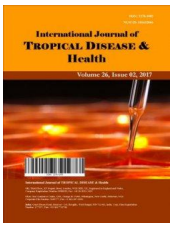

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A Retrospective Review of Rifampicin-Resistant *Mycobacterium tuberculosis* between 2015 and 2017 in Port Harcourt, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Author RMN designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors OEA and GMF managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: The diagnosis and treatment of drug resistant tuberculosis (TB) is a significant challenge for the control of TB in Nigeria.
Aim: The study was carried out to assess the prevalence of rifampicin-resistant TB at the point of initial diagnosis among subjects suspected of TB.
Methods: A retrospective review of *Mycobacterium tuberculosis* (MTB) and rifampicin resistance detected by GeneXpert™ analysis between 2015 and 2017 in Braithwaite Memorial Specialist Hospital was carried out.
Results: A total of 6733 samples were received and analyzed in the period under review, 1252 (19%) were positive for *Mycobacterium tuberculosis* and 5841 (81%) were negative. The

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prevalence of *Mycobacterium tuberculosis* was 24.56%, 20.11% and 16.86% from 2015 to 2017 respectively. There was a significant decline in the prevalence of MTB from 2015 to 2017 (χ^2 = 33.59, p = 0.0001). Rifampicin (RIF) resistance was 5.42%, 5.86% and 6.22% respectively from 2015 to 2017; but the trend was not statistically significant (χ^2 = 0.21; p = 0.6418).

Conclusion: The study showed that despite a decrease in the prevalence of tuberculosis infection there was an increase in rifampicin resistance from 5.42% to 6.22% between 2015 and 2017. There is an urgent need to improve the management of TB in the Port Harcourt metropolis to improve treatment outcomes and to prevent the proliferation of drug resistant strains.

Keywords: Gene Xpert; rifampicin-resistance; trend; tuberculosis.

1. INTRODUCTION

Mycobacterium tuberculosis (MTB) still remains one of the major public health concern and the cause of several deaths [1,2]. Nigeria ranks the third among the 22 high tuberculosis (TB) burden countries after India and Indonesia. According to the World Health Organization (WHO) approximately 480,000 new cases of multidrug resistant TB (MDR-TB) occurred in 2014 globally [3]. Tuberculosis is a major public health challenge with a high mortality rate especially in low and middle-income countries. It is the most common opportunistic infection observed in human immunodeficiency virus (HIV) infected persons with an increased likelihood of mortality [4]. WHO reports that 26% of persons with TB infection in Nigeria are infected with HIV, while the country has the third largest TB burden in the world [5-7]. Drug resistant TB is a growing global health problem, posing a challenge to the control of TB, while also prolonging treatment time, limiting treatment options and increases cost of treatment [2,6]. In some settings, drug resistance has been linked with treatment failure and death in 10-30% of TB cases. The estimates based on modeling predict MDR-TB prevalence in Nigeria to range from 1.8% (0.0 to 4.3%) for new cases up to 7.7% (0.0 to 18.0%) for previously treated patients (Boehme et al., 2010). Despite antiretroviral therapy (ART), TB remains a major cause of morbidity and mortality among persons with HIV infection in Sub-Saharan Africa [2]. Prompt and accurate diagnosis of TB and timely initiation of appropriate treatment decreases TB transmission and mortality [8-10]. To aid prompt TB diagnosis, the WHO in 2010 endorsed the Cepheid Xpert® MTB/RIF (Xpert) as a first line tool for diagnosis of HIV-associated TB [6,11]. Xpert is a nucleic acid amplification test that simultaneously detects MTB and rifampicin resistance, and has demonstrated high sensitivity (79.7–100%) as well as shorter diagnostic turnaround time (<2 hours) when compared to TB culture [10-12 hours]. As at 2015, 60% of countries recommended Xpert as the initial TB test for persons with possible drug-resistant (DR) TB, and 69% recommended it as the initial diagnostic test in cases of presumptive HIV associated TB [13-15]. In resource poor settings such as Nigeria, drug resistant testing is almost always based on tests from GeneXpert analysis which only detects Rifampicin resistance. The early detection of drug resistance will definitely aid the managing physician for effective treatment of the patient. An assessment of the trend in *Mycobacterium tuberculosis* prevalence and Rifampicin-resistance was assessed in Rivers State, Nigeria.

2. METHODS

2.1Study Design

A retrospective analysis of the prevalence of TB and rifampicin resistance at the Braithwaite Memorial Specialist Hospital between 2015 and 2017 was carried out.

2.2 Study Area

The study was conducted in GeneXpert TB laboratory at the Braithwaite Memorial Specialist Hospital in Port Harcourt, the capital city of Rivers state, Nigeria.

2.3 Study Population

The study population consisted of 6,733 persons presenting with symptoms suggestive of tuberculosis and sent for initial laboratory diagnosis, without prior treatment at the pathology department of the hospital between 2015 and 2017.

2.4 Specimen Analysis

Samples were obtained from each informed patient and tested with GeneXpert instrument and was reported as: (1) MTB detected and

rifampicin resistance detected, (2) MTB detected but rifampicin resistance not detected, (3) MTB not detected, or (4) MTB detected but indeterminate. Patients with indeterminate results had the test repeated using fresh samples, and results of the repeat Xpert test were documented as the final Xpert result. Based on the WHO case definition, a patient was classified as having pulmonary TB if sputum sample was positive by sputum microscopy or Xpert (bacteriologically confirmed case) or if sputum microscopy and Xpert were negative but the treating physician made a diagnosis of pulmonary TB and initiated full TB treatment (clinical diagnosis) [15-17].

2.5 Data Collection and Analysis

Data from laboratory records between 2015 and 2017 was collected and imputed into the Microsoft Excel sheet and analysis. Frequency count and percentage was used to analyze the number of *Mycobacterium tuberculosis* detected by GeneXpert™. Chi-square for trend was used to analyze the prevalence of *Mycobacterium tuberculosis* and rifampicin-resistance in the different years of the period under review. All analysis was done with the Epi Info software at a 95% confidence interval and a p-value of less than 0.05 was considered significant.

2.6 Ethical Consideration

Ethical approval for the study was obtained from the research ethics committee of the Rivers State Primary Health Care Board prior to commencement of the study (RIV/ADM/90/S.II/VOL.XI/564).

3. RESULTS

Demographic information of the subjects was not available at the time of the study. Of the 6733 samples received and analyzed in the period under review, 1252 (19%) were positive for *Mycobacterium tuberculosis* and 5841 (81%) were negative. The prevalence of TB was found to be 24.56%, 20.11% and 16.86% respectively in 2015, 2016 and 2017. There was a significant decline in the prevalence of MTB from 2015 to 2017 (χ^2 = *33.59, p = 0.0001*). In 2015, rifampicin-resistance was 5.42%, in 2016, it was 5.86% and 6.22% in 2017 (Table 1).

Table 1. Distribution of rifampicin resistance 2015–2017

Year	Number of MTB positive cases	Percentage RIF resistance (n, %)	χ^2 for trend (p-value)
2015	240	13 (5.4)	
2016	256	15 (5.8)	0.21 (0.6418)**
2017	756	47 (6.2)	

*RIF- Rifampicin, MTB- Mycobacterium tuberculosis **Trend is not statistically significant (p>0.05)*

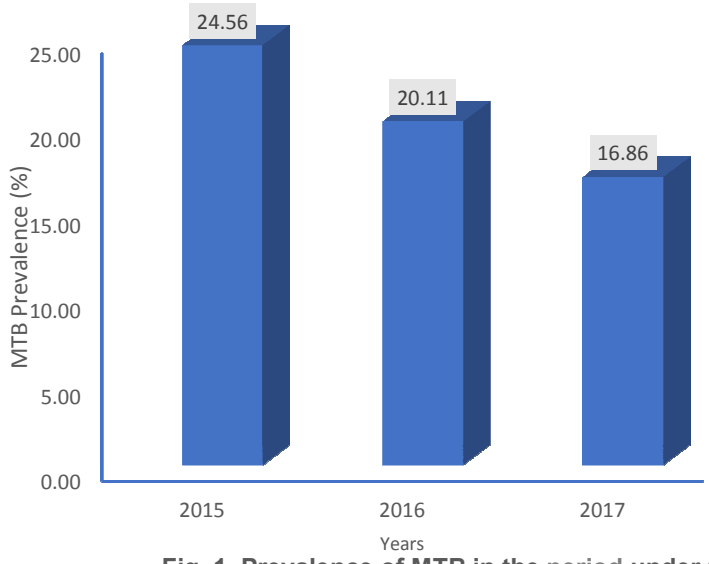

Fig. 1. Prevalence of MTB in the period under review

4. DISCUSSION

The occurrence of drug-resistant TB among treatment naïve subjects of people that are newly diagnosed of TB is a major challenge to the control of pulmonary TB in the country. This could be an indication of a higher level of latent tuberculosis or the low level of active diagnosis of TB in a high-burden country such as Nigeria [18-20].

The average prevalence of TB in the period under review was 20.5%. This is higher than the national average of between 11 – 15% as reported in previous studies (Table 1 shows the trend of rifampicin resistance in the period under review. In 2015, RIF-resistance was 5.42%, in 2016, it was 5.86% and 6.22% in 2017 [21-26]. This high prevalence may be attributed to the metropolitan nature of Port Harcourt city. It has been reported that people from neighboring states seek medical attention in the city due to the presence of secondary health care institutions [22,27]. There was a significant decline in TB prevalence from 24.56% to 16.86% in 2015 and 2017 respectively ($c2 = 33.59$, $p = 0.0001$). Rifampicin resistance was found to increase from 5.42%, to 6.22% in 2017 compared to the year 2015. The observed increase in RIF-resistance may be attributed to poor treatment adherence, treatment relapse and latent TB activation in some settings [28,29,30]. The prevalence of drug resistant TB among the study subjects were lower than naïve subjects (7.6%) compared to 62.5% as reported by Dinic et al from South West Nigeria [17]. This prevalence could also be an indication of the prevalence of MDR-TB among the TB infected subjects, which is consistent with the 6% reported by Nwofor et al. [31]. In Nasarawa State, Nigeria, Audu et al. showed that the overall prevalence of rifampicin resistant mycobacterium tuberculosis was carried out by 12.1% MTB positive patients who constituted 18.8% of the total analyzed data [4]. It also showed high prevalence of rifampicin resistance among patients from other facilities (62.8%) and host facility (37.2%). The resistance rate was higher in Nasarawa compared to Port Harcourt. The reduced prevalence in the host facility in Nasarawa may be due to the fact that the host facility serves as a referral centre, and suspected drug resistant cases were referred to the Gene Xpert laboratory [32-34]. This also confirms a report from India that showed that patients referred from facilities outside the facility hosting the laboratory carrying out the diagnosis may have higher prevalence due to selective referrals.

A study carried out on 446 sputum specimens sent to TB Referral Hospital Igbogene, Yenagoa Nigeria between January to December 2016 had 102 (22.9%) of the sputum specimens positive for *Mycobacterium tuberculosis*. Out of the 102 positive MTB, 15 (14.7%) showed rifampicin resistance. Their study has established a high prevalence of rifampicin resistance in Yenegoa state. Rifampicin resistance in Yenegoa in 2016 was higher than rifampicin resistance in 2015, 2016 and 2017 in Port Harcourt Referral hospital. In South Africa, rifampicin resistance ranged between 7.3% to 10%. Previous studies in In Indonesia report that 20.5 to 22% culture isolates showed resistance to at least one first-line TB drug [35-36]. These findings indicate treatment failures associated with the occurrence of drug resistant TB infection, even among newly diagnosed treatment-naïve subjects [35].

5. CONCLUSION

Despite the decrease in the prevalence of tuberculosis (TB) observed, there was an increase in the occurrence of rifampicin resistance in the period under review. There is an urgent need to improve the management of TB in the Port Harcourt metropolis to improve treatment outcomes and to prevent the proliferation of drug resistant strains. Keeping to medications, prompt detection and consistent follow up should be adhered to in order to reduce the development and spread of drug resistant *Mycobacterium tuberculosis*. We recommend that anti-TB resistant survey and active case findings for TB should be carried out on quarterly basis in all the states in Nigeria.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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