Prevalence of Rifampicin-Resistant Tuberculosis among Patients Previously Treated for Pulmonary Tuberculosis in North-Western, Nigeria

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Abstract

Background: Drug-resistant tuberculosis (TB) is a significant public health problem. Greater than 90% of rifampicin (RIF)-resistant isolates were also isoniazid resistant, and hence, rifampicin resistance (RR) is frequently used as a surrogate for multidrug-resistant TB. **Setting:** This study was conducted at Infectious Disease Hospital Kano in North-Western Nigeria. **Objectives:** The aim of this study was to determine the prevalence of RR among patients previously treated for pulmonary TB (PTB). **Materials and Methods:** A total of 120 patients previously treated for PTB with current clinical features of PTB were recruited into this study. Relevant clinical information were obtained using a questionnaire. The sputum was collected and analyzed by the Gene Xpert MTB/RIF® machine to detect RR tuberculosis infection and blood screened for HIV infection. **Results:** The mean (±standard deviation) age of the participants was 35.9 ± 14.3 years and they comprised 73 (60.8%) males and 47 (39.2%) females. HIV-seropositive rate was 11.7% among the participants. Of the 120 participants, PTB was detected in 35 (29.2%) of the participants by Gene Xpert MTB/RIF and 29 of them were cases of relapse. Five patients (4.2%) had RR tuberculosis and 80% of them were below the age of 45 years. **Conclusion:** The prevalence of RR is not high among previously treated PTB patients in this study when compared with other previous studies. This finding is a window for evaluating the efficacy of current interventions in the region and evidence for the consolidation of existing control policies.

Keywords: Drug resistance, multidrug-resistant tuberculosis, rifampicin, tuberculosis

Introduction

The increasing incidence of drug-resistant tuberculosis (DR-TB) is a notable global health challenge.[1] TB drug resistance (TDR) types are mono-resistance, poly-resistance, multidrug resistance (MDR), extensively drug resistance (XDR), and rifampicin resistance (RR). MDR-TB is defined as a form of TB infection caused by *Mycobacterium tuberculosis* strains that are resistant to treatment with at least two of the most potent first-line anti-TB drugs: rifampicin (RIF) and isoniazid (INH).[2]

Previous treatment for TB is the strongest risk factor for the development of MDR-TB, and this is partly due to acquired drug resistance.[3,4] Acquired resistance emanates due to inappropriate chemotherapy regimens, inadequate or irregular drug supply, unsatisfactory patients compliance, lack of supervision of treatment, and the absence of infection control measures in hospitals and communities.[5] Other identified risk factors include poor management of TB control programs, poverty, rapid population growth, and uncontrolled urbanization.[1]

Recently, a new form of TB-drug resistance known as extensively drug resistance (XDR-TB) has been reported.[4,6] It is a subset of MDR-TB with additional resistance to any of the fluoroquinolones (ciprofloxacin, ofloxacin, etc.) and one of the second-line injectable drugs, namely kanamycin, capreomycin, and amikacin.[7] XDR-TB has been reported in 100 countries.[4] On an average, an estimated 9.0% of people with MDR-TB

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have XDR-TB.[4] Other descriptive terminologies used for resistant TB include, total anti-TDR-TB or super XDR.[8] TDR-TB is defined as resistance to all first-line and second-line anti-TB drugs.[8] The emergence of TDR-TB though well described is yet to be recognized.[4]

RR is resistance to RIF detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to RIF, in the form of mono-resistance, poly-resistance, MDR, or XDR.[2]

Rifampicin (RIF) is one of the most important anti-TB antibiotics; it exerts its bactericidal activity by inhibiting the early steps of gene transcription by binding to the β-subunit of RNA polymerase (*rpo* β) encoded by the *rpo* β gene.[9] Its inclusion in the anti-TB regimen has shortened the duration of TB treatment.[10] RR has been reported by previous studies to be a useful surrogate marker for the detection of MDR-TB.[11,12] It had been estimated that >90.0% of RIF-resistant TB were also resistant to INH, making RIF-resistance a reliable indicator of MDR-TB.[13,14] To this end, several genotypic methods for rapidly detecting RIF-resistance conferring mutations have been developed. Some of these methods include DNA sequencing, line probe assay, single-strand conformation polymorphism, DNA microarrays, RNA/RNA mismatch, molecular beacons, and most recently Xpert® MTB/RIF.[15,16]

TDR is not a new occurrence in Nigeria. It was described as early as 1976 by Fawcett in Zaria.[17] Since then, there have been other reports of TDR in various parts of the country using mycobacterial culture and drug susceptibility test.[18-23] There is a paucity of data on the prevalence of TB-drug resistance among patients previously treated for the condition in North-western Nigeria. This work was, therefore, designed to determine the prevalence of RR-TB in pulmonary TB (PTB) patients with the previous history of anti-TB therapy and used it as a surrogate for MDR-TB infection.

MATERIALS AND METHODS

Study setting

This study was carried out at the Infectious Disease Hospital (IDH), Kano, the capital of Kano State, Northwestern, Nigeria between April and June 2015. IDH is a specialist and referral center for infectious diseases in Kano State and its environs.

Study design

This was a cross-sectional hospital-based study. Consenting patients who satisfied the inclusion criteria were recruited at the clinics. Inclusion criteria were clinical features of PTB, history of previous anti-TB therapy independent of the treatment outcome, and age ≥15 years.

Sample size

We used the Fisher's formula to obtain our sample size, $n = Z^2$ p $(1 − p)/w^2$ where, n = desired sample size, P (known prevalence from previous study) $=0.072$,[21] Z (standard deviation [SD] at 95% confidence interval) $=1.96$, W (degree of accuracy) $= 0.05$, $1 − p = 0.928$ $n = 1.96^2$ $(0.072 [0.928]/0.05^2)$, $n = 102.8$.

Addition of 10% attrition from a piloted samples: $102.8 + 10.8$ (10% of 102.8) $n = 113.1$. Therefore, a total of 120 patients were recruited for the study.

Sampling technique

Consenting patients who satisfied the inclusion criteria were recruited by consecutive sampling as they presented to the clinics at IDH.

Data collection

The sociodemographic and clinical information were obtained using a questionnaire, especially designed for this study by a trained social worker and who was monitored regularly to ensure quality control. The clinical information obtained from the participants includes reported symptoms and duration, previous treatment for TB, risk factors for TB, and HIV-SeroStatus.

Sputum collection and analysis

A total of 120 patients who satisfied the inclusion criteria were recruited for the study. One spot sputum specimen and 4.0 ml of venous blood specimen were collected from each of the participants. The sputum specimens obtained were analyzed using the Gene Xpert MTB/RIF® to detect *M. tuberculosis* infection and its susceptibility pattern to RIF. The blood specimens were used for HIV serology, and CD4 count estimation of the HIV-seropositive participants determine the prevalence of RR in HIV sero-negative and sero-positive participants.

Gene Xpert MTB/RIF® (Ceheid Inc., USA) system is a platform for rapid and simple to use nucleic acid amplification tests.

Principle of the test

The test is based on a real-time semi-nested PCR test principle which detects the presence of *M. tuberculosis* complex bacilli by using five molecular beacons probes which span the *rpoB* gene (gene that encodes the β-subunit of RNA polymerase) 81-bp RR-determining region, the test simultaneously determines susceptibility to RIF, which can be used as a surrogate marker for multidrug resistance. The probes can differentiate between the conserved wild-type sequence and mutations in the core region that are associated with RR. The results are interpreted by the Gene Xpert® from measured fluorescent signals and embedded calculation algorithms which will be displayed in the "View Results" window of the computer.

Methods of analysis

A volume of 1.0 ml of sputum sample was mixed with 2.0 ml of buffer to liquefy the sputum and was incubated at room temperature for 15 min inside a close tube. The closed tube was manually agitated twice during the 15 min' incubation. Thereafter, 2.0 ml of the diluted sample was transferred into

the cartridge for ultrasonic lysis of the Mycobacteria to release target DNA. The cartridge was loaded into the Gene Xpert machine (Cepheid) to proceed with the rest of the protocol. After 1½ h, the comprehensive test result was read on a computer screen and was ready for printing.

Blood collection and CD4 estimation

The 4.0 ml of venous blood sample collected was dispensed in aliquots of 2.0 ml each into a plain and ethylenediaminetetraacetic acid bottle. The serum was extracted from the samples in the plain bottles and then used for HIV serology using a parallel algorithm protocol.[24] The parallel algorithm protocol was achieved using Determine™ HIV-1/2 test kit, Uni-Gold™ Recombigen® HIV-1/2 test kit, and Stat Pak™ HIV-1/2 test kit. Determine™ HIV-1/2 test kit and Uni-Gold™ Recombigen® HIV-1/2 test kit were used as the first-line test kits, whereas Stat Pak™ HIV-1/2 test kit was used as a tie-breaker for discordant results.

Data analysis

All data generated from the study were analyzed using the IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. (IBM SPSS, 2012). Frequency and mean with SDs were generated to examine the characteristics of the study population in relation to demographic variables. The Chi-square and Fisher's exact test were used to determine the association between RR and relevant variables and values of $P < 0.05$ was considered statistically significant.

Operational definitions

Patients with a previous history of anti-TB therapy were those who had received >1 month of anti-TB drugs. They were categorized as follows:

a. Relapse: Those cured previously of TB or completed treatment for TB and now having TB or TB symptoms
b. Default: The patient whose treatment was interrupted for >2 consecutive months and now returned having TB or TB symptoms
c. Failure: Patients with positive-TB sputum smear after 5 months or culture at 3 consecutive months of anti-TB therapy. [25]

The respondents were grouped into different social classes using the Oyedeji's classification[26] as follow:

• I: Senior public servants, professionals, managers, large-scale traders, businessmen and contractor, senior military officers
• II: Intermediate grade public servants, and senior school teachers, nonacademic professionals, for example, nurses, owners of medium-sized business, secretaries
• III: Nonmanual skilled workers including clerks, typists, telephone operators, junior school teachers, drivers, artisans
• IV: Petty traders, laborers, messengers, lower cadre civil servants
• V: Unemployed, full-time housewives, students, subsistence farmers.

Ethical approval

Ethical approval was obtained from the Ethical Review Committee of Kano State Ministry of Health before the commencement of the study. The participants were adequately informed about the nature of the study and its benefits, voluntary withdrawal at any stage of the survey, and confidentiality of given information.

RESULTS

A total of 120 participants with clinical features of PTB and with the previous history of anti-TB therapy were recruited in this study.

General characteristics of the participating subjects

The mean (±SD) age of the respondents was 35.9 ± 14.3 years. The participants were mainly Muslims 117 (97.5%), and they comprised 73 (60.8%) males and 47 (39.2%) females. Fifty-seven (47.5%) had no formal education. Sixty (50.0%) participants were in Social class IV. PTB was detected in 35 35 (29.2%) of the participants using the gene Xpert machine [Table 1].

Table 1: General characteristics of the participants (*n*=120)

Variables	Parameters	Frequency, *n* (%)
Age, mean (years)		35.9±14.3
Gender	Male	73 (60.8)
	Female	47 (39.2)
Marital status	Single	51 (42.5)
	Married	69 (57.5)
Religious affiliation	Christianity	3 (2.5)
	Islam	117 (97.5)
Highest educational level	Nonformal	57 (47.5)
	Primary	18 (15.0)
	Secondary	27 (22.5)
	Tertiary	18 (15.0)
Occupational status	Employed	70 (58.3)
	Un-employed	50 (41.7)
Family type	Extended	48 (40.0)
	Nuclear	72 (60.0.)
Social class	I	2 (1.7)
	II	-
	III	4 (3.3)
	IV	60 (50.0)
	V	54 (45.0)
TB category	Relapse	104 (86.7)
	Default	12 (10.0)
	Failure	2 (1.7)
HIV status	Reactive	14 (11.7)
	Nonreactive	106 (88.3)
Genexpert	Yes	35 (29.2)
	No	85 (70.8)
Rifampicin resistance	Yes	5 (4.2)
	No	115 (95.8)

TB: Tuberculosis

Prevalence of rifampicin resistance by sociodemographic characteristics

Five patients (4.2%) had RR among the clinically diagnosed PTB cases. Among the bacteriologically confirmed PTB cases, 14.3% (5/35) had RIF resistant. The participants in the age group of 24–35 years had the highest RR. RR by sociodemographic characteristics was not statistically significant [Table 2].

Rifampicin resistance in relationship to tuberculosis categorization

Table 3 shows that out of the 35 bacteriologically confirmed cases of previous PTB, 29 of them were relapsed, 4 returned after default, and 2 were treatment failure. There was no association between the RIF resistance and the TB category ($P = 0.243$).

Rifampicin resistance in relationship to the HIV status

Fourteen patients (11.7%) were HIV-seropositive, and TB/HIV co-infection was 5.7%. Table 4 shows the RIF resistance relationship to the HIV serostatus of the participants. RIF resistance had no significant association with HIV infection in this study ($P = 0.212$).

Discussion

Several studies worldwide have established that previous treatment with anti-TB therapy is an important risk factor for inducing TB-drug resistance.[27,28] Globally, 3.5% of new TB cases and 20.5% of previously treated cases were estimated to have MDR-TB.[4] Most federal and state specialist hospitals in Nigeria do not have facilities for mycobacterium culture and drug susceptibility test but with the help of donor agencies, many now have Gene Xpert MTB/RIF for rapid and simple detection of TB and RiF resistance.[4]

The prevalence of RR among previously treated patients in this study was 4.2%. This level of resistance was higher than the findings of Idigbe *et al*. who reported 2% in Lagos, Nigeria.[20] However, our prevalence was lower than 7.2% reported by Rasaki *et al*. in Ilorin,[21] 8.6% by Olusoji *et al*. in Sagamu,[22] and 19% by Lawson *et al*. in three cities of Nigeria.[23] The variation in prevalence rates might be due to variation in the method of TB detection (Culture/DST or GeneXpert), categories of TB patient studied, and endemicity of TB and level of TB control practices in the different study population. Higher prevalence rates can be attributed to poor TB control practices and noncompliance with preventive guidelines leading to inadequate treatment. Inadequate treatment also leads to a selective pressure that favors the multiplication of mutant organisms, emerging as resistant clones. These clones may continue to replicate in the presence of the sub-lethal dose to become predominant, leading to the recrudescence of the disease that is then resistant to the antituberculous medication.[28]

Table 2: Prevalence of rifampicin resistance by the sociodemographic characteristics

Variables	Parameters	No RIF resistance, *n* (%)	RIF resistance present, *n* (%)	χ^2	*P*
Age (years)	15-24	28 (24.3)	1 (20.0)	2.487	0.778
	25-34	34 (29.6)	2 (40.0)		
	35-44	26 (22.6)	1 (20.0)		
	45-54	11 (9.6)	0 (0.0)		
	55-64	9 (7.8)	0 (0.0)		
	65-74	7 (6.1)	1 (20.0)		
Gender	Male	69 (60.0)	4 (80.0)	0.804	0.370
	Female	46 (40.0)	1 (20.0)		
Marital status	Single	49 (42.6)	2 (40.0)	0.013	0.908
	Married	66 (57.4)	3 (60.0)		
Religious affiliation	Christianity	3 (2.6)	-	0.134	0.715
	Islam	112 (97.4)	5 (100.0)		
Highest educational level	Non-Formal	55 (47.8)	2 (40.0)	1.641	0.650
	Primary	18 (15.7)	-		
	Secondary	25 (21.7)	2 (40.0)		
	Tertiary	17 (14.8)	1 (20.0)		
Occupational status	Employed	67 (58.3)	3 (60.0)	0.060	0.656
	Un-Employed	48 (41.7)	2 (40.0)		
Family type	Extended	48 (41.7)	-	3.478	0.062
	Nuclear	67 (58.3)	5 (100.0)		
Social class	I	1 (0.9)	1 (20.0)	10.829	0.246
	II	-	-		
	III	4 (3.5)	0 (0.0)		
	IV	58 (50.4)	2 (40.0)		
	V	52 (45.2)	2 (40.0)		

RIF: Rifampicin

Table 3: Association between rifampicin resistance and tuberculosis category (*n*=35)

TB category	RIF		χ^2	P
	Resistance, *n* (%)	Susceptible, *n* (%)		
Relapse	3 (60.0)	26 (86.7)	2.826	0.243
Default	1 (20.0)	3 (10.0)		
Failure	1 (20.0)	1 (3.3)		

RIF: Rifampicin, TB: Tuberculosis

Table 4: Association between rifampicin resistance and HIV status (*n*=35)

HIV status	RIF		χ^2	P
	Resistance, *n* (%)	Susceptible, *n* (%)		
Reactive	1 (20.0)	1 (3.3)	1.560	0.212
Nonreactive	4 (80.0)	29 (96.7)		

RIF: Rifampicin

This study also showed that the age group of 25–34 years had the highest RR and 80% of the RR were below the age of 45 years. The occurrence of RIF resistance in young adults in this sample is similar to two previous studies in Nigeria,[10,21] that reported a higher prevalence of RR among the age group 24–32 years and 31–40 years, respectively.

We found a preponderance of male participants with RR, but this finding was not statistically significant. The study is in agreement with previous studies in Nigeria,[22,23] and with a national anti-TB drug-resistant study in Tanzania.[29] The disparity in gender distribution to TB-drug resistance could be attributed to the rate of exposure of male participants to the risk factors of TB infection such as smoking, alcoholism, and related vitamins deficiency, which could make them more susceptible.

In this study, RR was significantly higher among the relapse cases than in cases of treatment failures and the defaulters. If we use this as a proxy for MDR-TB, this finding would be in contrast to the report documented by the WHO, where MDR-TB was significantly higher in treatment failure group (49.0%) compared to (32.0%) in defaulters and relapse cases.[16] These results cannot be compared with other local studies[10,25] on RR because information on TB category was omitted.[25]

RIF resistance was detected in one of the two patients with TB/HIV coinfection. There was no significant association between HIV status and RR in this study. This is in agreement with the report by the global network of supranational reference laboratories assembled by the WHO's Global Project on Anti-tuberculosis Drug Resistance Surveillance, that failed demonstrate the association between drug resistance TB and HIV.[16] Similarly, Rasaki *et al.*,[21] in North Central Nigeria, reported that HIV coinfection was not found to be significantly

associated with anti-TDR. It is surprising that HIV infection was not associated with RR in some of the mentioned studies because HIV has been shown to influence TDR by favoring the risk of transmission of drug-resistant strains of *M. tuberculosis*.[30-32]

These contrasting findings may be explained by the lack of a sufficiently large sample size of these previous studies that reduced their chance of detecting a true effect and answering the research question of interest.

Limitation of the study
RR in this study was used as a proxy for MDR-TB infection. It would have been more appropriate to detect RIF and INH resistance simultaneously using other molecular methods like line probe assay or culture and DST. This would enable the actual prevalence rate of MDR-TB to be ascertained in the region. However, infrastructures needed for these test are limited because of the logistic, quality control, and financial resources. Furthermore, carrying out a sub-group analysis also overstretches the data which could lead to errors in interpretation; it may not be possible to comment on the association between RR and some categorical variables because of the power of the study. This study may serve as a template for other surveys and add to the existing knowledge on TDR.

CONCLUSION

The prevalence of RR is not high among previously treated PTB patients in this study when compared with other previous studies. This finding is a window for evaluating the efficacy of current interventions in the region and provides evidence for consolidation of existing policies.

Conflicts of interest
There are no conflicts of interest.

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