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Research Paper

DETERMINATION OF MAJOR FACTORS PREDICTING MDRTB AMONG PRESUMPTIVE MDRTB CASES IN PLATEAU STATE – NIGERIA

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Abstract

Introduction: A retrospective cohort study was carried out to determine **of** major factors predicting MDRTB Among presumptive MDRTB cases in Plateau State – Nigeria, using a structured questionnaire and medical information abstracted from the medical records of patients. **Methods:** Smear positive and negative patients between ages 15 and 75 years with presumptive cases of MDRTB were sampled for this study. The mean ages of the respondents were 36.89 ± 10.40 for males and 31.89 ±12.81 for females. They were either new TB cases or retreatment cases. Sputum samples were inoculated on Lowenstein Jensen medium and incubated at 37^{o}C for 8 weeks. Cultures were examined for mycobacterial growth, isolates were identified by Ziehl Neelson technique and SD bioline MTB Ag. *Mycobacterium tuberculosis* isolates were subjected to drug susceptibility testing to first-line anti Tuberculosis Drugs by indirect agar proportion method according to standard conventional mycobacterial procedures. Regression analyses were performed to determine the association of variables with MDRTB and those significant variables in the bivariate analysis were subjected to multivariate logistic regression to identify independent determinants of MDRTB. Statistical significance was declared at p-value less than or equal to 0.05. **Results:** The result indicated that there was a high prevalence of MDRTB among previous treated TB cases 61 (36.5%) compared to the new cases 5(7.7%). The result also showed that history contact with an infected TB patient has high prevalence of MDRTB 47 (33.8%) compared to those that did not had contact 19(13.7%). There was a statistically significant difference between history of contact with TB patient and MDRTB. **Conclusions:** The study discovered that the major potential determinant factors for MDRTB in the study area were contact with TB patient and previous history of TB treatment. Contact with TB patients was independently associated with MDRTB (p.> 0.05, OR: 1.992; CI: 2.05 - 7.09) and that patients who had contact with TB patients are 7 times more likely to be

infected with MDRTB compared to those who had no contact. Also, previous TB treatment was independently associated (P > 0.05; OR: 6.906; CI: 2.63 -18.10) with MDRTB and that patients who had previous history of TB treatment were 8 times more likely to acquire MDRTB than treatment naïve cases.
Key words: Resistance, Factors, Multiple, Drug, Mycobacterium, Tuberculosis, Presumptive.

INTRODUCTION

Drug -resistant TB is presumed to be a man-made problem culminating from consequences of individual or combined factors which are related to management of TB treatment and control program. Behavioral and environmental factors, economic status, and poor infection control practices have also been identified as major contributing factors to the occurrence and spread of MDR-TB. The resurgence of TB in Nigeria has been attributed to HIV epidemic, poverty and drug resistance. MDR-TB is caused by the transmission of multi-drug resistant *Mycobacterium tuberculosis* strains in new cases, or the selection of single drug-resistant strains induced by previous treatment (1).

The emergence of MDR-TB has become a threat to public health across the globe and Nigeria in particular, with high prevalence rate of HIV/AIDS which tends to aggravate the situation. The aim of this study was to determine the major predictors of MDR-TB in Plateau State, North- Central Nigeria. Most cases of MDR-TB and XDRTB remained poorly detected due to insufficient laboratory infrastructure for diagnosis especially in a vast majority of clinical settings in the developing world where culture and drug susceptibility testing (DST) are either not available or inadequate. Delay in the diagnosis of drug-resistant TB due to cumbersome and time-consuming culture and DST techniques in poor setting has contributed to ongoing transmission with the major consequences of majority of patients dying while awaiting results of diagnostic tests.

The main barrier that challenges the control of TB is a high burden of multidrug resistant TB (MDRTB). MDRTB can be minimized by making right identification of its predictors (2). The major contributing factor identified for the spread of MDRTB is poor infection control (2). In 2008, there were 440,000 new MDRTB cases and 150,000 deaths worldwide (3). MDRTB kills an estimated 110,000 individuals every year and nearly half a million new cases of MDRTB emerge every year. Among the newly emerging MDRTB cases, only 3% get serious treatment globally (4).

The emergence of MDRTB has become a threat to global health and Nigeria in particular. The study is a retrospective cohort study conducted at PSSH and JUTH with analysis performed at the Zankli research center, Bingham University Teaching Hospital. To establish major predictors of MDR TB. Presumptive MDR TB patients were interviewed using structured questionnaires. Unavailable information /data were obtained from their medical records. *M. tuberculosis* isolates from 139 MDRTB patients were tested for susceptibility to first-line anti-TB drugs using the standard proportion method. The study subjects are made up of new case TB and previously treated case TB who were presumptive MDRTB patients referred to PSSH and JUTH TB centers during the study period (2015-2017).

MATERIALS AND METHODOLOGY

Interviews were conducted with the study participants using a pretested structured questionnaire. Clinical records and other information were extracted from the medical record files. The questionnaires encompassed variables to assess socio-demographic factors, clinical factors and social and behavioral factors. The data from cases were collected in the inpatient ward for admitted patients, through extraction (abstraction) and during DOTs clinic for out-patients.

The information included demographic and epidemiological data (age, sex, tribe, residence, senatorial district), clinical data (history of TB treatment, treatment outcome, HIV status) and bacteriologic data (results of sputum smear test for AFB). Patients were classified as new if they had never been treated for TB for < 4 weeks, and as previously treated if they had ever been treated for TB or receiving anti TB drugs for ≥4 weeks. The study protocol conformed to the national guidelines for epidemiologic research.

Smear positive new cases, and smear positive and negative previously treated case patients between ages 15 and 75 years, with presumptive cases of MDR TB were sampled for this study. New TB case were either on anti-tuberculosis drugs (ATD) or not, Cat II failure, Cat I failure and retreatment cases (failure, relapse, interrupted, return after default) were the different categories of TB patients studied

This include new cases and retreatment cases (failure, relapse and default). For the new cases they were all smear positive while for retreatment they were being queried for treatment failure, default or relapse cases either were smear negative or positive. The study proceeded with cases that were TB patients with culture positive

Mycobacterium tuberculosis, resistant to at least isoniazid and rifampin. Controls were culture positive mycobacterium susceptible to anti- TB drugs.

Sputum smear examination was performed at the TB Diagnostic centers on 2 sputum specimens from each patient, collected during 2 consecutive days, by using Ziehl- Neelson method. A smear positive case patient was defined by ≥1 positive smear result with ≥1 acid- fast bacilli per 100 high power microscopic fields, as recommended by WHO. Smear- positive case- patients were asked to produce an extra on- the- spot sputum sample, which was stored in a refrigerator (4^{o}c) until transported in cold boxes to the National Reference Centre for mycobacteria at the Bingham University Abuja for culture, identification and DST. Specimens were transported weekly.

For cultures, samples were placed into 2 solid media (Lowenstein – Jensen) one containing glycerol and the other pyruvate. *M. tuberculosis* was identified by using ZN, SD- Bioline MTB64 TB Ag screening kit. Drug susceptibility test of first- line anti TB drugs (i.e. rifampin, isoniazid, streptomycin and ethambutol) was performed on all positive culture samples by the indirect proportion method on LJ Medium.

Statistical Data Analysis

Social demographic and clinical data of presumptive MDR-TB patients was extracted from the questionnaires and other information abstracted from medical records of patients in the MDR-TB clinic/ward in JUTH. Data were entered and analyzed using statistical package for Social Sciences (SPSS) for windows version 23 (Chicago Illinois) used as an add-in in Microsoft Excel. Descriptive statistical techniques were used to obtain summary values for cases. Bivariate analysis was performed to identify the crude association between dependent and independent variables. The dependent variables were TB occurrence, Drug resistance and presence of MDR-TB and the independent variables include different socio demographic, environmental (socio-economic status), clinical issues, demographic and behavioral (behavior related) variables. Statistical significance was determined using $P< 0.05$ as a cut-off point and odds ratio was used to see the strength of association.

Those variables which showed significant association in bivariate analysis were entered in a logistic regression procedure for multi-variable logistic analysis, in order to assess the independent predictors of MDR-TB among the study participants. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated to evaluate the

magnitude of association between risk factors and TB occurrence, Drug resistance, MDR-TB.

RESULTS

Analysis of demographic and epidemiological factors associated with MDRTB are as showed in Table 1. Multiple drug resistance was found more (28.1%) in males than females (19.4%). No significant difference (P< 0.05) was found between gender and MDRTB infection. In relation to age, MDRTB was found to be higher (15.8%) in age group 27-37 years. There was no significant statistical association (P< 0.050) between age group and MDRTB infection. Considering tribe as a factor in MDRTB infection, it was discovered that MDRTB was more common (12.9%) among the other tribes (minority ethnic groups) than the majority tribes of Berom, Tarok, Mwaghavul, Goemai and Ngas. There was no significant statistical association (P< 0.05) between tribe and MDRTB.

Result of type of residence in regard to MDRTB infection as showed in Table 1 indicated that respondents in the urban area had the highest occurrence (20.1%) of MDRTB as compared with rural dwellers who had 17.9%. Also, the type of residence (urban or rural) showed no significant statistical association (P>0.05) between residence type and MDRTB.

Analysis of clinical and behavioral factors associated with multiple drug resistance are as shown in table 2 below. The analysis indicated that respondents with history of previous tb treatment had the highest rate of multiple drug resistance (43.9%) when compared to their counterparts with new cases (naive). Multiple drug resistance was found to be significantly (p=0.001) associated with previous tb treatment than those with new cases. In relation to contact with tb patients results indicated that those who had contact with tb patients (MDRTB rate 33.8%) were significantly associated with multiple drug resistance (p=0.042) when compared to those that did not have any contact.

In relation to multiple drug resistance among those who were MDRTB negative, 33.1% had MDRTB; those who were positive for HIV, 10.1% had MDRTB. There was no significant difference (P=0.821) between MDRTB infection and HIV status of an individual. With regard to smear result, it was discovered that respondents who were

smear positive had MDRTB prevalence of 35.3% while those who were negative had 12.2% MDRTB cases. It was also not statistically significant (P=0.694).

Table 3 showed the analysis of socio-economic and behavioral factors associated with MDRTB. The result revealed that multiple drug resistance was found more (28.1%) in married than divorced (2.2%) and singles (17.3%). No significant difference was found (P=0.05). Also, MDRTB was found to be more in unemployed (34.4%) than in employed respondents (15.1%). This was statistically insignificant(P=0.80) and therefore no association between MDRTB infection and employment status.

Results according to income found that MDRTB was higher (32.4%) among respondents with lower income than those with higher income (15.1%). There was no significant statistical association (P=0.82) between income and MDRTB infection. Analysis of religion with regard to MDRTB showed that the respondents who were of Christians religion had more TB (35.3%) when compared with their Muslims counterparts who had MDRTB rate of 11.5%. There was no significant statistical difference (P= 0.65) between religion and MDRTB infection. Considering smoking as a risk factor, those who do not consume alcohol had more cases of MDRTB (41,7%) than non-smokers (5.8%). Also, those who do not consume alcohol had more cases of MDRTB (41.7%) compared to consumers who had (5.8%).

All variables which had shown statistically significant association during the bivariate analysis such as previous TB treatment and contact with TB patients were collectively entered in the multivariable analysis to determine factors associated with the development of multiple drug resistance TB (MDRTB) as showed in Table 4. In the multivariate logistic regression analysis, two variables were found to be independently predictors of MDRTB after controlling possible confounders. Respondents who had previous history of TB treatment (OR =6.906; CI: 2.63 – 18.13; P < 0.05) were about seven times more likely to develop MDRTB when compared with those that were not previously treated. Also, respondents who had contact with tuberculosis patients were about twice more likely to develop mdrtb when compared with those that did not have contact with TB patients (OR= 1.99; CI:1.019 – 3.89).

Table 1
Demographic and Epidemiological Factors Associated with TB Occurrence, Drug Resistance and MDRTB among Patients in Plateau State, Nigeria.

Variables	Occurrence N(%)	P	Drug resistance N(%)	P	MDRTB N(%)	P
Gender						
Male	93(40.1)	0.477	61(43.9)	0.551	39(28.1)	0.227
Female	46(19.8)		36(25.9)		27(19.4)	
Age group						
≤26	35(15.1)	0.290	23(16.5)	0.602	16(11.5)	0.341
27-37	44(19.0)		33(23.7)		22(15.8)	
38-48	39(16.8)		26(18.7)		16(11.5)	
>48	21(9.1)		15(10.8)		12(8.6)	
Tribe						
Berom	36(15.5)	0.224	22(15.8)		14(10.1)	
Goemai	6(2.6)		4(2.9)	0.198	4(2.9)	0.319
Hausa/Fulani	38(16.4)		26(18.7)		16(11.5)	
Mwaghavul	13(9.4)		11(7.9)		8(5.8)	
Ngas	6(2.6)		2(1.4)		0(0.0)	
Tarok	5(2.2)		5(3.6)		3(2.2)	
Unknown	8(3.4)		6(4.3)		3(2.2)	
Others	27(11.6)		21(15.1)		18(12.9)	
Type of residence						
Urban	66(28.4)	0.059	42(30.2)	0.174	28(20.1)	0.271
Rural	45(19.4)		37(26.6)		25(17.9)	
Unknown	28(12.1)		18(12.9)		13(9.4)	
Region of residence						
Central	24(10.3)	0.063	17(12.2)	0.519	11(7.9)	0.727
Northern	72(51.8)		49(35.3)		34(24.5)	
Southern	13(5.6)		11(7.9)		7(5.0)	
Unknown	30(12.9)		20(14.4)		14(10.1)	

Table 2
Clinical and Bacterial Factors Associated with TB Occurrence, Drug Resistance and MDRTB among Patients in Plateau State, Nigeria.

Variables	Occurrence N(%)	P	Drug resistance N(%)	P	MDRTB N(%)	P
Treatment history						
New cases	26(11.2)	0.001	13(20.0)	0.001	5(3.6)	0.001
Previously treated	113(48.7)		84(50.3)		61(43.9)	
Contact with TB patients						
No	28(12.1)	0.958	22(15.8)	0.437	19(13.7)	0.042
Yes	111(47.8)		75(53.9)		47(33.8)	
HIV status						
Negative	111(47.8)	0.008	71(51.1)	0.960	46(33.1)	0.821
Positive	20(8.6)		19(13.7)		14(10.1)	
Unknown	8(3.4)		7(5.0)		6(4.3)	
Smear status						
Negative	28(43.8)	0.002	25(17.9)	0.600	17(12.2)	0.694
Positive	111(66.1)		72(51.8)		49(35.3)	

Table 3
Socio-economic and Behavioral Factors Associated with TB Occurrence, Drug Resistance and MDRTB among Patients in Plateau State, Nigeria.

Variables	Occurrence N(%)	P	Drug resistance N(%)	P	MDRTB N(%)	P
Marital status						
Single	54(23.3)	0.981	36(25.9)	0.449	24(17.3)	0.754
Married	80(57.6)		56(40.3)		39(28.1)	
Divorced	5(2.2)		5(3.6)		3(2.2)	
Employment status						
No	97(41.8)	0.876	63(45.3)	0.213	45(32.4)	0.800
Yes	42(18.1)		34(24.5)		21(15.1)	
Income						
<10,000	97(34.1)	0.833	63(45.3)	0.226	45(32.4)	0.822
≥10,000	42(18.1)		34(24.5)		21(15.1)	
Education status						
Illiterate	52(22.4)	0.421	36(25.9)	0.633	25(17.9)	0.611
Literate	87(37.5)		61(43.9)		41(29.5)	
Religion						
Christianity	96(41.4)	0.256	69(49.6)	0.857	49(35.3)	0.652
Islam	39(16.8)		26(18.7)		16(11.5)	
Unknown	4(1.7)		2(1.4)		1(0.7)	
Smoking						
No	121(52.2)	0.192	84(60.4)	0.274	58(41.7)	0.677
Yes	18(7.6)		13(9.4)		8(5.8)	
Alcohol consumption						
No	116(50)	0.216	83(59.7)	0.938	58(41.7)	0.563
Yes	23(9.9)		14(10.1)		8(5.8)	

Table 4
Factors Associated with the Development of Multiple Drug Resistance TB (MDRTB) - Multivariate

Characteristics	OR	95% C. I.		P
		Lower limit	Upper limit	
Contact with TB patient				
Yes	1.992	1.019	3.894	0.044
No	1.0			
Treatment history				
Previously Treated Case	6.906	2.631	18.129	0.001
New case	1.0			

OR – Odd Ratio; CI Confidence Interval

DISCUSSION

Analysis of demographic and epidemiological factors associated with MDRTB found that more males had MDR TB when compared to their female counterparts. No significant difference was found between gender and MDR TB infection. This result coincided with that of Sagwa et al. (4), reported higher percentage of MDR-TB in males and low in females. Also, this result coincided with Delgado et al. (5), who reported that the percentage of MDR TB in males was 76% and that of females was 24%. Tuba et al. (6) studied anti-tuberculosis drug resistance in South-East of Turkey and found that males were more than females. Our study did not observe any significant difference between gender and MDR-TB compared with studies in Georgia which revealed that women were at higher risk of MDR-TB compared with men (7). The reason canvassed by the study was that the role of women as care givers may have predisposed them to developing MDR-TB, as they have longer contact with sick MDR-TB patients than men.

In relation to age, MDRTB was found to be higher in age group 27-37 years. There was no significant statistical association between age group and MDRTB infection. The age group 27-37 years had higher incidences of MDR TB than older age of above 48 years. The younger age of the patients could be a possible risk factor for MDR TB compared to Non-MDR TB patients. There was no significant difference in the age of patients affected with MDRTB and Non- MDRTB groups. Similar finding was obtained by Elmi et al. (8) where they found young age (25-44 years) to be associated with MDRTB patients. The finding in this study is consistent with that of Jamil et al. (9) who in a cross- sectional study in Allahabad, India, found that MDRTB was more common in 26-45 years of age group.

Considering tribe as a factor in MDRTB infection, it was discovered that MDRTB was more among the other tribe (minority ethnic groups) than those in majority tribes. There was no significant statistical association between tribe and MDRTB. The result of the type of residence in regard to MDRTB infection revealed that respondents in the urban area had higher occurrence of MDRTB as compared to rural dwellers. There was no significant statistical association between residence and MDRTB.

The analysis of clinical and bacteriological factors indicated that respondents with history of previous TB treatment had the highest rate of MDRTB in comparison to their naïve counterparts. This could be associated to the fact that as susceptible *M tuberculosis* are being killed during therapy, resistant mutants are been selected and

proliferates leading to MDR M. tuberculosis. The report of this study is consistent with surveys conducted in several WHO centers around the world. Suarez et al, (10) found that previous TB treatment have been widely recognized as the strongest risk factor for the development of MDRTB.

In the same vein, the respondents who had early contact with TB patients were significantly associated with multiple drug resistance when compared to those that did not have any contact. The high rate of MDRTB among respondents with history of contact with TB patients is an indication that MDRTB is easily transmitted through contact than drug susceptible *M. tuberculosis.*

Multivariate logistic regression analysis of factors associated with the development of multiple drug resistance to tuberculosis (MDRTB) showed that respondents who had contact with tuberculosis patients were about twice more likely to develop MDRTB when compared with those that did not have contact with TB patients (OR=1.992, CI:1.019 – 3.894). Those with previous treatment history were about seven times more likely to develop MDRTB in relation to those with new cases (OR= 6.906, CI: 2.831 – 18.129). The prevalence of infection among contacts of MDRTB cases is similar to the prevalence among contacts of cases without MDRTB (11). The report of this study corroborated the work of Jamil et al, who found that family history of TB contact of participants was not found to be statistically significant in cases of MDRTB. Similar finding was observed by Casal et al. (12) reported positive history of contact with tuberculosis in 22.5% MDRTB patients. In closed communities such as prisons and hospitals, MDRTB has been transmitted between immunocompetent as well as immunodeficient individuals (13). Since, TB is an air-borne disease, bacteria spread through air when people who have an active TB infection expel infectious aerosol droplets. Personal contact with TB patients and uses of patients' personal belongings play a vital role in the MDRTB development and transmission. Several studies have shown that TB contact as strongest determinants of MDRTB (14) A statistical association was observed between TB contacts and MDRTB in the present study.

Although, there was high incident cases of MDRTB among HIV negative than HIV positive, there is conflicting evidence as to whether HIV is an independent risk factor for DRTB. In a study conducted in Namibia, it was found that HIV infection was negatively associated with MDRTB, i e HIV infection was ''protective '' against MDRTB. As suggested by other studies, this may have been due to HIV infected persons dying at a

higher rate than non-HIV infected persons, such that HIV infected persons were less likely to live to the point of either developing MDRTB or die before being diagnosed with MDRTB.

This study did not indicate any statistical association between HIV and MDRTB which contradicted the report of other studies which revealed that study participants who had HIV were three times at higher risk than those who had no HIV infection to develop MDRTB. Even though this association has a marginal statistical significance showing that HIV infection is not a strong predictor of MDRTB infection in TB patients (15). A finding with a strong statistical association was identified in the Netherlands which indicated that MDRTB was significantly associated with HIV infection (OR=3.43, P=0.015) (16). But in agreement with this study, most of the studies in different parts of Africa did not find any association between HIV infection and MDRTB. Three studies in South Africa found no association between HIV infection and MDRTB (17).

Analysis of socio-economic and behavioral factors associated with MDRTB revealed that

respondents who were of the Christian religion had more episodes of MDRTB than their counterparts in the Islam religion. This probably could be due to the purdah system which placed restriction on the Muslem women population who when infected with MDRTB could not easily access to TB care facilities, thus under diagnosed. Considering smoking as a risk factor for MDRTB, respondents who did not smoke cigarette had higher rates of MDRTB cases than smokers. This may be attributed to the fact that non-smokers access and visit health care facilities than smokers, therefore their MDRTB can easily be diagnosed.

This study found that consumers of alcohol had more cases of TB and drug resistance while MDRTB was found more with non-alcohol consumers. There was no association between alcohol consumption and TB, which differ from other studies which concluded that alcohol had a stronger association with tuberculosis (18). Other studies that investigated the role of alcohol consumption and smoking in the risk of developing tuberculosis and found that smoking was associated with tuberculosis only in the group of drinkers (19). However, alcoholics should also be counselled effectively to wean them away from these unhealthy behaviors and minimize bad conduct. This increase in incidence of MDRTB among non-alcohol consumers could be attributed probably to the

ability of non-alcohol consumers to seek proper and effective healthcare services than alcohol consumers. All these factors were not significantly associated with TB occurrence, drug resistance and MDRTB.

Also, the assessment of socioeconomic and behavioral factors associated with MDRTB revealed high rate of MDRTB among married respondents than unmarried (Divorced and singles). This could be attributed to the close contacts of infected partners have with their spouses which could facilitate transmission of MDRTB. This reason was confirmed by this study, as there was high prevalence of MDRTB among those with close contacts to TB patients.

Multiple drug resistant TB was higher among respondents with lower income than those with higher income. Also, MDRTB was found to be more in the unemployed respondents than in the employed. This probably as unemployed patients are more vulnerable because of poor housing and living conditions, as a result of their low socioeconomic status. Gomes et al (20) found that 51.8% of MDRTB cases were among unemployed patients. This may be due to low socioeconomic state, ignorance and illiteracy. Also, it may be due to illness that cause debilitation of the patients making them unable to take up conventional jobs. In the overall, the report of this study agrees with that of Toungoussova and colleagues who found in their study that unemployment, alcohol abuse, low education and low socioeconomic status were not associated with MDRTB (21).

Multivariate analysis showed only previous TB treatment and history of contact TB Patient, showed that factors was independently associated with MDRTB drug resistance. In concordance with previous studies globally, this study established that previous TB treatment and close contact with MDRTB case patients was significant predictors of MDRTB. History of previous TB treatment predisposes an individual to multidrug resistant TB. This occurred as a result of the selection of drug resistant mutant as drug susceptible *M. tuberculosis* are killed during therapy of drug susceptible organisms.

In conclusion, this study revealed that of the risk factors associated with MDRTB, only history of previous TB treatment and contact with TB patients was independently associated with MDRTB.

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