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Predictors and Spatiotemporal Variation of Multi-drug-resistant Tuberculosis in the Upper West Region of Ghana: a 5-year Retrospective Study

Musah Baatira[1,3], Emmanuel Appiah-Brempong[2], Mustapha Adams[4], Aabalekuu Simon[7]*, Eugene Sackeya[1,5], Richard Nomo Angmortey[1,6], Martin Muonibe Beru[1,6], Noella Anglaaere[3], Veronica Dooh[3,8], Aliyu Mohammed[1], Daniel Boateng[2], & Emmanuel Kweku Nakua[1]

[1]Department of Epidemiology and Biostatistics, School of Public Health, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana
[2]Department of Health Promotion and Disability Studies, Kwame Nkrumah University of Science and Technology, Kumasi; Ghana
[3]St. Joseph's Midwifery Training College, Jirapa, Upper West Region, Ghana
[4]SD Dombo University of Business and Integrated Development Studies, Department of Applied Statistics, Wa, Ghana
[5]Tatale District Hospital, Tatale, Northern Region, Ghana
[6]Tamale Teaching Hospital, Tamale Metropolitan, Tamale - Ghana
[7]Department of Public Health Upper West Regional Health Directorate, Wa, Ghana
[8]Department of Maternal and Child Health, University of Ghana, Accra, Ghana

***Corresponding author:** Aabalekuu Simon, Department of Public Health Upper West Regional Health Directorate, Wa, Ghana.

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Abstract

Introduction: *Tuberculosis (TB) control and prevention in the Upper West Region of Ghana is challenged by the emergence of rifampicin and isoniazid resistance; multidrug-resistant tuberculosis (MDR-TB). The situation makes TB treatment less effective, prolonged, and expensive, and sometimes medicines used to treat MDR-TB result in unbearable side effects that deter patients from medication adherence. Therefore, this study aims to assess the Predictors of MDR-TB in the Upper West Region of Ghana from 2017 to 2021 to guide policy interventions in that Region.*

Method: *The study employed a cross-sectional design using secondary data. A purposive sampling technique was used to select three Districts with the highest number of confirmed TB cases and a simple random sampling technique was applied to sample a total of 318 confirmed TB cases from the three selected districts for the study. Descriptive statistics were used to estimate the median age of the cases, proportions, ratios, and logistic regression analysis to establish associations between the dependent and independent variables at a 95% confidence interval (CI).*

Results: *The multivariable logistic regression showed that smoking [AOR=6.42(95% CI=1.34–30.79)], TB retreatment [AOR=1.87 (95% CI=0.4-4.7)], and persons 70 years and above [AOR= 4.27 (95% CI=1.04–17.53) were independent predictors associated statistically with the prevalence of MDR-TB in the region. Generally, defaulting TB retreatment, age category, and smoking were identified as independent predictors with no hotspots of MDR-TB discovered within the study period.*

Conclusion: *Ghana Health Service and the National TB Control Program should regularly organize In-service training sessions for laboratory staff on DST and intensify health education on the predictors of MDR-TB in the region to reduce its prevalence further.*

Keywords: Tuberculosis, Multi-Drug-Resistant Tuberculosis, Predators, Retrospective Study, Upper West Region.

Introduction

Tuberculosis, mainly caused by a bacterium, Mycobacterium tuberculosis, is one of the major causes of morbidities and mortalities across the globe, especially, in low-income countries [1]. In 2019, close to 10 million people suffered from TB worldwide, out of which about 1.4 million, representing a case fatality rate of 14 percent died of the disease and its related complications. This disturbing global TB case fatality rate is largely attributed to the ineffectiveness of first-line TB medicines because of the presence of medicine-resistant Mycobacterium strains [2].

The annual number of people reported to be given treatment globally because of Multidrug-Resistant tuberculosis (MDR-TB) or rifampicin-resilient tuberculosis (RR-TB) has also seen an increasing trend within the above-stated period from 2015 through 2019. That is, from 122 726, 156205, and 177099 in 2015, 2018, and 2019 respectively.

As disturbing as the situation is in Sub-Saharan Africa, Ghana's TB burden (smear positive) has been estimated at 111/100, 000 in adults and 356/100,000 bacteriological TB cases in the general population with MDR-TB being a serious emerging public health problem in Ghana [3].

An estimated percentage of 3.3 new TB cases and 20% of those previously treated with anti-TB medicines developed MDR-TB in 2014 globally. About 480,000 people were infected with MDR-TB in the period under review whilst about 190,000 of them died, with over half of the MDR-TB deaths (54%) recorded in only three countries; India, China, and the Russian Federation. Additionally, MDR-TB treatment takes longer time than expected, has almost unbearable side effects, reduced rates of cure, higher case fatality rates compared with other TB cases, stricter treatment protocol, and the second-line medicines use to treat MDR-TB cases are sometimes very difficult to come by, therefore, leaving its sufferers with psychosocial hitches which could eventually lead to treatment non-adherence [4].

The second Ghana national TB prevalence survey carried out in 2013, after fifty-seven years cited in Ghana's Ministry Of Health report (2020), revealed an alarming prevalence of the tuberculosis disease in Ghana as 290 TB cases in every 100, 000 people in Ghana. The gravity of the TB prevalence, as stated above, is such that it is more than four (4) folds the WHO-recommended prevalence of 70 TB cases per 100, 000 people in the stated year. The survey report further revealed a higher TB prevalence in males compared with females. However, the disease is consistently more prevalent among females who are HIV positive than males with the same status of HIV.

Further, scarcity of second-line TB medicines, their unbearable side effects, and inequitable distribution of same to treat those who need it result in the rapid spread of MDR-TB in the communities which consequently makes preventable morbidities and mortalities become serious public health threats [5].

Despite the tremendous efforts by the Ghana National TB Control Program and other supportive programs such as free TB treatment, enabler packages for TB patients, community sensitization, and the use of directly observed therapy (DOT) to reduce the prevalence and or incidence of MDR-TB in Ghana, the disease continues to be a serious public health threat in the country and for that matter, the Upper West region of Ghana.

These worrying developments call for urgent investigations into the predictors of MDR-TB, which are not known in the region so that hotspots for the disease in the Upper West Region can be identified and prioritized to influence policies and programs regarding resource allocation and other effective interventions to control MDR-TB in the Upper West Region and beyond [6].

The study seeks to identify the predictors of MDR-TB cases in the Upper West Region and estimate the MDR-TB burden in the Region so that hotspots or otherwise of MDR-TB could be identified for equitable distribution of resources for effective interventions and recommendations made to policymakers, NGOs, local authorities, philanthropies and so on to address the problem of MDR-TB in the region [7].

Method

Study Approach and Design

A cross-sectional study design was employed using secondary data; a five-year retrospective review of predictors of multi-drug-resistant tuberculosis in the Upper West Region of Ghana from 1st January 2017 to 31st December 2021 using a quantitative approach was done. We collected all types of confirmed tuberculosis cases recorded in the tuberculosis registers/treatment cards (TB 01 card) and laboratory registers as supplementary sources of data at the various health facilities in the selected districts and entered the District Health Information Management System 2 (DHIMS2) and excel for cleaning and analysis. We include age, gender, occupation, marital and HIV status, diabetes status, nutritional status, smoking status, history of tuberculosis treatment, and history of TB treatment interruption, as the variables of interest [8].

Cochran's sample size estimation formula of 1963 cited in was used to estimate a minimum sample size of 318 confirmed TB cases for the study.The estimated prevalence (P) of MDR-TB among all confirmed TB cases (both new cases and cases with a history of anti-tuberculosis treatment) in the Upper West Region was unknown, an estimated Ghana national MDR-TB prevalence (1.3 percent in new TB cases and 25 percent in TB cases with a history of anti-tuberculosis treatment) of 25.0%, the higher prevalence between the two categories of confirmed TB cases (new and old TB cases) in Ghana according to was used to estimate the sample size of 289 confirmed TB cases. Since the study used random sampling techniques to select the TB treatment cards (secondary data) for the study, there was the possibility of misplaced or missing cards (TB 01 cards) or values when a particular treatment card was randomly selected, hence, the need to add 10% of the estimated sample size to cater for the unforeseeable misplaced/missing cards or variables to still make up for a higher statistical power of this study. Therefore, final sample size (n)= (1.1*289) = 317.9 = 318 TB treatment cards.

We again used a multi-stage sampling technique to sample 318 confirmed TB cases from the Upper West Region with the aid of a randomizer [Microsoft Excel v.2021 RAND function [9, 10].

At the regional level, three districts with the highest number of confirmed TB cases within the study period (Wa Municipal, Wa

West, and Nadowli-Kaleo) were purposively selected for the study. At the district level, since details of TB case management are monitored or recorded in the TB treatment card (TB 01 card) or folder, these cards for the entire district and the entire period under study(Wa municipal =462,Wa West=225,Nadowli-Kaleo=233) were stratified according to the year of case confirmation, and allocation of cases randomly selected from a particular year based on the year's proportion contributed to the sample size (318) using the TB case ID number on the treatment card.

However, all 12 MDR-TB cases from the three selected districts (with 920 confirmed TB cases) were recruited into the study using purposive sampling, because MDR-TB is a rare disease and the cases were only 12 in number, probability sampling would have proportionately recruited at most 5 MDR-TB cases into this study, which would have been inadequate for running other analysis. Notwithstanding, 5 MDR-TB cases were used to calculate the period prevalence with 318 being the population at risk within the study period. An MDR-TB case was identified from the TB treatment card using the clinician's final diagnosis. Therefore, the sampling frame was 920 (Wa Municipal=462,Wa West=225,and Nadowli-Kaleo=233) treatment cards.

Finally, a sample size of 158 (2 MDR-TB and 156 non-MDR-TB), 82 (5 MDR-TB and 77 non-MDR-TB), and 78 (5 MDR-TB and 73 non-MDR-TB), TB 01 cards for Wa Municipal, Nadowli-Kaleo, and Wa West respectively, were randomly selected with a randomizer (the RAND function of a Microsoft Excel 2021), using the TB case IDs in the TB database to form the regional sample size (n) of 318. The selected TB 01 forms were further assessed to ensure they met the inclusion criteria and contained the variables of interest for the study.

The data were exported into excel from the server (Kobo collect), transferred into the Stata statistical software v.16, cleaned, and validated by checking and correcting data entry errors. The data was also checked for outliers and all changes made were chronologically documented and reported.

The R statistical software and Stata version 16 were used to analyze; descriptive statistics (proportions, percentages, central location, and spread), logistic regression analysis (prevalence or odds ratios) at a 95% confidence interval (CI) for a possible association between outcome variables (MDR-TB) and predictor variables (age, gender, occupation) [11, 12].

Table 1: Results were presented using tables, graphs, proportions or percentages, ratios (odds ratios, prevalence ratios)

Variables	Number of observations (N=318)	Percentages (%)
Sex		
Males	223	70.13
Females	95	29.87
Age (in years)		
1-20	33	10.38
21-40	141	44.34
41-60	87	27.3
61-80	44	13.84
81-100	13	4.09
Median (IQR)	39 (±26)	
Residence	N=318	
Wa Municipal	158	49.69
Nadowli-Kaleo		
Wa West	82	
78	25.79	
24.52		
Religion	N=177	
Christianity	59	33.33
Islam	31	17.51
Traditional	87	49.15
Smoker	N=182	
Yes	30	16.48
No	152	83.52
Married	N=237	
Yes	177	74.68
No	60	25.32
Diabetic	N=180	
Yes	1	0.56

No	179	99.44
HIV positive	N=314	
Yes	45	14.33
No	269	85.67
Undernourished	N=308	
Yes	79	25.65
No	229	74.35
MDR-TB	N=318	
Yes	12	3.77
No	306	96.23

Out of the 318 TB treatment cards that were included in the assessment, 223 (70.13%) were males. Most (141) of the TB treatment (TB 01) cards assessed, representing 44.34% were within the age range of 21-40 years, with 39 years and 26 years respectively being the median and interquartile range whilst the least number of TB treatment cards assessed were within the age range of 81 to 100 years (13, 4.09 %). Married couples among the study subjects were 177 out of 237 records assessed, representing a percentage of 74.68% whilst the majority (152/182) of the study subjects were non-smokers. Concerning HIV co-infection, 14.33% (45 out of 314) of the TB treatment cards evaluated were found to contain HIV-positive results whilst 79 (25.65%) of the 308 TB treatment cards assessed were found to contain body mass index (BMI) less than 18.5 kg/m²

Table 3 below presents the crude and adjusted effect estimates (odds ratios) of predictor variables after their regression on MDR-TB. At the bivariate level of analysis, being 70 years or above [COR= 4.40 (95% CI: 1.27–15.20) p=0.019] and being a current or past smoker [COR= 4.77 (95% CI: 1.37–16.55) p= 0.019] were both associated with higher odds of having MDR-TB. The crude analysis also shows a marginal association indicating lesser odds of being diagnosed with MDR-TB among urban dwellers as compared to rural dwellers [COR=0.14 (95% CI: 0.02–1.09) p=0.060]. However, the association was not statistically significant at a 5% significance level.

Table 2: Predictors of Multi-Drug-Resistant Tuberculosis (MDR-TB)

Background variables	COR (95% CI) p-value	AOR (95% CI) p-value
Age category		
Below 70 years	1.00	1.00
70 years+	4.40 (1.27–15.20) 0.019 *	4.27 (1.04–17.53) 0.044 *
Gender		
Female	1.00	1.00
Male	0.96 (0.29–3.17) 0.943	0.61 (0.15–2.52) 0.494
Marital status		
Not married	1.00	
Married	2.38 (0.52–10.93)	
Religion		
Christianity	1.00	
Islam	0.46 (0.05–4.29) 0.494	
Traditional	1.20 (0.34–4.30) 0.776	
Settlement		
Rural	1.00	1.00
Urban	0.14 (0.02–1.09) 0.060	0.18 (0.02–1.49) 0.111
Completed 6-month treatment		
No	1.00	1.00
Yes	0.19 (0.06–0.58) 0.004 *	0.13 (0.04–0.47) 0.002*
Current or past smoker		
No	1.00	1.00
Yes	4.77 (1.37–16.55) 0.014 *	6.42 (1.34–30.79) 0.020 *
Nutritional status		
Normal	1.00	
Undernourished	1.36 (0.41–4.55) 0.615	
A drug sensitivity test done		

No	1.00	
Yes	2.80 (0.61–12.89) 0.185	
Outcome of treatment		
Not cured	1.00	
Cured	0.22 (0.07–0.69) 0.009 *	
Hosmer-Lemeshow goodness of fit test: 7.03 (p=0.2182) Akaike's Information Criterion: Null model (110.5858), Adjusted model (97.11967) Likelihood ratio test χ^2 (p-value): 23.47 (0.0003)		

COR: Crude odds ratio | AOR: Adjusted odds ratio | CI: Confidence interval | * Statistically significant at p<0.05

The multivariable logistic regression shows that age category and smoking status are independent predictors of MDR-TB. Specifically, after adjusting for confounding, persons aged 70 years or above have 4.27 times higher odds of being diagnosed with MDR-TB as compared to those below 70 years and the association is statistically significant [AOR=4.27 (95% CI: 1.04–17.53) p=0.044]. Similarly, compared to those who do not smoke, current or past smokers have higher odds of having MDR-TB after adjusting for other factors [AOR=6.42 (95% CI: 1.34–30.79) p=0.020]. Persons who completed the 6-month TB treatment were however 87% less likely to have MDR-TB compared with those who had treatment interruption or did not complete the regimen [AOR: 0.13 (95% CI: 0.04–0.47) p=0.002].

The final model is considered a good fit after computing relevant post-estimation tests (Goodness of fit tests). Specifically, the likelihood ratio test and Akaike Information Criterion (AIC) indicate that the adjusted model is better than the null model. The Hosmer-Lemeshow test also shows that overall, the model is a good fit ($\chi 2$ = 7.03, p=0.2182) and the area under the Receiver Operating Characteristic (ROC) curve (0.8131) indicates that the adjusted model has appreciable discrimination (Figure 4.5 below).

Figure 1 shows the area under the Receiver
Operating Characteristic (ROC) curve (0.8131), a goodness of fit indicator. The curve indicates that the adjusted model of the multivariate regression analysis is better than the crude or unadjusted model. The ROC curve scale ranges from 0.5 to 1.0

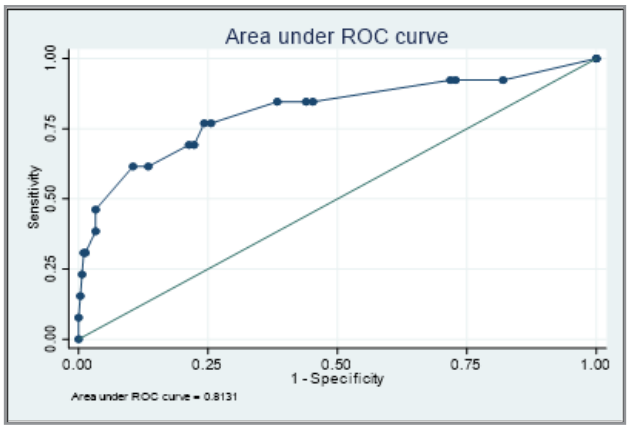

Figure 1: Area under the ROC curve for the fitted multivariable logistic regression model

Discussion

The study discovered that most (70.13%) of the study subjects were males and the age category with the most dominant number of study subjects (141/318, 44.34%) was 21-40 years with 39years and 26years being the median and interquartile range respectively. The findings are consistent with a study carried out in Colombia which found that 69% of the 19,720 deaths recorded as a result of TB infection happened in males and about 45% of the deaths were reported in older adults aged 65 years and above [13]. This study findings also agree with another study conducted in Iran which found that factors such as unemployment, sex or gender, age, low level of education, and quality of health care delivery were associated with TB and its treatment success in that country. The study further discovered that treatment failure or patients defaulting to TB treatment, home, and social class of patients contributed immensely to the treatment outcomes of TB cases in Iran. Additionally, just as it has been found in this study, sex was linked with being a protective factor for females, and age category influenced treatment outcomes of TB patients in Columbia, Indonesia, Iran, and Nigeria respectively [14].

The possible reason for which sex could be a risk factor for males but a protective one for females could be that men are usually involved in more risky lifestyles and behaviors such as smoking, drunkenness, mining operations, and so on, and young people from 21 to 40 years are often the most exuberant group to be involved in such risky behaviors. These factors are likely to increase their vulnerability to getting the infection compared with females and other age categories respectively. Therefore, public health authorities should make it a practice to always sensitize and provide an enabling environment for the said categories of people to keep them away from such risky behaviors to reduce the prevalence of TB cases among those vulnerable groups in the Upper West Region.

The multivariable logistic regression shows that age category

and smoking status (being a current or past smoker) are independent predictors of MDR-TB. After adjusting for other confounding variables, persons aged 70 years and above have 4.27 times (327%) the likelihood of being diagnosed with MDR-TB as compared with those below 70 years, and the association is statistically significant. Similarly, compared to those who were non-smokers, current or past smokers had higher odds (AOR= 6.42 (542%)) of having MDR-TB after adjusting for other factors. Again, persons who completed the 6-month TB treatment regimen were, however, 87% less likely to have MDR-TB compared with those who had treatment interruption or did not complete the treatment regimen. Similarly, a study carried out in Colombia concluded that 69% of the 19,720 deaths recorded as a result of TB infection happened in males and about 45% of the deaths were reported in older adults aged 65 years and above. On the other hand, researchers identified a varying range of MDR-TB predictors across Africa: A study conducted in Sudan concluded that being a smoker, TB medication failure and place of residence significantly predicted MDR-TB in that country, with people living in rural communities associated with close to 200% likely the prevalence of MDR-TB compared to their counterparts living in the urban areas of Sudan; In Nigeria, West Africa, the average age of MDR-TB patients in treatment centers was 35.71 years, most of the patients (66.4 percent and 56.4 percent), according to the study, were males and married respectively and close to 84 percent of the study subjects were found to be HIV negative, which means that other factors apart from HIV status predicted the development of MDR-TB in that country, again, anemia was prevalent in more than half (68.5%) of the patients undergoing treatment at the centers. The study further concluded that most (87.25 %) of the MDR-TB cases under treatment were retreated cases with 12.75% constituting incident cases [15]. Also, research conducted in Ghana identified previous TB treatment as the most significant factor associated with MDR-TB in the countr.

The reason for the strong association between retreated TB cases and MDR-TB in many studies across the world could mainly be a result of non-medication adherence during treatment with the first-line TB medicines or the tubercle bacilli becoming resistant to the drugs due to constant mutation of the Mycobacterium tuberculosis, therefore, healthcare providers should always put stringent interventional measures (such as the creation of more treatment centers for TB patients) in place to ensure stricter medication adherence during TB treatment. Furthermore, DST and culture should always be conducted on all TB cases before medication commences, this could make it possible for drug-resistant strains of the tubercle bacilli to be detected early enough and kept on second-line TB medications for effective results.

Conclusion

The likelihood of MDR-TB was found to be approximately 7.26 times higher in subjects who defaulted TB treatment regimen compared with those who completed the regimen. The study eventually identified four independent predictors of MDR-TB in the Upper West Region of Ghana from 2017-2021. The predictors of MDR-TB were: Defaulting TB treatment or Loss to follow-up, History of previous TB treatment (being a retreated TB case), age of the patient (70 years and above), and Smoking status (being a current or past smoker). Treatment default or loss to follow-up could be associated with an access problem (geographic, financial, cultural barriers, etc.) or a utility issue (stigma, bad attitude of health professionals which deters people from seeking health care, etc.).

The study therefore recommends that people aged 70 years and above should always be educated on the risks associated with the aged and the need for regular medical check-ups to stay healthy in old age, educate the youth and everyone else in the Upper West Region on the dangers of being a primary or secondary smoker and the need for behavior or lifestyle modification to have good health and stay productive and work towards achieving the SDGs by 2030.

Ghana Health Service and the National TB Control Program should regularly organize In-service training sessions for laboratory staff on DST and intensify health education on the predictors of MDR-TB in the region to reduce its prevalence further.

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Declarations

Ethics Approval and Consent to Participate

This study was approved by the Committee on Human research, publication and ethics reference number CHRPE/AP/308/22. All participants provided informed consent before participating in the study.

Consent for Publication

Consent for publication was obtained from all participants included in the study.

Availability of Data and Material

The datasets generated and/or analyzed during the current study are available upon request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contribution (S)

Conceptualization: MB., MA., ES., RNA., MMB., AS., NA., VD., AM., DB., EKN., EAB.
Data Curation: MB., MA., ES., RNA., MMB.
Data Analysis: MB., MA., ES., RNA., MMB.
Methodology: MB., MA., ES., RNA., MMB., VD. AS., AM., DB., EKN., EAB.
Project Administration: MB., NA., MA., VD, AS.
Supervision: EAB., AM., DB., EKN.
Validation: EAB., AM., DB., EKN.
Writing-Original Draft: MB., MA., ES., RNA., MMB

Writing – Review And Editing: EAB., AM, DB., EKN., AS.

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