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Prevalence and risk factors associated with drug resistant TB in South West, Nigeria

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ABSTRACT

Objective: To determine the prevalence and risk factors associated with drug resistant tuberculosis (TB) in South West Nigeria. **Methods:** A retrospective study conducted among pulmonary tuberculosis (PTB) patients from Oyo and Osun States in South West Nigeria who had their culture and drug susceptibility test performed at the institute of tropical medicine Antwerp, Belgium between 2007 and 2009. Data on the patient's characteristics were retrieved from the TB treatment card. Univariate analysis was performed to assess the risk factors for drug resistant tuberculosis. The Level of significance was at $P<0.05$. **Results:** Among the 88 patients who had drug-susceptibility test result, there were 50 males and 38 females. Of the 88 patients, 55 (62.5%) had strains resistant to at least one or more anti-drugs. The proportion of TB cases with resistance to a single drug was 12.7%. The multi-drug resistant TB (MDR-TB) rate was 76.4%. The only significant factor for the development of drug resistance and MDR was the history of previous anti TB treatment ($P<0.01$). Other factors such as age [*OR* 0.86 (0.35-2.13); $P=0.72$] and gender [*OR* 1.24 (0.49-3.14); $P=0.62$] were not significantly associated with drug resistance TB. **Conclusions:** The study highlighted a high prevalence of MDR-TB among the study population. History of previous TB treatment was associated with MDR-TB. There is an urgent need to conduct a national TB drug resistance survey to determine the actual burden and risk factors associated with drug resistance TB in the country.

1. Introduction

Multidrug resistant tuberculosis (MDR-TB) defined as resistance to at least rifampicin and isoniazid, has become a major threat to the control of tuberculosis worldwide. Globally, annual estimates of 500 000 people are infected with the resistant bacteria. Three countries namely China, Indonesia and Russia are said to harbour about 50% of the total burden of MDR-TB worldwide[1]. Several African countries have low rates of MDR-TB largely because there have not been systematic nationwide surveys to determine the burden of the disease and the lack of laboratory capacity to conduct such a large scale surveys.

Nigeria is ranked 4th among the 22 high burden countries with tuberculosis. The country has an estimated TB prevalence rate of all cases to be 311/100 000 population and 131/100 000 for the infectious smear positive cases[2]. Nigeria being the most populous African country with a projected population of about 150 million people is expected to have an estimated number of over 400 000 TB patients annually. Of this number the country is only able to notify about 100 000 TB cases annually[3]. This suggests that a large number of patients are receiving treatment outside the DOTS programme. These patients may not have access to high quality drugs and may not be treated in line with national guidelines[4] thereby predisposing such patients to fail first line treatment and candidates for resistant TB. About 10% of notified TB cases annually are retreatment cases[3]. These are patients who have received first line anti-TB treatment in the past, patients that return to treatment after default, relapse and patients who failed first line treatment. These patients are high priority suspects for MDR-TB infection.

The WHO currently estimates MDR TB prevalence rates of 1.9% and 9.3% among new and retreatment TB cases

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respectively in Nigeria[2]. The country is yet to have a national drug resistance survey to determine the actual burden of the disease. However, some hospital based data have reported MDR-TB rates of 4% in Abuja. 17.6% (it ranged from 4% to 31% among different categories of patients) and 53.6%[5] in Ibadan[6,7], Nigeria. This study therefore was embarked upon to determine the prevalence and factors associated with the development of MDR-TB in two states TB programmes in the South-Western geopolitical zone of Nigeria.

2. Materials and methods

This is a retrospective study of TB patients attending treatment with a in Oyo and Osun states South West, Nigeria with a total population of 9 million inhabitants. Patient's sputum specimen was subjected to culture and drug susceptibility testing at the Antwerp Institute of Tropical Medicine in Belgium from July 2007 to December 2009 supported by Damien Foundation Belgium.

Three sputum samples were obtained from each patient for routine diagnostic purpose in the field, but for the study purpose we obtained another two sputum specimens from the positive ones. Sputum was first cultured at Ibadan University College Hospital (UCH) Laboratory using Ogawa media method for Mycobacteria isolation, and after the growth of the bacteria. The colonies from the culture samples were sent to the Supranational Laboratory at Antwerp Institute of Tropical Medicine in Belgium. The specimen was shipped to Antwerp using sterile 2 mL cryovials. Two cryovials were prepared per strains; in the first cryovial, 1 mL of 1% CPC, and 2% Nacl were added. The harvested colonies are transferred into the 2 mL. In the second one, the harvested colonies were transferred directly, without any preservative component (dry colonies). Results of the sample isolates were received on average of about 4 months after the samples were sent. Details of respondent's socio-demographic characteristics and history of previous treatment were obtained from their treatment cards and TB registers at their respective treatment centres. Data was initially entered into an excel sheet and analysis was done using EPI Info 2002.

3. Results

3.1. Characteristics of patients

Of the 134 patients sputum specimens sent to the supranational laboratory in Antwerp, Belgium. A totol of 88 (65.7%) were positive for MTB culture. Drug-susceptibility testing was done against the standard first line anti-TB drugs such as rifampicin (RIF), isoniazid (INH), ethambutol (EMB) and streptomycin (SM). Demographic data of the 88 strains were analyzed. There were 23 new and 65 retreatment patients. Fifty (50) were males and 38 were females. Majority of the patients were in the age group 25-34 years (45.8%), followed by the age group 35-44 years (25.3%) age group as shown in Table 1. There was no statistically significant difference in the mean age for male and females (35.9±10.0 *vs* 33.5±9.3; P=0.26).

3.2. Risk of drug-resistant tuberculosis

Of the 88 patients, 55 (62.5%) had strains resistant to at least one or more anti-TB drugs. The prevalence of different patterns of resistance is shown in Table 2. Overall, 55 strains were resistant to one or more anti-TB drugs. The proportion of TB cases with resistance to a single drug ranged from 0% for EMB to 5.5% for RIF.

Table 1
Age and sex distribution of patients enrolled in the study.

Age group (years)	Male	Female	Total [*n* (%)]
<15	1	0	1(1.2)
15-24	2	6	8(9.6)
25-34	23	15	38(45.8)
35-44	9	12	21(25.3)
45-54	7	4	11(13.3)
>55	3	1	4(4.8)
Total	45	38	83(100.0)

Age for 5 male patients was missing.

MDR-TB showed a prevalence of 76.4% which ranged from range of 0% for INH+RIF to 56.4% for INH+RIF+SM+EMB.

The prevalence of poly resistance to anti-TB drugs was 10.9% which ranged 1.8% RIF+SM/EMB to 3.6% for INH+SM ±EMB. The overall resistance to drugs tested ranged from 63.6% for EMB to 89.1% SM as outlined in Table 2.

Table 3 showed the factors associated with the development of any resistance to first line drugs. The most significant factor associated with any resistance was the history of previous anti TB treatment [*OR* 17.3 (4.51-72.7); P=0.01]. Other factors such as age [*OR* 1.49 (0.51-3.90); P=0.47] and gender [*OR* 0.64 (0.24-1.69); P=0.31] were not significantly associated with the development of any resistance.

While comparing MDR-TB and Non MDR-TB patients (*i.e.* other resistance pattern and susceptible) there was no significant difference in age [*OR* 0.86 (0.35-2.13); P=0.72] and gender [*OR* 1.24 (0.49-3.14); P=0.62]. However, there was a significant association between history of previous anti-TB treatment and the development of MDR-TB (P<0.01) as shown in Table 4.

4. Discussion

The MDR-TB prevalence of 76.4% was high compared to what had been reported earlier by previous studies in the country[5-7]. This may be related to the fact that majority of the study population were patients who had history of previous anti-TB treatment and are therefore a high risk group for the development of MDR-TB.

The history of previous treatment was the most significant

Table 2

Pattern of first-line anti-tuberculosis resistance of 55 *M. tuberculosis* strains in Nigeria.

Resistance profile	Previously treated TB patients (*n*=51)	New TB patients (*n*=4)	Total *n* (%) (*n*=55)
Mono resistance	2	5	7(12.7)
INH only	1	1	2(3.6)
RIF only	0	3	3(5.5)
SM only	1	1	2(3.6)
EMB only	0	0	0(0)
MDR	42	0	42(76.4)
INH+RIF	0	0	0(0)
INH+RIF+EMB	1	0	1(1.8)
INH+RIF+SM	10	0	10(18.2)
INH+RIF+SM+EMB	31	0	31(56.4)
Poly resistance	5	1	6(10.9)
INH+SM+EMB	2	0	2(3.6)
INH+SM	2	0	2(3.6)
RIF+SM	0	1	1(1.8)
EMB+SM	1	0	1(1.8)
Overall resistant to			
INH drug	47	1	48(87.3)
RIF drug	42	4	46(83.6)
SM drug	47	2	49(89.1)
EMB drug	35	0	35(63.6)

Table 3

Analysis of the association between patient's demographic characteristics and the development of resistance to at least one first line anti-TB drug.

		Culture positive (*n*=88)	Resistance (*n*=55)	Susceptible (*n*=33)	*OR* (95% *CI*)	*P*-value
Age group (years)	≤34	49	34	15	-	-
	≥35	34	21	13	1.49(0.51-3.90)	0.47
	Sub-total	83	55	28	-	-
Gender	Male	50	29	21	-	-
	Female	38	26	12	-	-
	Sub-total	88	55	33	0.64(0.24-1.69)	0.31
Previous treatment	Yes	65	51	14	-	-
	No	23	4	19	17.30(4.51-72.7)	<0.01
	Sub-total	88	55	33	-	-

Table 4

Analysis of association of demographic characteristics with the development of MDR-TB.

		Total resistance (*n*=88)	MDR-TB cases (*n*=42)	Non MDR-TB cases (*n*=46)	*OR* (95% *CI*)	*P*-value
Age group (years)	≤34	48	26	22	-	-
	≥35	35	16	19	0.86(0.35-2.13)	0.72
	Sub-total	83	42	41	-	-
Gender	Male	50	25	25	-	-
	Female	38	17	21	1.24(0.49-3.14)	0.62
	Sub-total	88	42	46	-	-
Previous treatment	Yes	65	42	23	-	-
	No	23	0	23	undefined	<0.01
	Sub-total	88	42	46	-	-

factor associated with MDR-TB. This finding is consistent with the systematic reviews done in Europe on the risk factors for MDR-TB[8-11] and in surveys conducted in several countries by the World Health Organization[12].

The current national TB guideline and recommendations for the treatment of category 2 patients (previously treated TB patients) simply adds streptomycin to the four first line anti-TB regimen. This practice only serves to amplify resistance in these patients who are likely to have developed resistance to some or all of the previously used first line anti-drugs[13,14]. The situation is further complicated in many developing countries that lack the laboratory capacity for culture and DST for the diagnosis of resistant TB cases. The laboratory challenge however can be surmounted temporarily by the introduction of rapid diagnostic tools using bio-molecular techniques which can be used for the

diagnoses of MDR-TB within 24-48 h. These tools can at least make diagnosis of MDR-TB and patents can be placed on standardized while awaiting DST results. This action will in no doubt decrease or break the transmission chain to uninfected populations. In the near future all new TB patients should be screened with these rapid tools so that appropriate treatment can be commenced at the outset and prevent amplification of resistant strain. Though the rapid diagnostic methods are not a replacement for standard solid or liquid cultures, they can be important in the rapid scale up of laboratory services in developing countries where the required bio-safety standards and cost may be a limiting factor.

Our study did not observe any significant difference between gender and MDR TB compared with studies in Georgia which reveal that women were at higher risk of MDR TB compared with men[9]. The reason postulated 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 at home with sick MDR-TB patients than men especially when the MDR-TB treatment was not widely available in the country. In the current global drug resistance survey report, the association between gender and MDR-TB was not clearly demonstrated. Some countries in the former Soviet Union reported a higher prevalence among males compared to females[1]. This was thought to be related to alcohol dependency and imprisonment status where more men than women are involved. Other studies for example in South Africa have demonstrated an increase risk in women[1]. The report concluded that access to health care services and exposure to other risk may be responsible for the differences observed between gender and MDR-TB status.

The study is not without limitations. Firstly the small sample size may limit the generalization of the study results. Secondly, a sizeable proportion of culture negative and contaminated samples for *Mycobacterium tuberculosis (M. tuberculosis)* may be attributed to several factors, such as inclusion of specimen with very few bacilli resulting from good microscopy performances, excessive transit time during transport. These factors however are not thought to have caused a systemic bias. In addition HIV status was not considered in his study because of incomplete information on the HIV status.

In spite of the limitations in this study, it has provided useful information for the country in determining the resistance profile that assisted in the development of a standardized category IV treatment for multidrug resistant TB regimen and the approval of second line drugs for the treatment of MDR-TB patients by the Green Light Committee (GLC). There is however, an urgent need to carry out a national drug resistance survey to estimate the actual burden of MDR-TB patients in the country.

Conflict of interest statement

We declare that we have no conflict of interest.

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