Annals of Health Research
Volume 4, Issue No 1: 53-59
January-June 2018
DOI: 10.30442/ahr.0401-1-07

ORIGINAL RESEARCH

Rifampicin resistance among patients with Tuberculosis at the Olabisi Onabanjo University Teaching Hospital, Sagamu

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Abstract

Background: Tuberculosis (TB) is a major public health problem in Nigeria. The emergence of multidrug-resistant Tuberculosis poses a threat to global Tuberculosis control and if not effectively addressed, may wipe out the achievements of previous efforts in controlling Tuberculosis.
Objectives: To determine the prevalence and factors associated with rifampicin resistance among patients receiving care for TB at the OlabisiOnabanjo University Teaching Hospital, Sagamu.
Methods: A retrospective study of presumptive Tuberculosis cases managed between January 2013 and December 2016 at the Directly Observed Treatment clinic, OlabisiOnabanjoUniversity Teaching Hospital Sagamu, Ogun State, Nigeria, was done. One sputum sample was obtained from each patient for the Gene Xpert® test to diagnose TB and to determine rifampicin resistance among patients with confirmed Mycobacterium tuberculosis infection. HIV screening was also carried out on all the patients using HIV Rapid Test kits. The sociodemographic data were retrieved from the presumptive Tuberculosis register.
Results: A total of 1572 presumptive TB patients was screened for TB, out of which 187 (11.8%) were confirmed to be infected with *Mycobacterium tuberculosis* (MTB). A total of 20 (10.7%) of the 187 MTB patients had rifampicin resistance using the Gene Xpert® method. The Rifampicin resistance rate was significantly associated with re-treatment TB category, but not with age, sex or HIV status.
Conclusion: The study showed rifampicin drug resistance among confirmed TB patients. There is a need to decentralise the use of Gene Xpert® test for TB to the peripheral facilities and make it a point of care test for presumptive TB patients.

Key words: Gene Xpert®, Drug resistance, Rifampicin Resistance, Tuberculosis.

Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), is a major public health problem in both high and low income countries. About one-third of the world's population is infected with TB and about 10% of this infected population has a lifetime risk of falling ill with the disease. [1] In 2016 alone, TB killed about 1.5 million people (1.1 million HIV-negative and 0.4 million HIV-positive) and with this, TB ranks alongside HIV as a leading cause of death worldwide. [2] Nigeria ranks 10th among the "20+10" high-burden TB countries in the world, (referring to 20 countries with the highest number of cases in absolute terms, as well as 10 countries with the largest per capita case rate that do not already appear among the first 20 countries and that meet a minimum threshold in terms of absolute numbers of cases) [3] with a prevalence rate of 323 per 100,000 population and

an incidence rate of 338 per 100,000 population for all forms of TB.

In 2008, the World Health Organization (WHO) launched the survey report on the worldwide threat posed by the emergence of multi-drug resistance tuberculosis (MDR-TB) to the global TB control efforts and submitted that drug resistance TB may wipe out the achievements of previous efforts for the control of TB, if not effectively addressed. [5] The WHO reported 480,000 cases of multidrug-resistant TB and 190,000 deaths globally in 2014. In addition, the first National Drug Resistant (DR)-TB survey in Nigeria conducted in 2012 reported a Multidrug-resistant TB prevalence rate of 2.9% among new TB cases and 14.3% among re-treatment cases, giving an overall crude prevalence rate of 4.8% among all treatment categories. [5]

Several reasons have been adduced to the emergence of drug-resistant TB. These reasons include poor compliance with the first line anti-TB drugs, unregulated access to anti-tuberculosis drugs associated with indiscriminate use of the medications, inappropriate combinations by practitioners not trained in the proper use of drug therapy in tuberculosis, irregular supply of recommended drugs, poor case detection rate and unguided discontinuation of therapy due to side-effects of drugs. [6-11]

Recently, the National TB and Leprosy Control programme provided the WHO-recommended GeneXpert® as a screening test for drug-resistant TB and for the diagnosis of MTB where it is available. The Gene Xpert® test detects both *Mycobacterium tuberculosis* and resistance of the mycobacterium to rifampicin within 2 hours. [12] The detection of rifampicin resistance, which is a surrogate for MDR-TB, makes the Gene Xpert® test an attractive screening tool for the diagnosis of TB and MDR-TB compared with the standard diagnostic methods such as the line probe assays and TB culture using Löwenstein-Jensen medium. The latter takes between ten day and six weeks for the results to be available. [13] With the increasing availability of Gene Xpert® and other newer molecular diagnostic techniques for drug resistant-TB, the actual burden of drug resistance in the country can be ascertained. Recent reports from the WHO indicated that in the year 2016, the prevalence of MDR/Rifampicin resistant -TB was 4.3% among new TB cases and 25% among previously-treated TB cases in the country. [14] This report suggested an increase in the rates both among new and re-treatment TB patients. Despite the increasing burden, very few local studies have been conducted in Nigeria using the new Gene Xpert® diagnostic tool. In addition, few studies have been conducted on the prevalence of rifampicin-resistant TB in the south-west geographical region of the country because drug resistance is not routinely examined as part of the laboratory work-up for TB cases. [15] Therefore, this study was designed to determine the prevalence and socio-demographic factors associated with rifampicin resistance among diagnosed TB patients at the Olabisi Onabanjo University Teaching Hospital, Sagamu.

Methods

This study retrospectively examined TB patients seen at the TB clinic of the Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu, Ogun State, Nigeria between January 2013 and December 2016.The Olabisi Onabanjo University Teaching Hospital is a tertiary hospital located in Sagamu, Ogun State, Nigeria. It is a 247-bed capacity hospital, which caters for patients referred from hospitals located within and outside Ogun State.

Definition of Terms - (According to the National TB and Leprosy Control Guidelines)
Presumptive TB patient is a patient who has had a cough for two weeks or more.
New TB patient: refers to a diagnosed TB patient

who has never had treatment for TB, or who has taken anti-TB drugs for less than four weeks, irrespective of the site of the disease.

Re-treatment TB patient (Previously treated) TB Case refers to a diagnosed TB patient who had received four weeks or more of anti-TB drugs in the past irrespective of the site of the disease.

Procedure of TB diagnosis

One sputum sample was obtained from each patient for the Gene Xpert® test. The sputum sample was mixed with the reagent that was provided with the assay and thereafter, the cartridge containing this mixture was placed in the Gene Xpert® machine. The processing of the sample is fully automated and takes less than two hours. The Gene Xpert® MTB/Rif assay is a nucleic acid amplification test which simultaneously detects the DNA of *Mycobacterium tuberculosis* complex and resistance to rifampicin. The result indicates whether or not MTB (*Mycobacterium tuberculosis*) Complex target DNA is detected in the sputum sample and if MTB is detected, whether resistance to rifampicin is present. [13] A positive MTB result will be displayed as high, medium, low or very low. The result of the test is automatically generated and printed out by the computer attached to the Gene Xpert® machine.

Ethical consideration: Ethical clearance was not sought for this study because the study was based on routinely reported data by the National Tuberculosis and Leprosy Control Programmes (NTBLCP) with no personal identifiers of patients but the principle of the Helsinki Declaration on human subject research was adhered to.

Data collection and analysis

Socio-demographic data, category of patient, results of HIV test were extracted from the NTBLCP reporting tools. HIV test was conducted in line with the national guidelines on HIV testing and counseling. The first HIV rapid test kit used was *Determine* (determines HIV-1/2 Alere Determine™, Japan 2012) and if this was positive, then the Uni-Gold™ (Trinity Biotech PLC, Wicklow, Ireland, 2013) rapid test kit was used in the series. A concordant result was regarded as positive. In cases of a discordant result, STAT-PAK® was used as the tie- breaker. The Gene Xpert® test results were retrieved with no personal identifier from the presumptive TB register over a four-year period from January 2013 to December 2016. The retrieved data were stored in a safe place where only the investigators had access to. The data were entered into Excel sheet for corrections and data cleaning before it was transferred into SPSS version 22 statistical software for analysis. The necessary descriptive and inferential statistics were conducted and the association between the socio-demographic factors and rifampicin resistance was carried out using Chi-Square statistical test and the level of significance was taken at $P< 0.05$.

Results

A total number of 1572 patients were presumptive TB cases, of which 187 (11.8%) were diagnosed with tuberculosis. Eighty-seven (46.5%) were less than 35 years old and 100 (53.5%) were aged 35 years and above with a mean age of 38.6 ±13. 4 years. The cases comprised 111 (59.4%) males and 76 (40.6%) females giving a male-to-female ratio of 1.5:1. A positive HIV test was obtained in 47 (25.1%) patients and the majority of the patients were re-treatment TB cases as shown in Table I.

Table II shows a rifampicin resistance rate of 10.7% among the diagnosed MTB patients. Table III assessed some socio-demographic factors associated with rifampicin resistance among confirmed MTB patients. There was a significant association between rifampicin resistance positivity and the risk category of the TB patients. Those who were in the re-treatment category were significantly more likely to have rifampicin resistance.

Table I: Baseline characteristics of diagnosed TB patients (n = 187)

Characteristics		*Frequencies*	*Percentages*
Age groups (Years)			
	<35	87	46.5
	≤35	100	53.5
Sex	Male	111	59.4
	Female	76	40.6
HIV Status			
	Negative	140	74.9
	Positive	47	25.1
TB Risk group			
	New	84	44.9
	Retreatment	103	55.1

Mean Age 38.6 ± 13.4 years

Table II: Pattern of Rifampicin resistance among diagnosed TB patients (n= 187)

Gene Xpert® Results	*Frequencies*	*Percentages*
MTB detected/Rifampicin -resistance detected	20	10.7
MTB detected/Rifampicin -resistance not detected	167	89.3
Total	187	100

Table III: Some socio -demographic and clinical factors associated with Rifampicin resistance among diagnosed TB patients

Factors	*Rifampicin-resistance detected (n = 20)*	*Rifampicin-resistance not detected (n = 167)*	*Total*	*P values*
Age Group				
<35	5(5.7)	82(94.3)	87(100)	
≥35	15(15.0)	85(85.0)	100 (100)	0.057
Sex				
Male	13 (11.7)	98(88.3)	111 (100)	
Female	7 (9.2)	69 (90.8)	76(100)	0.638
HIV Status				
Non- Reactive	12 (8.6)	128 (91.4)	140 (100.0)	
Reactive	8 (17.0)	39(83.0)	47 (100.0)	0.111
Risk Group				
New	3(3.5)	81(96.4)	84(100.0)	0.004*
Re-treatment	17(16.5)	86(83.5)	103(100.0)	

*Fishers Exact Test

Discussion

This study showed the prevalence of rifampicin resistance among diagnosed TB cases to be 10.7%. This prevalence rate was higher than 6% reported in another study conducted in Kaduna, northern Nigeria, [16] 8% in Iran (Central Province) [17] and 6.8% in Northeast China. [18] However the prevalence rate reported in this study was lower than the 13% rate reported in Benue State, Nigeria. [19] The higher prevalence rate of rifampicin resistance among diagnosed TB patients in Benue as well as in Sagamu, both in Nigeria, compared to Iran and China may be related to the differences in the socioeconomic status and the better TB control programmes in the latter countries. In addition, some other factors such as erratic drug supply for drug-susceptible patients, non-adherence to first line anti-TB drugs among others, need to be put into consideration to forestall further development of drug-resistant TB in Nigeria.

Rifampicin resistance is currently used as a proxy screening test for MDR in Nigeria because of the high correlation between rifampicin resistance and MDR. [20] There is a need for the decentralization of access to the Gene Xpert® machine as a point of care test for all TB patients in the country. The decentralization will assist in prompt detection of rifampicin resistant patients who can be further evaluated for MDR-TB and this will enhance prompt treatment, prevent continued transmission of the resistant strain in the country.

Most of the patients with rifampicin resistance noted in the present study were TB re-treatment cases. Previous treatment for Pulmonary TB has been described as a risk factor for drug-resistant TB as reported in various studies. [21 -25] This finding is similar to a previous observation made in the 2012 Nigeria National DR-TB Prevalence Survey report [5] and the WHO Global Report of 2012. [2] The re-treatment category comprises of TB patients who have had previous exposure to anti-TB drugs for more than four weeks according to the NTBLCP national guidelines. This group includes patients who failed previous TB treatment regimen, patients who defaulted from TB treatment and later returned for treatment, patients who relapsed after previous completion of treatment and those who have been managed for TB in facilities outside government TB facilities without proper documentation. [26] These patients could have acquired drug-resistant TB bacilli during or following a course of anti-TB chemotherapy.

This study showed that HIV status was not significantly associated with rifampicin resistance, though there has been some postulations linking HIV infection with TB drug resistance due to drug malabsorption in HIV-infected patients and this has been shown to predispose to treatment failure and drug resistance. [27, 28] The result of the present study is consistent with similar studies conducted in Calabar, Nigeria, [15] Ethiopia, [29] and Tanzania [30] which reported that HIV infection was not significantly associated TB drug resistance.

Limitation of study:
The study was a retrospective study of secondary data. Therefore, some variables of importance were not adequately captured routinely in the National TB and Leprosy Control Programme report tools and this limited the scope of the study.

Conclusion

The study showed a relatively high prevalence of rifampicin-resistant TB compared with what was reported in the 2012 National MDR-TB survey in Nigeria. Re-treatment category of TB cases was the only risk factor associated with rifampicin resistance in TB. The provision of quality anti-TB drugs to drug-susceptible patients and ensuring that these patients adhere to treatment guidelines will reduce the need for re-treatment and subsequently, the emergence of drug- resistant TB. There is a need to make Gene Xpert® a point of care test for early diagnosis of rifampicin-resistant TB. Clinicians should have a high index of suspicion for rifampicin-resistant TB in patients who have been on anti-TB chemotherapy for more than four weeks without clinical improvement. Further research will be required to capture a wide spectrum of variables which may be determinants of drug resistance in TB.

Conflicts of Interest: None
Funding: Self-funded
Authors' Contributions: DOJ conceived and designed the study and made significant intellectual contributions to the initial draft. BJO collected the data and wrote the initial draft of the manuscript. SKJ provided statistical support and participated in drafting the initial manuscript. EAA and SAA reviewed and made significant intellectual contributions to the final manuscript.
Publication History: Submitted 10-November 2017; **Revised** 24-February 2018; **Accepted** 28-March 2018.

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