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PREVALENCE AND OUTCOMES OF MULTI DRUG RESISTANT TUBERCULOSISIN AKWA IBOM STATE NIGERIA: A RETROSPECTIVE STUDY

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ABSTRACT

The emergence and management of multidrug resistant tuberculosis is a challenge for global tuberculosis control. This study determined treatment outcomes among a cohort of drug resistant tuberculosis(DR-TB) patients in Akwa Ibom State, Nigeria and identified factors associated with poor treatment outcomes. We conducted a retrospective study using data obtained from the DR-TB register in the University of Uyo Teaching Hospital, and from the State DR-TB community-based register managed by the Tuberculosis and Leprosy Control Unit of Akwa Ibom State for the period 2012 to 2020. Treatment outcomes were assessed for patients diagnosed with DR-TB, multidrug resistant Tuberculosis(MDR-TB). The prevalence of MDR-TB in this study was found to be 0.85/100000. Majority of the patients were aged 21-40years, male, newly diagnosed TB cases, and had no prior exposure to TB medications. Our findings revealed a low MDR-TB treatment success rate among patients, and about 15% died during treatment. Multivariable regression analysisshowed that none of the patients' characteristics had significant association with their treatment outcome.MDRTBremains a public threat in the study area. We recommend that surveillance and control of drug resistant TB should be emphasized by DOTs programs, through early detection of cases and routine investigations to assess for drug resistance.

INTRODUCTION

Tuberculosis (TB)is among the oldest diseases known to mankind, yet remains one of the top 10 causes of death worldwide today, as well as the leading global infectious disease killer. It is a disease of major public health importance, especially in low- and middle- income countries. In 2019, about 10million people had tuberculosis, with 1.4million deaths, making it one of the top ten causes of death globally(WHO, 2020a). Nigeria is one of the eight countries that account for two-thirds of the world's TB burden, ranking 7th among the 30 high TB burden countries globally and 2nd in Africa. With a high national TB prevalence of 219/100,000, the country accounts for 4% of the estimated incidence cases globally(WHO, 2020a).

Tuberculosis is caused by the bacillus *Mycobacterium tuberculosis (M. tb)*, which is spread when people who are sick with TB expel bacteria into the air; for example, by coughing. The disease typically affects the lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB). TB is a curable disease and has effective treatment using multiple drugs.(WHO, 2020). The recommended treatment is with a standard 6 months course of 4 antimicrobial drugs under the supervision of a health worker or a trained person(WHO, 2020b). However, improperly managed treatment cases reduce patients' compliance rate and give rise to resistance to the antimicrobial therapy, leading toDrug Resistant TB.

Drug-resistant tuberculosis (TB) is a significant global public health problem. There are different forms of DRTB, ranging from Mono drug-resistant TB being resistance to only one

anti-TB drug, Polydrug resistance which is resistance to either Isoniazid or Rifampicin and any other anti-TBdrug, and Multidrug resistance TB(MDRTB) - resistance to Isoniazid and Rifampicin- the major anti-TB drugs and finally XDRTB, being resistance to Isoniazid and Rifampicin with resistance to other drugs like the fluoroquinolones and the injectable medications.The drug-resistant forms of TB, especially multidrug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) cause significant challenges for control of pulmonary TB and management of TB patients(WHO, 2020b). However, because greater than 90% of rifampicin (RIF)-resistant isolates are also isoniazid resistant, MDR-TB is frequently used as a surrogate for rifampicin resistance (RR).

MDR-TB is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, the two most powerful, first-line anti-TB drugs. MDR-TB is treatable and can be cured by using second-line anti TB drugs. However, second-line treatment options are limited and require extensive chemotherapy (up to 2 years of treatment) with medicines that are expensive and toxic(Dean et al., 2017; Onyedum et al., 2017).In 2018, WHO announced a change to a fully oral regimen as one of the preferred options for MDR-TB treatment, replacing injectable agents by more potent alternatives such as Bedaquiline (the first-ever medicine to be developed specifically for the treatment of MDR-TB)(Update Public Health, 2018).

Globally, a total of 206,030 people with multidrug- or rifampicin-resistant TB (MDR/RR-TB) were detected and documented in 2019, showing a 10% increase from 186,883 in the previous year(WHO, 2020). A meta-analysis of the prevalence of drug resistant TB in Nigeria revealed that the rate of any drug resistance among new TB cases was 32.0% and among previously treated cases 53.0% while multidrug resistance among new and previously treated TB cases was 6.0% and 32.0% respectively(Onyedum *et al*., 2017). The following group of TB patients fulfil the criteria of presumptive MDR-TB which are then further tested to confirm MDR-TB diagnosis: smear positive previously treated patients who define as relapse, return after default (RAD), and failure; new smear positive pulmonary TB patients whose sputum remains smear positive at month 2 or 3 of treatment; symptomatic close contacts of known MDR-TB patient, and new smear positive with Human Immunodeficiency Virus (HIV) infected patients. All presumptive MDR-TB cases are first evaluated by GeneXpert testing. The next investigation carried out before commencement of treatment was the Line Probe Assay (LPA). This test was carried out in the TB reference laboratory and showed resistance to other first and second line medication thereby confirming the type of resistance (MDR, Pre-XDR, XDR) involved.

Akwa Ibom State is located in the South-South region of Nigeria and is one of the states in the oil rich Niger delta region. It is located in the coastal southern part of the country. The state is bordered on the east by Cross River State, on the west by Rivers State and Abia State, and on the south by the Atlantic Ocean. It has a population of about 5.5 million based on the 2006 National population census report and a land mass of 7,081km^2. Akwa Ibom climate is tropical. The state capital is Uyo. It is rapidly urbanizing with the nearby LGAs, merging into semi-urban suburbs within the capital city. Majority of the people live in the rural areas, with farming and fishing being their major occupations. Akwa Ibom State government declared that the poverty and unemployment levels are high(AKSG, 2020).

Akwa Ibom state has a high burden of TB and HIV. Akwa Ibom State contributed 12% to all forms of TB cases notified nationwide in 2016. The state also has the highest HIV prevalence rate of 5.5% compared to the National average of 3.2%(FHI360 and USAID, 2019). There are pockets of high TB burden communities in some LGAs in Akwa-Ibom State.Diagnosis of MDR-TB in Akwa Ibom state commenced in 2012. All patients diagnosed with MDR-TB were treated as in-patients in the apex tertiary institution, UUTH. However, in 2014, the Akwa Ibom State TB, Leprosy and Buruli Ulcer Control Program (AKSTBLBCP) commenced community-based treatment of MDR-TB. Under this intervention, all MDR-TB patients are treated at home. Initially, DOTS Officers who were community volunteers and CHEWs were trained and assigned the task of daily treatment of each patient. They would carry out daily visits to deliver

injectable second line treatment drugs over a period of two years until the patient was cured or died. They also educated them on the compliance and side effects of the drugs. With the introduction of oral drugs for MDR-TB, the program design has changed.

With the introduction of the all-oral regimen for MDRTB treatment in 2020, all patients receive their treatment as DOTS in specially designated centres for MDRTB in the state.To commence this regimen, patients require baseline investigations such as Electrocardiogram, Hepatitis B surface antigen, Hepatitis C, Electrolyte, urea and creatinine, Full Blood Count, Fasting Blood sugar, Chest xray, liver function test, Serum Amylase and pregnancy test for women of reproductive age.However, the Line Probe Assay (LPA), is the most important investigation carried out before commencement of treatment as it shows resistance to other 2nd line medications. This distinguishes the type of resistance (MDR, Pre-XDR, XDR) involved and henceimprove the choice of medications to be used.This test is carried out in the TB reference laboratory, located outside the state. The nearest reference Laboratories include Calabar, Port Harcourt and Amachara. However, monthly, all DRTB patients are seen in these four centers located in Uyo, Ikot Ekpene, Oron and Eket(Update Public Health, 2018).

There is currently no published information about treatment outcomes in patients with DR-TB in Akwa Ibom, Nigeria. The aim of this study was to determine the prevalence and assess treatment outcomes among patients with Gene Xpert and culture-confirmed MDR-TB in Akwa Ibom state, Nigeria between 2012 and 2020.

METHOD

The registers used for the study were obtained from two sources in Akwa Ibom. The first register was in the MDR-TB ward which is an inpatient setting, under the Department of Internal Medicine in UUTH. The second register was obtained from the DRTB office of the AKSTBLBCP, which documents community-based treatment of MDR-TB cases. Information from the two registers were synchronized to arrive at our findings.

A retrospective review of the TB registers of patients screened for *Mycobacterium tuberculosis* and RR-TB using Xpert MTB/RIF assay at the University of Uyo Teaching Hospital and the State Ministry of Health MDR-TB Register between January 1, 2012 and December 31, 2020 was conducted. This included all patients starting treatment with second-line TB drugs for confirmed or presumptive MDR-TB.

Data collection was done via a standardized abstraction chart. The variables abstracted included: demographic characteristics; previous TB treatment exposure; HIV serostatus; results of sputum AFB, sputum culture and GeneXpert analysis. In our study, we assessed the overall prevalence of MDR-TB for the study period to be the average prevalence of MDR-TB in the 8 years of the study period. The prevalence for each year was calculated as the number of confirmed MDR-TB cases divided by the total number of confirmed TB cases in the state. All cases were notified and obtained from the AKSTBLBCP registers.

Data collected were entered into an excel spreadsheet and analyzed using IBM SPSS version 22 (New York). Results were presented in tables as frequencies and percentages. Continuous data was presented using mean and standard deviation. Cox regression analysis was used to calculate odds ratio for association between treatment outcomes and variables.

Ethical clearance for the study was sought and obtained from the Institutional Health and Ethics Research Committee of University of Uyo Teaching Hospital. Permission was also obtained from the AKS Ministry of Health.

RESULTS

A total of 226 individuals were diagnosed with MDR-TB in Akwa Ibom state between 2012 and 2020. As shown in table 1, majority were aged 21-40 years (53.1%) and the mean age was 37.5 ± 14.8. Most were male (65.5%), and were newly diagnosed patients (63.4%). There was a

statistical difference in the mean age between the males and female patients in the study. Most of the data was obtained from the State Ministry of Health (SMOH).

Table 1: Sociodemographic characteristics of MDR-TB patients in AKS

Demographic characteristic	Frequency (n=226)	Percent (%)
Age		
<20	24	10.6
21-40	120	53.1
41-60	67	29.6
>60	15	6.6
Mean	37.5 ± 14.8	
Sex		
Female	78	34.5
Male	148	65.5
Treatment site		
SMOH	166	73.5
UUTH	60	26.5
Previous treatment (n=148)		
Yes	34	23.0
No	114	77.0
Registration group (n=219)		
Newly diagnosed	137	63.4
Treatment after failure	16	7.4
Treatment after loss to follow up	13	6.0
Other previously treated TB patients	43	19.9
Transferred in from another center	7	3.2

All patients showed resistant patterns on Gene Xpert. Of the 226 patients, Acid fast bacilli (AFB) was done for 128, out of which about half showed positive results. Also 110 patients had sputum culture done with 51.8% positive. A little over a third of the patients were HIV positive (37.6%) (Table 2).

Table 2: Investigation results and HIV status of MDRTB Patients in AKS

	Frequency	**Percentage (%)**
Gene Xpert (Resistant)	226	100.0
Acid fast Bacilli (n=128)		
Positive	63	49.2
Negative	65	50.8
Sputum culture (n=110)		
Positive	57	51.8
Negative	50	45.5
Contaminated	3	2.7
HIV status (n=209)		
Positive	79	37.8
Negative	130	62.2

Figure 1 shows the trend in MDR-TB prevalence in AKS between 2012 and 2020. The total number of confirmed MDR-TB cases was 226, and confirmed TB cases was 26,761. Thus, the overall prevalence of MDR-TB during the study period was 0.85%. The prevalence of MDR-TB in the state remained stable until 2017 where it there was an upsurge, peaking in 2018 at 2.2%. Afterwards, a gradual decline was observed uptill 2020.

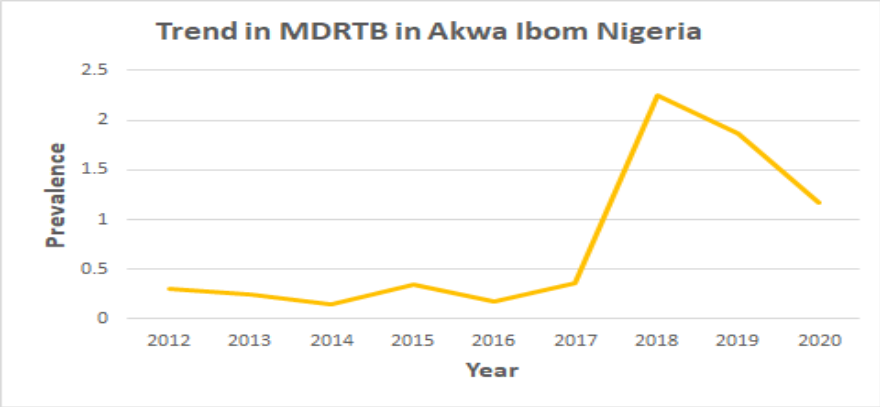

Figure 1: Trend in MDR-TB in Akwa Ibom state, Nigeria.

Treatment regimen for 207 of the respondents was found in register. Majority of the patients were treated using the standard regimen for MDR-TB 199 (96.1%), while 3.9% were treated using individualized regimen. Of these, 7 (3.4%) were treated with Bedaquilline while 1 (0.5%) was treated with Delamanid.

For the outcome of treatment, only about half of the patients in both treatment centers were cured (68.3% in UUTH and 61.7% in SMOH), while about 15% of the patients died in both centers. In UUTH, 15% defaulted from treatment while 7.4% of those treated in SMOH were lost to follow up (table 3). Outcomes for 85(51.2%) of the patients seen in the SMOH register were unavailable.

Table 3: Outcome of treatment

	Frequency	**Percentage**
UUTH (n=60)		
Cured	41	68.3
Defaulted (left against medical advice)	9	15
Died	9	15
Transferred	1	1.7
SMOH (n=81)		
Cured	50	61.7
Treatment completed	9	11.1
Treatment failure	1	1.2
Loss to follow up	6	7.4
Referred	2	2.5
Died	13	16.0
Total (n=141)		
Cured	91	64.5
Treatment completed	9	6.4
Defaulted/loss to follow up	15	10.6
Treatment failure	1	0.7
Transferred/referred	3	2.1
Died	22	15.6

Table 4 shows the distribution of outcome of treatment by thecharacteristics of the patients. Those over 60 years of age had the highest proportion of cure (75.0%), followed by those less than 20 years of age (68.8%), while the 21-40years age group had the highest proportion of death (18.2%). A higher proportion of females (70.3%) were cured compared to males (62.5%),

and a higher proportion of males were lost to follow-up (12.5%) compared to females (5.4%). Thirty-three (64.7%) of HIV positive patients were cured after treatment, while 69.5% of the HIV negative patients were cured. However, one of these associations were statistically significant on regression analysis.

Table 4: Analysis of treatment outcomes and patient characteristics

Sociodemographic characteristics	Cured	Treatment completed	Loss to follow up	Treatment failed	Died	OR (95% CI)	P value
Age							
<20	11(68.8)	1 (6.2)	2(12.5)	0(0.0)	1(6.2)	0.08(-1.95-2.11)	0.937
21-40	47(64.4)	5(6.8)	7(9.6)	1(1.4)	12(16.4)	0.67(-1.01-2.34)	0.436
41-60	27(61.5)	2(4.5)	6(13.6)	0(0.0)	8 (18.2)	0.86 (-0.84-2.56)	0.322
>60	6(75.0)	1(12.5)	0(0.0)	0(0.0)	1(12.5)	-	
Sex							
Female	26(70.3)	1(2.7)	2 (5.4)	1(2.7)	5(13.5)	0.39(-0.57-1.35)	0.425
Male	65 (62.5)	8 (7.7)	13(12.5)	0(0.0)	17(16.3)	-	
Previous treatment							
Yes	17(65.4)	4(15.4)	1 (3.8)	1 (3.8)	2 (7.7)	-0.73(-1.34-0.89)	0.371
No	33 (63.3)	4 (7.5)	6 (11.3)	0(0.0)	10 (18.9)	-	
HIV status							
Positive	32 (64.0)	3 (6.0)	6 (12.0)	1 (2.0)	8 (16.0)	0.28(-0.89-0.76)	P=0.597
Negative	55 (70.5	5 (6.4)	6 (7.7)	0 (0.0)	12 (15.4)	-	

DISCUSSION

This study aimed to identify the outcome of MDR-TB in Akwa Ibom state, Nigeria, between 2012 and 2020. Using the MDR-TB registers, a retrospective analysis of patients seen was carried out. Two hundred and twenty-six (226) persons were diagnosed with MDR-TB, majority were aged 21-40 years, male, and newly diagnosed patients. About half of the patients had AFB testing and sputum culture done and half of these were positive. A little over a third of the patients were HIV positive. Majority of the patients were treated using the standard regimen for MDR-TB, Outcomes showed that about two thirds of the patients in both treatment centers were cured and while fifteen percent of the patients died in both centers.

The proportion of males in this study was nearly double that of females. This is in agreement with the fact that being male has been identified as a risk factor for TB(Marçôa *et al*., 2018; Pokam *et al*., 2013).A similar study reported a 60.5% prevalence of MDR-TB among males compared to 39.5% among females (Uzoewulu *et al.*, 2014). Majority of the patients were between 21-40 years. This age category and the mean age are similar to that seen in a previous study (Uzoewulu *et al.*, 2014). These are young people in their productive ages, which implies compromise of productivity.

Several studies have established that previous treatment with anti-TB therapy is an important risk factor for inducing TB-drug resistance (Onyedum *et al*., 2017). In contrast to these findings, our study showed that nearly two-thirds of the patients with MDR-TB were newly diagnosed TB patients with no previous exposure to anti-tuberculous drugs. This finding suggests that the patients were primarily exposed to multi-drug resistant *M. tb* strains ab initio. Similar findings were seen in Eastern African Republic of DRC and Djibouti, where over 45% of DR-TB patients had no prior TB history or treatment(Boyer-Cazajous *et al.*, 2014; Bulabula *et al.*, 2019).

A little over a third of the patients were HIV positive In a similar study, 33.8% of the participants were positive for HIV infection, out of which twenty-six (12.6%) had co-infection of tuberculosis and HIV (Oyedeji *et al.*, 2020). This is in contrast to a study in Zimbabwe, where over half of the MDR-TB patients (52.8%) were HIV positive (Gonah and Maphosa, 2020). Due to their compromised immune system, HIV-infected patients have been found to be

at a higher risk of developing latent TB activation and resultant unfavorable treatment outcomes, such as treatment failure (WHO, 2014). Also, poor adherence to treatment may contribute to the development of multidrug resistance, due to higher pill burden, overlapping or additive adverse drug reactions (ADRs) and drug–drug interactions (Singh *et al.*, 2020).

This prevalence of MDRTB in this study was 0.85%.This was similar to a previous study which reported that the prevalence of MDR-TB was 0.5% among new cases and 2.3% among previously treated cases (Iem *et al*., 2019).Also, a pooled prevalence of MDRT-TB of 2.1% was demonstrated among new cases of TB in Sub-Saharan Africa (SSA) by a meta-analysis (Musa *et al*., 2017).Our findings were, however,low compared to many studies in our environment.In a systematic review of the prevalence of MDRTB in Nigeria, multidrug resistance among new and previously-treated cases was 6.0% and 32.0%respectively(Onyedum *et al.*, 2017).In a study among patients in a Chest Clinic, the prevalence of MDR-TB from the fifty-seven isolates was 10.5% (Oyedeji *et al.*, 2020).Even higher results have been documented by other studies, including an overall prevalence of MDR-TB of 28.1%(Mdivani *et al.*, 2008). Previously treated and new cases had a prevalence of 7.0% and 3.5% MDR-TB, respectively. The study highlighted a high prevalence of MDR-TB among the study population. History of previous TB treatment was associated with MDR-TB(Daniel and Osman, 2011).

Majority of the patients received standard regimen for MDR-TB treatment. In this scenario, individual drug sensitivity testing (DST) is not done. Instead, data from representative patient populations are used to base regimen design. All patients that fall into a particular category receive the same regimen. On the other hand, each regimen is based on the patient's past history of TB treatment and individual DST results in Individualized regimen (WHO, 2014). Standardized regimens are more commonly used, especially in resource poor setting where DST is only limited to one or two first line medications (World Health Organization, 2014). Two new drugs, Bedaquiline and Delamanid were recently added to manage difficult-to-treat MDR-/XDR-TB cases. A high proportion of unsuccessful treatment outcome (43%) was observed among patients who were enrolled in standardized treatment regimens as reported by a systematic review (Kibret *et al*., 2017).

Outcomes for TB have been rather mixed as some studies have shown high cure rates as well as a high mortality rate. Cure was achieved in 83% and 74% of patients on 9- versus 20/24-months MDR-TB regimens respective(Bulabula et al., 2019). A meta-analysis of 14 studies reported a 55.6% cure rate and 63.5% treatment completed rate. Also, they reported that 12.6% of the patients died, 14.2% defaulted from therapy, and 7.6% failed therapy (Kibret *et al*., 2017). In our study, 64.5% of the patients achieved cure, while 15.6% died. This shows that patients with MDR-TB exhibited a low treatment success rate compared to the World Health Organization 2015 target of at least 75 to 90% (World Health Organization, 2011).About one tenth of the patients defaulted treatment which could possibly explain the spread of the MDR-TB strain in the population, leading to the high prevalence of new cases among MDR-TB cases.

On multivariable regression analysis, we found no significant association between the patient characteristics and their treatment outcomes. A similar study in South Africa however, found that male sex, low weight at diagnosis, and poor oral drug adherence were associated with unfavorabletreatment outcome; however, injectable drug adherence, positive baseline smear and HIV status were not associated with treatment outcome (Elliott *et al*., 2014). In addition to this, Saha *et al.* reported that younger age and resistance to fewer drugs were associated with favorable outcomes (Saha *et al*., 2017).

Limitations

This study was retrospective and relied on the records maintained routinely in the MDR-TB diagnosis and treatment centers. As expected of data-based studies, we had missing data and thus could adequately report on the outcomes for some patients on the registers. However, the

program managers reassured us that the database captured all patients as they were supervised with routine and periodic checks to ensure minimal loss to follow up.

CONCLUSION

The prevalence of MDR-TB in this study was found to be 0.85%. Majority of the patients were aged 21-40 years, male, newly diagnosed TB cases, and had no prior exposure to TB medications. Over a tenth of the patients defaulted from treatment, and about 15% died, which is a serious public health concern that needs to be addressed urgently. On multivariable regression analysis, none of the patients' characteristics had significant association with their treatment outcome. Our findings revealed a low MDR-TB treatment success rate among patients, when compared to the WHO target of 75-90%.

We recommend improved surveillance and control of MDR-TB, especially in the light of the oral drug regimen. Proper monitoring of DOTS programs should be emphasized by the TB Control program as TB naïve patients comprised the majority of those with MDR-TB. Adequate contact tracing for early detection and treatment of infected contacts to reduce spread of primary TB.Finally, prompt initiation of patients to care by making LPA testing readily available for ease of diagnosis of type of DRTB.

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