT hospital, Addis Ababa, Ethiopia, 2020

Variables	Participant		COR (95% CI)	AOR (95% CI)
	Case N (%)	Control N (%)		
Number of rooms			**p-0.12**	**p-0.019**
in the house	25(62.5)	38(47.5)	1.84(0.8-4)	**3.61(1.2-10.6)***
1 room only	15(37.5)	42(52.5)	1	1
2 and above room				
Smoke			p-0.084	p-0.87
Yes	12(30)	13(16.3)	2.20(0.9-5.4)	1.2(0.3-3.8)
No	28(70)	67(83.8)	1	1
Previous history of use of microbial drug/Anti TB drug			p-0.000	**p-0.000**
Yes	26(65)	12(15)	10.52(4.3-25.7)	**12.77(4.2-38.6)***
No	14(35)	68(85)	1	1
TB contact history			p-0.018	**p-0.001**
Yes	15(37.5)	14(17.5)	2.82(1.2-6.6)	**7.62(2.3-25.4)***
No	25(62.5)	66(82.5)	1	1
Hospitalization			p-0.043	p-0.291
Yes	9(22.5)	7(8.8)	3.02(1.1-8.8)	2.12(0.5-8.6)
No	31(77.5)	73(91.3)	1	1
COPD			p-0.207	p-0.781
Yes	15(37.5)	21(26.3)	1.68(0.7-3.7)	0.86(0.3-2.5)
No	25(62.5)	59(73.8)	1	1
Education			p-0.28	p-0.330
No schooling	4(10)	13(16.3)	1.18(.3-4.3)	0.91(0.15,5.3)
Primary School	10(25)	11(13.8)	0.40(0.1-1.2)	0.27(0.06,1.1)
Secondary school	14(35)	23(28.8)	0.59(0.2-1.5)	0.68(0.2,2.2)
College and above	12(30)	33(41.3)	1	1

***significant at level of p<0.05**

Accordingly, room number of the house (AOR=3.61, 95% CI=1.2-10.6), previous history of use of antimicrobial/Anti TB drug (AOR=12.77, 95% CI=4.2-38.6) and TB contact history (AOR=7.62, 95% CI=2.3-25.4) was significantly associated with MDR TB infection. Respondents who live in households with only one room were 3.6 times more likely to develop MDR TB than patients living

in household having two or more rooms. Respondents who have previous history of use of antimicrobial drugs were 12.7 times more likely to have MDR TB compared to those who have no previous use of antimicrobial history. Respondents who have history of contact with TB patient were 7.6 times higher risk of developing MDR TB infection than those who have no history of contact with TB patient.

6. DISCUSSIONS

This study is primarily tried to access the determinants factors of MDR TB infection among the newly diagnosed MDR TB patients at ALERT hospital Addis Ababa Ethiopia. Accordingly there was identified that living in a house with only one room, previous treatment with anti TB drug for less than one month and history of contact with TB were strong predictors of MDR TB infection while variables like smoking history, age, sex, HIV infection and hospitalization history were not showed association. But some variables like smoking and hospitalization history were showed significant association during bivariate analysis and became no significant during multivariate analysis. Presence of HIV infection, age less than 30 years, smoking and hospitalization have showed association with MDRTB infection were showed association in other studies(27,28). Probably the difference could be due to the difference in study area and methodology.

This study revealed that living in household with only one room increases risk of acquiring MDR TB infection. Thus respondents who live in households with only one room were 3.6 times more likely to develop MDR TB than patients living in household having two or more rooms. This could be due to increased risk of acquiring resistant strains of TB causing agent in crowded places as the infected host releases the agent. This study is similar with the finding from the study conducted at St. Peter's TB Specialized Hospital in Addis Ababa of Ethiopia, indicated that patients living in a household with only one room were 5 times at higher risk of having MDR-TB than those living in a household with more than one room(32)**.** Similarly the study conducted in Oromia region Nekemte hospital shows that patients living in a household with only one room were 5.4 times at higher risk of having MDR-TB than those living in a household with more than one room(34).

This study also revealed that respondents who have previous history of use of antimicrobial/anti-TB/ drugs were 12.7 times more likely to have MDR TB compared to those who have no previous use of antimicrobial/anti-TB/ history.This antimicrobial drug mainly first line anti TB treatment where the person were treated or taken for less than one month improperly. This improper use is the result of actions including below optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of treatment which makes the TB causing agent to be resistant. In line to this as the prevalence of MDR TB increases globally and in low socioeconomic countries, the systematic review study in Ethiopia have showed the higher prevalence ranging 11-72% of MDR TB among retreated TB patients(9). As in other high TB-incidence setting, most MDR-TB patients initially undergo first-line TB treatment till they are considered treatment failures and have access to MDR-TB diagnostic services. The study conducted in St. Peter TB Specialized and All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre (ALERT) Hospitals, Addis Ababa Ethiopia showed that having history of previous TB treatment was about 12 times more common among cases

compared to controls(32). Similarly the finding of this study is consistent with the studies conducted elsewhere, in Ethiopia and Belarus(3,28,31,33–37).

The other determinant factor for MDR TB infection identified in this study were the previous history of contact with TB patient. Accordingly, respondents who have history of contact with TB patient were 7.6 times higher risk of developing MDR TB infection than those who have no history of contact with TB patient. This means the chance of having TB contact history among MDR TB cases were 7.6 times higher compared to non MDR TB cases. This finding was consistent with the study conducted in Addis Ababa, Ethiopia at St. Peter TB Specialized and All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre (ALERT) Hospitals, where those patients who had contact with known TB patients were about 2 times more likely to develop MDR-TB than non MDR TB cases (controls)(32). On the other hand this may show us delaying of diagnosis and treatment starting of MDR TB patients than non MDR TB patients due to sub-optimal availability of diagnostic and treatment services in low income countries like Ethiopia.

So this delaying of diagnosis will increases the duration of infectious period with low infection prevention practices and knowledges in the community will promote higher transmission of the diseases thus increasing its burden.

7. STRENGTH AND LIMITATION OF THE STUDY

The strength of this study is that the comparative nature of the study is helpful to compare groups with appropriate sample size for both groups. This study has some limitations like the nature of this study was a case control study design, which is difficulties to establish temporal causality and is prone to recall bias. However, this is the most applicable study design in this case. In addition to this, the study is unable to generalize to the population because of the health-facility nature of this study. I believe these findings are good in providing future directions, despite these limitations.

8.CONCLUSSION

In conclusion this study revealed that having history of previous anti-TB treatment exposure, living in only one room house hold and having previous TB contact history were identified to be the determinants of MDR-TB infection in the study setting. Respondents who live in households with only one room were 3.6 times more likely to develop MDR TB than patients living in household having two or more rooms. Respondents who have previous history of use of antimicrobial drugs were 12.7 times more likely to have MDR TB compared to those who have no previous use of antimicrobial history. Respondents who have history of contact with TB patient were 7.6 times higher risk of developing MDR TB infection than those who have no history of contact with TB patient.

9.RECOMMENDATION

There is a need to support existing and come up with new policies TB control program targeting especially on peoples or patients having history of previous anti-TB exposure, TB contact history and number of room at house hold level. Also policy on proper use of antibiotic (correct regimen and complete dose of drug) to the patient should be improved in order to decrease resistant to antimicrobial drug. Health care workers should prescribe correct drug regimen, follow drug adherence of the patients that started treatment and Implementation of adequate TB infection control practices at health facilities is very important.

Similarly community awareness should be given on the way of decreasing the MDR TB disease transmission or burden like early diagnose or screening and on good drug adherence. The result also implied that awareness on the mode of transmission has to be provided for people living in a household with only one room whenever there are patients living together, by which we can decrease transmission of drug resistance strains of TB.

Other studies should be repeated with other study methods like follow up study which may strength and identify other determinants of MDR TB than factors described here.

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38. For conceptual framework.

11. APPENDIX

Appendix I: Information Sheet

Title of the research Project: Determinants of Multidrug-Resistant Tuberculosis among newly MDR TB patients, in All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre (ALERT) Hospitals, Addis Ababa, Ethiopia 2019.A Facility Based Case Control Study

Principal Investigator: Tsige Kidanemariam (BSc.)

Advisor: Dr Eshetu Girma

Name of the organization: Addis Ababa University, School of Public Health

Addis Ababa

Sponsor: _ self-sponsored

Introduction

My name is Tsige Ki/Mariam-and I am a student at Addis Ababa University School of Public Health offer masters' degree. I am doing a research on determinants of Multidrug-Resistant Tuberculosis as a part of my study course. I am going to give you information and invite you to be part of this research. Before you decide to be part of this research you can talk to me if there is anything you are not comfortable with about the research. If there is any word that you don't understand while I am giving the information, please stop me and ask me, I will explain to you.

Purpose of the Research

The aim of the study is to assess determinants of Multidrug-Resistant Tuberculosis. Many literatures in various parts of the world including Ethiopia state the occurrence of MDR-TB is mainly attributable to human error, although genetic factors are also believed to contribute to a certain extent. Therefore this study aims at assessing determinants of factors leading to development of drug resistant need to be understood to develop/design appropriate control strategies for national program.

Voluntary participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive as any member of this community will continue and nothing will change. If you choose not to participate in this research, you will be offered all the services that are routinely offered. You may change your mind later and stop participating even if you agreed earlier.

Confidentiality

The information that is collected for this research will be kept confidential. It will be stored in a file using codes, without your name. And it will not be exposed to anyone. In addition it will be used only for this particular research but no other purposes.

Benefits

Your participation in this research may not directly provide you a certain benefit as an individual. But it helps us in assessing determinants of Multidrug-Resistant Tuberculosis.

Risks and Side effects

There are no side effects and known risks related with this kind of research so far. The only discomfort you might feel will be giving us your precious time for interview which is about 20 minutes.

Who to contact

This is research reviewed and approved by Addis Ababa University School of Public Health Ethical Review Committee. If you wish to ask questions now or later you can use the contact addresses below.

1. Tsige Ki/Mariam Mobile: 0911367429
   E-mail: kimariamtsige@gmail.com

2. Dr.EshetuGirma: E-mail:yanetushetu@gmail.com
   Mobile: 0910818859

Appendix II: Informed consent

Greeting:

My name is _____. I am here to collect information from you.

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive as any member of this community will continue and nothing will change. Any information you give will be kept confidential. Your participation in this research may not directly provide you a certain benefit as an individual. There are no side effects and known risks related with this kind of research so far and it takes only about 20 minutes of participation.

Up to now you have been given all information that I feel you should know regarding this research project that you are being asked to participate in. I think you have understood the issues in detail. Thank you for your cooperation and listening!!!

Are you willing to participate?

Yes ☐ continue

No ☐ (stop the interview)

Name of Data collector_____ date collected _____ Signature _____

Name of Supervisor _____ Signature _____

Appendix III: Questionnaire

Table 7 questionnaire for the study

	SECTION I. SOCIO DEMOGRAPHIC VARIABLES			
S.N	Question	Response	Option	Skip
101	Age	----------years		
102	Sex	Male..... 1 Female 2		
103	Religion	Muslim……	1	
		Orthodox……	2	
		Protestant……	3	
		Other specify……	4	
104	Educational	No schooling……1 Primary school----------.2 Secondary school--------- -3 College and above -------- 4		
105	Occupational	Farmers & day labourers.....1 House wife.....2 Private business ……3 Government employee----4 Others(specify)----------5		
106	Current marital status	Married……..1 Separate----------2 Divorced----------3 Never married---------4		
107	Number of rooms in residence	1.....1 2-3.....2 4-5.....3 5+.....4		
108	Family size	1-3 ..... 1 4-6 ..... 2 7-11.....3		
109	BMI	Over weight (25-29.9)…….. 1 Normal (18.5-24.9) ……. 2		

		Under weight (<18.5) ……. 3	
110	Family monthly income	----------	
Section 2 – Behavioral factors			
201	Have you ever smoke	Yes …….. 1 No..... 2	
	If the answer is "Yes" How long you smoke	3 years ……. 1 5 years ……..…… 2 10 years ……... 3 >10 years ……. 4	
202	Have you ever drink alcohol	Yes ……..1 No 2	
	If the answer is "Yes" drinking habit	Occasionally …… 1 Every week …….. 2 Every day …… 3 Stopped ……. . 4	
203	Have you ever imprisoned	Yes .....1 No …….. 2	
Section 3 – Clinical risk factors			
301	Previous history of use of microbial drug lower-than – recommended doses	Yes .....1 No 2	
302	HIV status of the patient	Unknown.....1 Reactive.....,, 2 Non-reactive.....3	
303	Diabetes mellitus status of the patient	Unknown.....0 Yes ..... 1 No 2	

304	Known TB contact history	Yes.....1 No..... 2	
305	History of hospitalization	Yes----------1 No----------2	
306	Smear result at the time of diagnosis	Negative ----------1 Positive ----------2	
307	Disclosure statue of the patient	Disclosed.....1 Did not disclose.....2	
308	History of chronic obstructive pulmonary disease(OCPD)	Yes……1 No…….2	
309	History of psychiatric disorders	Yes……..1 No…….2	

THANK U FOR YOUR PARTICIPATION IN THE STUDY!!!