



Rifampicin resistance among notified pulmonary tuberculosis (PTB) cases in South-Southern Nigeria

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ABSTRACT

Background: Rifampicin resistant pulmonary tuberculosis (RR-PTB) remains a global health burden especially in low income countries and among HIV positive individuals.

Objective: This study seeks to measure the prevalence of RR-PTB among confirmed PTB cases in Delta State South-Southern, Nigeria and to determine the correlation between various factors affecting the prevalence of RRTB among notified pulmonary TB cases.

Material and methods: The study is cross-sectional and retrospective in design and was carried out in Delta State, South-Southern Nigeria among participants with notified pulmonary TB cases. Gene Xpert registers for the selected facilities (Central Hospital Warri, Central Hospital Sapele and Federal Medical Center Asaba) for the year 2017 were retrieved, data extracted and analyzed.

Result: Prevalence of RR-PTB was 7.3% (47/643). Majority (11.3% and 11.4%) of RR-PTB cases were among ages 0–20 and 61–80 years respectively. The male group and HIV negative participants gave rates of 9.1% and 7.8% respectively. Rates reported for location of residence revealed that Delta Central had a rate that doubled Delta South and tripled Delta North.

Conclusion: Although our study figures are lower when compared to other reports for the study region, age grades 0–20 and 61–80 years, the male gender and residence in Delta Central were highlighted as independent variables that influence the distribution of RR-PTB. While a call for the sustenance and if possible augmentation of control and eradication efforts is of high essence, further studies aimed at identifying and understanding co-variables to the ones highlighted are recommended.

1. Introduction

Pulmonary tuberculosis (PTB) is a chronic infectious airborne disease caused by a group of acid fast bacteria called the Mycobacterium Tuberculosis Complex (MTC). PTB remains a major public health issue as one-third of the world's population has latent TB with 10% of this population developing active disease during their life time [1]. Ranking as one of the major causes of morbidity and mortality among infectious diseases globally [2], prevention of PTB, diagnosis and treatment has been complicated by the emergence of drug resistant strains.

The discovery and usage of antibiotics for the treatment of infectious

diseases brought about enormous relief that is presently being threatened by the emergence of resistant strains of these pathogens. PTB control was recording a success story until the advent of drug-resistant strains and the HIV/AIDS pandemic [3].

Drug-resistant PTB can be grouped as mono (non-susceptibility to one anti-TB drug), multi (resistant to rifampicin and isoniazid) and extensive (resistance to isoniazid, rifampicin, fluoroquinolone and any second line injectable drugs: amikacin, capreomycin and kanamycin) [4].

Rifampicin is arguably the most important drug in the chemotherapy of tuberculosis [5]. It is one of the two key drugs for short course chemotherapy (0–6 months) and has reduced toxicity. Thus, it

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encourages patient compliance as well as eliminates the need for long term therapy (18–24 months) [6]. Rifampicin mono-resistance is rare. It is mostly observed in association with resistance to isoniazid [7]. Thus, about 90% of rifampicin resistant PTB are actually multi drug resistant TB (MDR-TB) [7].

Globally, the prevalence of MDR-TB was 3.3% for newly diagnosed persons as at 2015 and 20% for patients with a history of anti-TB treatment [7]. Nigeria is one of the countries included among the 30 high burden countries for TB and drug resistant TB [1]. In Nigeria, 4.3% of new TB cases were caused by MDR strains while same was responsible for about 25% cases among individuals with a history of been previously treated for PTB [8].

Acquisition or emergence of DR-TB has been strongly linked to previous TB treatment. However, use of inferior regimens, previous exposure to quinolones, poor-adherence to anti-TB drugs, poor access to health-care, long term chemotherapy associated with rifampicin-resistant PTB and high burden of HIV/AIDS are factors also considered to be responsible for the rising incidence and prevalence of MDR-TB [8].

The Xpert MTB/RIF assay is a WHO endorsed point of care molecular assay that is able to assess simultaneously for the diagnosis of MTB and rifampicin resistance within 2 h [9]. It is a cartridge-based nucleic acid amplification test which is automated and can isolate the genomic material of MTC via sonication, amplify via PCR and identify using fluorescent probes called molecular beacons [10].

Treatment failure associated with PTB has been on the increase and this is largely attributed to drug-resistance and poor adherence to anti-TB drugs. Limited literature and data is available for rifampicin resistant PTB for the study region. The available ones exhibit sample bias as most are product of isolated surveys or specific health facilities. This study aims to measure the prevalence of rifampicin resistant PTB among confirmed cases of PTB in Delta State, Nigeria and to determine the correlation between rifampicin resistant PTB acquisition and variables such as participant's age, sex, retro-viral status and geographical location of residence.

2. Materials and methods

2.1. Study design and region

This is a cross-sectional retrospective study. The study was conducted in Delta State in South-Southern Nigeria. Delta State was carved out from the former Bendel State in 1991. The State is an oil and agricultural producing state with an estimated population of 4,112,448. Delta State is multi-ethnic and Asaba is its capital city, with a land mass of 18,050 km². Warri city is the economic nerve center as well as the most populated city in the state. The study area lies between longitude 5° 00 and 6° 45 East and latitude 5° 00 and 6° 30 North. It is bounded by Edo State (North), Anambra (East) and Bayelsa (South-East). Delta State has a wide coastal belt inter-laced with rivulets and streams, which forms part of the Niger Delta.

2.2. Sampling frame

The biggest Directly Observed Therapy (DOT) center for each of the three senatorial zones of the state was purposively selected to ensure adequate sampling and appropriate representation. These centers were Central Hospital Warri (Delta South), Central Hospital Sapele (Delta Central), and Federal Medical Centre Asaba (Delta North). Patients with suspected cases of PTB were seen at the chest ward of the selected facilities and educated on how to produce sputum sample for analysis. A wide mouth, dry and sterile container was given to them and they were sent to a restricted area to collect the sample. The samples were sent immediately to the Gene Xpert laboratory for analysis. For samples coming from outside sources, they were collected appropriately and transported in cold chain. Samples that were not processed and analyzed immediately were stored in a solar powered refrigerator. The Gene Xpert

registers for these health facilities were reviewed and data analyzed.

2.3. Inclusion and exclusion criteria

Individuals of all age group and sex with microbiologically confirmed cases of PTB from January through December 2017 were eligible for the study. Individuals with incomplete demographic or rifampicin susceptibility assay result were excluded from the study.

2.4. Data collection and management

Participant's age, sex, HIV status as well as location of residence were retrieved using data extraction format and recorded against rifampicin susceptibility testing results. Data recorded were analyzed using SPSS 23 and were expressed as simple frequency and percentage. Assay for statistical significance between rifampicin-resistance and other studied variables was analyzed using Pearson's Chi-Square or Fishers's exact test at a confidence limit of 95% and p-value lesser than or equal to 0.05 were regarded to be significant. A total of 670 participants were recruited for the study but 37 (5.5%) were excluded because of either incomplete demographics or Rifampicin susceptibility assay result.

2.5. Ethical clearance

Approval for data review and extraction was obtained from the Heads of department from where the data was generated and participant's confidentiality and privacy was not breached as identifiers were not extracted with the data.

3. Results

A total of 643 participants comprising of 395 (61.4%) males and 248 (38.6%) females were eligible for the study. Age grade 21–40 years participants accounted for bulk of the study population 337 (52.4%), HIV positive individuals were 101 (15.7%) while those residing in Delta South senatorial zone 311 (48.4%) gave the highest zone-based number of participants. Table 1 summarizes the characteristics of the studied population.

A prevalence of 7.3% (47/643) was recorded for rifampicin resistant PTB. Details are shown in Table 2.

Prevalence of rifampicin resistance in relation to other study variables (age, sex, retro-viral status and location of residence) gave different figures as shown in Table 3. Age grade 61–80 years gave the highest age-based prevalence of 11.4% which was closely followed by 11.3% recorded for age-grade 0–20 years. Males had a prevalence of 9.1% as against 4.4% reported for females. Retro-viral status based prevalence

Table 1
Characteristics of the studied population.

Variables	Frequency	Percentage
Age (Years)		
0–20	80	12.4
21–40	337	52.4
41–60	179	27.8
61–80	44	6.8
80 and above	3	0.5
Gender		
Male	395	61.4
Female	248	38.6
HIV status		
Positive	101	15.7
Negative	370	57.5
Unknown	172	26.7
Location of residence		
Delta south	311	48.4
Delta central	175	27.2
Delta North	157	24.4

Table 2
Prevalence of rifampicin resistant PTB.

Rifampicin resistance	Frequency	Percentage
Positive	47	7.3
Negative	596	92.7
Total	643	100

Table 3
Prevalence of rifampicin-resistant PTB in relation to other study variables.

Variables	Tested (n)	Positive n (%)	p-values
Age (years)			0.05
0–20	80	9 (11.3)	
21–40	337	15 (4.5)	
41–60	179	18 (10.1)	
61–80	44	5 (11.4)	
80 and above	3	0 (0.0)	
Gender			0.02
Male	395	36 (9.1)	
Female	248	11 (4.4)	
HIV status			0.60
Positive	101	5 (5.0)	
Negative	370	29 (7.8)	
Unknown	172	13 (7.6)	
Location of residence			0.02
Delta South	311	19 (6.1)	
Delta Central	175	21 (12.0)	
Delta North	157	7 (4.5)	

gave 7.8% for HIV negative participants, 7.6% for those with unknown status while HIV positives had a prevalence of 5.0% (Table 3). Assay for statistical significance reveals that age, sex and location of residence are independently associated with rifampicin resistant PTB acquisition with p-values of 0.05, 0.02 and 0.02 respectively. Details are shown in Table 3.

4. Discussion

This study reported 7.3% prevalence for rifampicin resistance (47/643) which is in consonance with the 7.2% reported by Rasaki *et al.*, for Kwara State, Nigeria [11], 6.9% recorded by Okonkwo *et al.*, for Nnewi, Nigeria [12], 7.3% by Coovadia *et al.*, for South Africa [13] and 7.4% for Iran by Velayati *et al.* [14], but is slightly higher than the 3.2–5.4% WHO prediction for Nigeria [6]. However, the 7.3% reported in this study is lower than the figures such as 14.7% for Yenagoa, Nigeria [6], 18.8% by Mac-Fiberesim *et al.*, for Nigeria [15] and 23% by Enya *et al.*, for Lagos [16]. The variation in rates recorded may be a product of the studied population and methodology employed.

Age grade 61–80 years and 0–20 years gave the highest rates of 11.4% and 11.3% respectively. This is in consonance with the record of Jeleta *et al.*, who reported age-group 52–58 and 17–23 years as the highest age based rates for rifampicin resistant PTB [7]. In contrast, several other Nigerian studies have reported age grade 20–40 years as the age group with the highest rates for MDR-PTB [11]. Younger age has been associated with PTB and MDR-PTB by various studies [17, 18]. The age variation that exists for the reported drug resistance rates maybe a reflection of localized socio-economic factors related to exposure opportunity and MDR-TB development. Assay for statistical association between age and rifampicin resistant PTB acquisition gave a p-value of 0.05 indicating an association between both. A notion supported by several other studies [7, 17, 18].

Gender-based prevalence gave a 9.1% (36/395) to 4.4% (11/248) ratio in favour of the male gender. This is in agreement with several reports from Nigeria, other parts of Africa and Asia [12, 13, 19]. The variation in gender-based prevalence recorded in the study may result from difference in TB susceptibility, behavioural factors and degree of exposure to infection sources. Assay for statistical association gave a p-value of 0.02 indicating a strong relationship between MDR-TB and gender and highlights the male sex as a risk factor for RRPT acquisition or emergence.

Rifampicin resistant PTB rates in relation to retro-viral status gave 5.0%, 7.8% and 7.6% for HIV positive, HIV negative and those with unknown status respectively. High rates of rifampicin resistant PTB have been recorded for persons with HIV/PTB co-infection in Brazil, USA and Ethiopia [7] but findings from our study is in contrast to theirs. However, Okonkwo *et al.* [12], reported 4.8% (2/42) incidence rate for HIV/PTB co-infected participants. Their findings correlates with figures recorded in this study. Mal-absorption of anti-PTB drugs, previous exposure to anti-PTB drugs and poor drug/regime adherence caused by increased drug toxicity associated with HIV/PTB co-chemotherapy may be responsible for higher figures obtained in the studies mentioned above. The reduced rates recorded in this study for HIV/PTB co-infected participants may be attributed to the fact that most of the study participants lack previous exposure to anti-PTB chemotherapy. Assay for association between rifampicin resistance and retro-viral status gave a p-value of 0.60 revealing the absence of a correlation between both variables.

Location of residence gave rates of 6.1% for Delta South, 12.0% for Delta Central and 4.5% for Delta North. P-value for association between location of residence and rifampicin resistant PTB acquisition gave 0.02 indicating a strong association between both. Peri-urban residence has been associated with an increase likelihood of MDR-TB acquisition according to the report of Flora *et al.* [20]. This may be responsible for our findings since Delta Central has few urban areas and more of semi-urban areas when compared with the other zones.

Assaying for rifampicin resistance is critical to effective control of PTB since high cost of therapy, increased toxicity; long-term therapy, psychosocial factors as well as emergence and transmission of MDR-TB can be effectively prevented if MTB strains are susceptible to rifampicin. Thus epidemiological studies such as this are very important in providing figures and highlighting variables that could be potential targets for further study. Although the study was retrospective in design (limited variables to measure and draw correlation with), its sample size and distribution eliminated sample size bias and increase the validity of results with regards to result generalization for the entire study region.

5. Conclusion

Figures reported for rifampicin resistance among PTB cases in this study may be lower than other reports but MDR-PTB still remains a major public health issue. Our findings should guide similar future research, aid PTB control policy formulation and assist with strategic implementation of interventions aimed at achieving the ultimate goal of eliminating PTB as a public health issue by 2050.

Declarations

Author contribution statement

Henry Ukwamedua, Johnson Etaghene: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Victor Omote: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Matthew Ejike Oseji, Imaria Celia Agwai, Harrison Agbroko: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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