

A retrospective assessment of rifampicin resistance in paediatric tuberculosis in a tertiary hospital in south west Nigeria

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Abstract

Objectives: Children infected with tuberculosis, including drug resistant tuberculosis serve as reservoirs for Tuberculosis (TB) and as indicators of recent or ongoing transmission in the community. The aim of this study was to evaluate the prevalence of rifampicin resistance in paediatric tuberculosis in Babcock University Teaching Hospital, Ilishan Remo, Ogun State, Nigeria

Methodology: This was a retrospective study that involved a review of medical microbiology laboratory records to analyze GeneXpert results of sputum samples obtained from pediatric patients with tuberculosis between January 2017 and March 2022. A convenience sampling method was used to select cases who met the study's inclusion criteria until the sample size was attained.

Results: The medical laboratory records of 1046 subjects were analyzed in this study of which 556 (53.2%) were males. The mean age of all the patients was 10.77 ± 4.38 years and majority of the respondents 445 (42.5%) were in the age group 11-15 years. Fifty patients (4.8%) had positive GeneXpert results of which 3 (6.0%) were Rifampicin resistant.

Conclusion: In order to lower the burden of TB globally more efforts should be made to reduce paediatric TB.

Une évaluation rétrospective de la résistance à la rifampicine dans la tuberculose pédiatrique dans un hôpital tertiaire du sud-ouest du Nigéria

Résumé

Objectif de l'étude: Les enfants infectés par la tuberculose, y compris la tuberculose pharmaco résistante, servent de réservoirs de tuberculose (TB) et d'indicateurs de transmission récente ou en cours dans la communauté. Le but de cette étude était d'évaluer la prévalence de la résistance à la rifampicine dans la tuberculose pédiatrique à l'hôpital universitaire Babcock, Ilishan Remo, État d'Ogun, Nigéria.

Méthode de l'étude : Il s'agissait d'une étude rétrospective qui impliquait un examen des dossiers de laboratoire de microbiologie médicale pour analyser les résultats GeneXpert d'échantillons d'expectorations obtenus auprès de patients pédiatriques atteints de tuberculose entre janvier 2017 et mars 2022. Une méthode d'échantillonnage de commodité a été utilisée pour sélectionner les cas répondant aux critères d'inclusion de l'étude. Critères jusqu'à ce que la taille de l'échantillon soit atteinte.

Résultat de l'étude : Les dossiers de laboratoire médical de 1 046 sujets ont été analysés dans cette étude, dont 556 (53,2 %) étaient des hommes. L'âge moyen de tous les patients était de $10,77 \pm 4,38$ ans et la majorité des répondants, 445 (42,5 %), appartenaient à la tranche d'âge de 11 à 15 ans. Cinquante patients (4,8 %) ont eu des résultats GeneXpert positifs, dont 3 (6,0 %) étaient résistants à la rifampicine.

Conclusion : Afin de réduire le fardeau de la tuberculose à l'échelle mondiale, des efforts supplémentaires doivent être déployés pour réduire la tuberculose pédiatrique.

INTRODUCTION

Tuberculosis (TB) is a global health security challenge which annually accounts for about 10 million infections and 1.5 million deaths globally (1,2). TB is prevalent in low and middle income countries (LMICs) and about half of the people with TB are found in 8 countries: Bangladesh, China, India, Indonesia, Nigeria, Pakistan, Philippines and South Africa. In recent times TB has become a leading cause of antimicrobial resistance (AMR) (3-9).

Tuberculosis is caused by *Mycobacterium tuberculosis* (MTB) an aerobic, non-spore-forming, non-motile, slow growing acid-fast bacillus (10-17). No age group is spared the scourge of Tb however adult TB has typically attracted more research and policy making than paediatric tuberculosis (18-21). The data concerning paediatric TB are dismal as it is estimated that in 2021 there were about 10.6 million cases of tuberculosis, globally; about 9.4 million of these cases were adults while 1.2 million were children and about 14% of these children died. (1, 5, 18-27).

Paediatric TB is a significant problem in Africa (28-32). Seventeen of the 30 high TB burden countries in the world are found in Africa (29, 31, 33). Paediatric TB in Africa accounts for about 322,000 annual cases (or a third of the global TB burden) (31). Nigeria has the highest burden of TB in Africa and is ranked 6th among high TB burden countries globally (33-40). In Nigeria, it is reported that about 6000 cases of paediatric TB occurred in 2015 representing 6% of the estimated global burden of paediatric TB cases (30).

More importantly, infected children are a marker of recent or ongoing transmission of TB in a community (41-47). They also serve as reservoirs for TB, in addition to being likely TB cases if not diagnosed or treated (41-47). Therefore an evaluation of the burden of paediatric TB may also help to determine the efficiency of TB control programs in communities and nations (19, 28). However, in Africa and many low and middle income countries with weak health systems paediatric TB is grossly under-reported, poorly diagnosed and inadequately managed due to lack of access to care, poor specimen collection and inadequate diagnostic facilities (30, 31, 48-52). In addition, poor disease notification and a paucity of research regarding paediatric TB makes it difficult to properly estimate the burden of paediatric tuberculosis and subsequently design effective strategies to curb the problem of

paediatric TB (19,43,44,48,52,53).

Ultimately the global health challenge posed by TB has become exacerbated by the emergence of antimicrobial resistance in both adult and paediatric TB (54-56). The roll out of the GeneXpert machine in the management of TB has made it possible to rapidly diagnose TB and also identify drug resistance (57-61). In the past the diagnosis of TB, particularly in low and middle income countries (LMICs) has involved microscopy using the Ziehl Neelsen stain (61-64). More elaborate techniques like culture and drug susceptibility are expensive and beyond the technical and financial capacities of laboratories in many LMICs (62). However the introduction of molecular techniques (such as GeneXpert) in the diagnostic ecosystem of tuberculosis has made it possible to implement and scale up TB diagnosis in resource constrained settings globally (61-64). A major advantage of GeneXpert is its rapid turn around time (<2hours) in contrast to culture and drug susceptibility which may take weeks to conduct (61-64). In addition GeneXpert is able to identify Rifampicin (RIF) resistance and therefore allows expedite and optimized decision-making in TB care (61-64).

Isoniazid, rifampicin, pyrazinamide, and ethambutol are the four first-line antimicrobials often used in the standard treatment for tuberculosis (65,66). Unfortunately, over the course of treatment, resistance to these medications may arise (65,66). Point mutations in the beta subunit of RNA polymerase (*rpoB*) gene that determine RIF resistance are the main cause of rifampicin resistance (67-70). Rifampicin-resistant tuberculosis (RR-TB; TB resistant to at least rifampicin) or multidrug-resistant tuberculosis (MDR-TB; RR-TB with documented resistance to isoniazid) affects roughly 2 million children worldwide, and 25,000–30,000 children are believed to contract RR-TB disease each year (71-72). RIF-resistant TB in children has been the subject of continuous research globally. A study done in China between January 2013 and December 2015 showed rifampicin resistance in paediatric patients was 6.9 percent (73) Another study conducted in Ethiopia revealed that 9.9% of all TB confirmed cases and 7.9% of paediatric TB patients were rifampicin resistant (74).

The growth of drug-resistant strains and the rise in the prevalence of pediatric tuberculosis are important public health issues, particularly in developing nations like Nigeria with high burdens of TB (29, 40,75). However, in contrast

to adult TB, there is a paucity of data in on the true burden of rifampicin resistance in paediatric TB (18-21). The aim of this study therefore was to evaluate the prevalence of rifampicin resistance in paediatric tuberculosis in the hospital.

MATERIALS AND METHODS

Study site

The study was conducted in the Department of Medical Microbiology, Babcock University Teaching Hospital, Ilishan-Remo, Ikenne Local Government, Southwest Nigeria. The hospital is a 240-bed tertiary hospital involved in teaching, research and specialist services. It serves Ogun State and neighboring States in southwest Nigeria.

Study Design

This retrospective study involved a review of medical microbiology laboratory records to analyze GeneXpert results of sputum samples obtained from pediatric patients with tuberculosis between January 2017 and March 2022. The study did not involve any contact with pediatric patients. Data collection involved the use of a data collection tool specifically designed for this study. Data collected included age, gender, presence of rifampicin resistance, HIV status, site of infection and type of specimen collected. All data were anonymized to ensure patient confidentiality. Patients were apportioned study identification numbers. Informed consent was not deemed necessary in this study because there was no contact with patients as it was a retrospective study.

Study inclusion criteria

The inclusion criteria included all patients age less than 18 years who had a diagnosis of tuberculosis and had undergone Gene Xpert testing between January 2017 and March 2022. All patients who did not meet this criteria were excluded from the study.

Sample size and sampling method

A convenience sampling method was used to select cases who fulfilled the study's inclusion criteria and to determine the sample size. The laboratory records were carefully evaluated to identify all cases who met the inclusion criteria. A total number of 1046 patients fulfilled the inclusion criteria.

Data analysis

Data analysis was done using IBM SPSS software version 20.0 Descriptive statistics were

used to analyze results based on frequency, gender, age, rifampicin resistance and HIV status. Bivariate analysis was done using the Chi square test and P values < .05 were considered significant.

Ethical approval

Ethical approval for this study was obtained from Babcock University Health Research and Ethics Committee (BUHREC No 693/22). As data were retrospectively obtained from the laboratory records and did not involve contact with patients nor recruitment of patients, informed consent was not deemed necessary. However, privacy and confidentiality of patients' data were protected in accordance with the Declaration of Helsinki.

RESULTS

In the 5-years, three months period under consideration, a total of 1046 paediatric patients submitted sputum samples to the medical microbiology laboratory for GeneXpert testing of which 556 (53.2%) were males. The mean age of all the patients was 10.77 ± 4.38 years and majority of the patients (445;42.5%) were in the age group 11-15 years (Table 1).

Fifty patients (4.8%) had positive GeneXpert results of which 3 (6.0%) were Rifampicin resistant. Thirty nine (3.7%) of the 1046 patients were HIV positive (Table 2). Bivariate analysis conducted showed that majority (34.0%) of TB cases were seen in age group 16-17 years with patients <1 year being the least affected (4.0%) $p=0.001$ (Table 3). Majority of TB cases were seen in females (56.0%) $p=0.679$ (Table 3). The majority (43.6%) of HIV cases were seen in the age group 11-15 years with the least seen in <1 year (0.0%) $p=0.005$. HIV was more common in females (53.8%) $p=0.296$ (Table 4). and the prevalence of HIV-TB co-infection was 4% $p=0.671$ (Table 5). No patient (0%) with Rifampicin resistance was HIV positive (Table 6) and all three patients (100%) with rifampicin resistance were males (Table 7).

DISCUSSION

The prevalence of tuberculosis among children in this study was 4.8%, which is higher than the findings reported in Zambia (1.58%) (76), Mozambique (1.65) (77), South Africa (1.3%) (78), and lower than reports from Zimbabwe (8.7%) (79), Uganda (10%) (80), Ethiopia (13.6%) (81), Bangladesh (32.97%) (82). However our findings were lower than studies done in Nigeria, in which the prevalence

of tuberculosis, following genexpert testing, was 19.8% (83) and 27.8% (84) respectively. The reason for variation might be due to the difference in the prevalence of tuberculosis in the general population, methods of sputum sample collection and diagnosis. While we used results of only Xpert MTB/RIF assay, the other studies applied microscopy and culture (76-84).

In this study, HIV cases were seen most in the age group 11- 15 years (43.6%) and no cases were seen below the age of 1 year. This is statistically significant ($P = 0.005$). The amount of HIV cases in females (53.8%) was more than the number of cases in males (46.2%) but the difference is insignificant ($P = 0.296$). The prevalence of tuberculosis among HIV positive children was 4%, but 36% among HIV negatives while the prevalence of TB among patients with an unknown HIV status was 60% (30). However, data did not show a statistically significant association between pulmonary tuberculosis and HIV infection ($P = 0.01$). According to the study, the odds of acquiring pulmonary tuberculosis among HIV negative children was 9 times higher than HIV positives but the difference is not significant.

The presence of rifampicin-resistant TB is a serious public health issue since children can independently become infected in the community (81, 85). Therefore, molecular typing of isolates from pediatric TB patients and their possible contacts is crucial to identifying the source of transmission (86, 87). The prevalence of rifampicin-resistant pulmonary tuberculosis infection in this study was 6.0%, which is higher than the findings reported in South Africa (0.66%) (88). However, it is lower than the findings reported in Ethiopia (7.9%) (81), China (30%) (89) and Nigeria (6.4%) (83). The difference could be the result of variations in study populations, study settings, study designs, and sociocultural practices. It is necessary to improve access to TB care, including public awareness and enlightenment (90, 91). Increased vaccine coverage is also advised to reduce the occurrence of paediatric tuberculosis (92).

CONCLUSION

The prevalence of rifampicin resistance among the subjects who tested positive for childhood tuberculosis was 6%. Appropriate measures including testing, isolation and treatment should be invested into the early detection and prevention of paediatric rifampicin resistant tuberculosis (93). Further studies are required to disaggregate reported childhood TB

cases in terms of type, site of disease, method of diagnosis, and previous treatment history, among others, which make programmatic interventions targeting specific childhood TB cases difficult (30,94). It must be stated that Genexpert is not a stand alone in the diagnostic ecosystem of TB (95, 96). However, challenges with scaling up (such as poor power supply) have made it difficult to improve coverage of the device in many countries (97). As such many countries still rely on case management and sputum microscopy which have low indexes of diagnosis for TB in children (98-100). Culture is expensive and novel methods such as next generation sequencing are clearly out of the reach of many TB endemic countries with weak and poorly funded health systems (101,102). The way forward lies in improving surveillance efforts, early detection and treatment of paediatric TB in Nigeria and other low and middle income countries (5, 30, 48). A major limitation of this study was that it was laboratory based and not integrated with clinical records of patients.

Conflicts of interest: None

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Table 1: Demographic Characteristics

Characteristics		n=1046 (%)
1. Gender	Male	556 (53.2)
	Female	490 (46.8)
2. Age	<1 year	12 (1.1)
	1-5 years	145 (13.9)
	6-10 years	284 (27.2)
	11-15 years	445 (42.5)
	16-17 years	160 (15.3)

Table 2: Clinical Details of Tb and HIV Infection

Characteristics		n=1046 (%)
1. TB infection status	Positive	50 (4.8)
	Negative	996 (95.2)
2. Rifampicin resistance status	RIF Resistance	n=50 (%) 3 (6.0)
	No RIF Resistance	47 (94.0)
3. HIV status	Positive	n=1046 39 (3.7)
	Negative	319 (30.5)
	Unknown	688 (65.8)
4. Clinical site of infection	Pulmonary	872 (83.4)
	Extra-Pulmonary	8 (0.8)
	N/S	166 (15.9)

Table 3: Bivariate Analysis Showing the Relationship between Age, Gender and Tb Status of the Respondents

VARIABLES		TB STATUS n=1046 (%)		χ^2	p-value
		Positive	Negative		
1. Age	<5 years	8 (16.0)	149 (14.9)	18.796	0.001
	6-15 years	25 (50.0)	704 (70.7)		
	16-17 years	17 (34.0)	143 (14.4)		
2. Gender	Male	22 (44.0)	468 (47.0)	0.171	0.679
	Female	28 (56.0)	528 (53.0)		

Table 4: Bivariate Analysis Showing Relationship between Age, Gender and HIV Status of the Respondents

VARIABLES		HIV STATUS n=1046 (%)			χ^2	p-value
		Positive	Negative	Unknown		
1. Age	<5 years	8 (20.5)	54 (17.0)	95 (13.8)	21.748	0.005
	6-15 years	27 (69.2)	196 (61.4)	506 (73.5)		
	16-17 years	4 (10.3)	69 (21.6)	87 (12.7)		
2. Gender	Male	18 (46.2)	161 (50.5)	311 (45.2)	2.436	0.296
	Female	21 (53.8)	158 (49.5)	377 (54.8)		

Table 5: Bivariate Analysis Showing Relationship between Tb Infection and HIV Status

VARIABLES		TB Infection n=1046 (%)		χ^2	p-value
		Positive	Negative		
HIV Status	Positive	2 (4.0)	37 (3.7)	0.789	0.671
	Negative	18 (36.0)	301 (30.2)		
	Unknown	30 (60.0)	658 (66.1)		

Table 6: Bivariate Analysis Showing Relationship between Rifampicin Resistance and HIV Status

VARIABLES		RIF Resistance status n=3 (%)		χ^2	p-value
		RIF resistance	No RIF Resistance		
HIV Status	Positive	0 (0.0)	2 (4.3)	0.158	0.924
	Negative	1 (33.3)	17 (36.2)		
	Unknown	2 (66.7)	28 (59.6)		

Table 7: Bivariate Analysis Showing Relationship between Gender and Rifampicin Resistance

VARIABLES		RIF Resistance status n=3 (%)		χ^2	p-value
		RIF resistance	No RIF Resistance		
Gender	Male	3 (100.0)	19 (40.4)	4.062	0.044
	Female	0 (0.0)	28 (59.6)		

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