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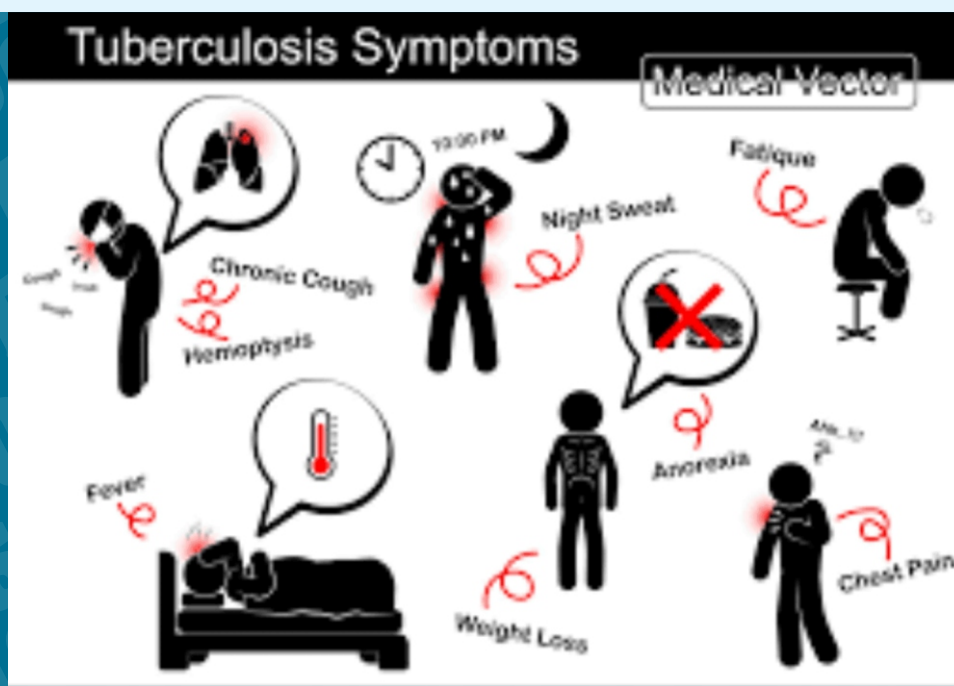
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## RIFAMPICIN RESISTANT TUBERCULOSIS IN A SECONDARY HEALTH FACILITY IN ILORIN, NIGERIA

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**Keywords:** Rifampicin resistant tuberculosis; Secondary health facility; Nigeria

### ABSTRACT

**Background:** Rifampicin resistant tuberculosis is an unrecognized and potentially serious treatment issue. Rifampicin resistance is a risk factor for poor outcome in tuberculosis. It is prevalent in Nigeria. Therefore, we sought to examine the pattern of Rifampicin resistance tuberculosis in Ilorin, Nigeria.

**Method:** One hundred and forty tuberculosis cases were referred to the chest clinic of Sobi Specialist Hospital, Ilorin from January to December, 2014. Sputum samples were obtained from them, smeared on glass slides, stained using Ziehl Neelsen Stain and later observed under light microscopy. The GeneXpert MTB/RIF assay was used to simultaneously detect TB and rifampicin resistance.

**Result:** The minimum age of the patients was 18 years, while the maximum was 83 years. The mean age was  $38.39 \pm 13.75$ . There was male preponderance 84(60%), compared to 56(40%) female. The Sobi Specialist Hospital made the highest referral. The tertiary hospital, the University of Ilorin Teaching Hospital had no functional GeneXpert facility as at the time of this study. Forty eight (34.3%) had smear-positive TB, while 92(65.7%) were sputum negative. Thirty two (38.1%) male out of 84 and 12(21.4%) female out of 56 were sensitive to Rifampicin, while 6(7.1%) male out of 84 and 4 (7.1%) female out of 56 were resistant to it. Forty four (31.4%) were MD-TB positive with a prevalence of 31.4%. Ten (7.2%) were Rifampicin resistant; this included 6 males and females. This was statistically significant.

**Conclusion:** Our study highlights that physicians should have a high index of suspicion for rifampicin resistant tuberculosis in patients refractory to anti-TB treatment. The MTB/RIF test is a useful method for rapid diagnosis of TB and detection of RIF-resistance strains. There is need for increasing effort to interrupt the transmission of RIF-TB.

### INTRODUCTION

According to the World Health Organization, nearly 2 billion people, one-third of the world's population have tuberculosis. Almost 95% of T.B cases are found in the developing world. Nigeria currently ranks 10<sup>th</sup> among the 22 tuberculosis high burden countries in the world.

According to the World Health Organization, 650,000 people are infected worldwide<sup>2</sup>. In Africa, 1.9% of new cases and 9.4% of diagnosed and

treated patients are infected by a multi-drug resistant strain. The WHO estimates a Multi-Drug Resistant (MDR)-TB prevalence rate of 3.1% and 1% among new and retreatment TB patients respectively in Nigeria<sup>3</sup>. Multi-drug resistance (MDR) TB is defined as tuberculosis disease caused by a strain of *Microbacterium tuberculosis* that was resistant to at least isoniazid and rifampicin<sup>4</sup>. Emerging Multidrug-Resistant Tuberculosis-TB (MDR) is one of the major concerns of Health policy makers<sup>5</sup>. Few studies had documented the presence of this disease

in Nigeria, with prevalent rates ranging from 4%-76.3%<sup>6-9</sup>.

In a case study conducted in the Infectious Diseases Hospital, Kano, out of 80 patients sampled, 52 were diagnosed to be Acid Fast Bacilli (AFB) positive and 28 were Acid Fast Bacilli negative; 61.5% and 38.5% prevalence were found in male and female patients respectively, with the age group 31-40 years having the highest prevalence of 28.8%<sup>10</sup>. Sputum smear microscopy remains the most common way to diagnose pulmonary TB. Depending on the report and method used, smear microscopy can accurately detect TB in 20% to 80% to TB cases using fluorescence microscopy methods<sup>11</sup>.

The acronym (MDR)-TB means: Multi-drug resistant TB, that is, TB in patients whose infecting isolates of *Mycobacterium tuberculosis* are confirmed to be resistant in vitro to both Isoniazid (INH) and Rifampicin. The categories of suspects are: failure to category 1 treatment, failure to convert at the end of intensive phase of category 2 or failure to category 2 treatment. Old cases (RAD, relapse, others etc), known symptomatic contacts of patients with DR-TB, TB/HIV co-infection.

The GeneXpert MTB/RIF assay is a molecular-based rapid test with potentials to revolutionize TB diagnosis. The regions of the target gene associated with RIF resistance (*rpoB* gene) is PCR amplified. Table 4. 5 wild type (A-E) sites of the *rpoB* gene rare present. Five molecular beacons are present and they bind only to the wild type *rpoB* gene. It can simultaneously detect *Mycobacterium tuberculosis* (MTB) complex DNA and mutations associated with rifampicin (RIF) resistance directly from sputum specimens in less than 2 hours, and it minimizes staff manipulation and bio safety risk<sup>12</sup>. Moreover, its ability to detect smear-negative TB provides a significant advantage, especially for people living with HIV. In December 2010, the World Health Organization (WHO) endorsed GeneXpert for the rapid and accurate detection of TB, particularly among People Living with HIV and people suspected of having HIV infection<sup>12</sup>.

There is currently no country-wide drug resistance survey hence, the exact data on the prevalence and pattern of rifampicin resistance tuberculosis is unknown. Moreover, there is paucity of data on

prevalence in Nigeria in general and in Ilorin in North-Central Nigeria in particular, hence the need for this study.

## MATERIALS AND METHODS

This study was conducted at the Chest Clinic of Kwara State Sobi Specialist Hospital, Ilorin, Nigeria. The target populations were tuberculosis suspects referred from the primary, secondary and tertiary health care facilities in Kwara State in particular and Nigeria in general. The chest clinic project of the Sobi Specialist Hospital Ilorin, Kwara State was commissioned on Thursday 7<sup>th</sup> of June, 2012. It was donated by Star Deep Water Petroleum Limited a major oil industry company. The aim was to assist in the diagnosis of Tuberculosis and Drug Resistance Tuberculosis and to serve as a referral center for tuberculosis cases. The hospital caters for patients with infectious diseases such as HIV and tuberculosis.

Ethical approval for the study was obtained from the Ethical Review Committee of the Kwara State Ministry of Health before the commencement of the study. The respondents were adequately informed about the nature of the study and its benefits as that they could opt out at any stage if they so desired. An interviewer administered questionnaire was used. However, for subjects who did not understand English, a local dialect version of the instrument was used.

The inclusion criteria were tuberculosis (TB) patients who previously received Category 1 (new case) treatment and were declared cured or completed a full course of treatment and had once again developed sputum smear-positive tuberculosis, or a TB patient who while on treatment remained or become again smear positive five months or later after commencement of treatment, or a TB patient who completed at least one month of treatment and returned smear positive after at least 8 weeks of interruption of treatment, or a TB patient already registered for treatment in one local government area (LGA) who is transferred to another LGA where they continued treatment, or a TB patient who did not easily fit into one of the above case definitions. The exclusion criteria was a TB patient who had never had treatment for TB or who had taken anti-TB drugs for less than 4 weeks. A total of 140 Drug Resistance Tuberculosis Suspects cutting across the various age groups and of both sexes were

referred between January and December, 2014.

Respondents were grouped into different occupational classes using Oyediji's classification<sup>13</sup> viz;

- I. Senior public servants, professionals, managers, large scale traders, businessmen and contractors senior military officers.
- II. Intermediate grade public servants, and senior school teachers, non-academic professionals e.g. Nurses, owners of medium sized businesses secretaries.
- III. Non-manual skilled workers including clerks, typists, telephone operators, junior school teachers, drivers, artisans.
- IV. Petty traders, labourers, messengers, lower cadre civil servants.
- V. Unemployed, full-time house wives, students, subsistence farmers.

The predictive value of a positive tests is calculated as follow:

$A/(A+B) \times 100$ , where A represents those with oral lesions, B represents those without oral lesions and A + B, the total sample respondents.

Three sputum specimens were collected from each respondent. The first sample was taken on the spot, the second sample was also an early morning sample and third was taken on the spot when the client returned to the consulting room with the second sample.

The sputum was collected into a dry, clean, transparent, wide-mouthed leak proof container. The sides of the specimen containers were labeled correctly with the patient's name and referral centre. The smear was heat-fixed with flame after complete air drying. Carbol fushin was applied onto the slides and heated gently for 5 minutes, the washed and drained. It was decolorized for three minutes, washed thoroughly, and covered with methylene blue for one minute. The slides were then washed, drained and ready for microscopy after drying<sup>14</sup>. The stained and dried smear was viewed under oil immersion as a fine red rod against blue background. Interpretation of results was done using WHO guidelines<sup>14</sup>. Presence of pinkish red rods indicated presence of acid fast bacilli while absence of pinkish red rods meant absence of acid fast bacilli. AFB counts, recording and reporting were as follows:

**Table 1: Acid Fast Baccilli report**

|                                                    |                         |
|----------------------------------------------------|-------------------------|
| No AFB seen in at least 100 fields                 | 0                       |
| 1-9 AFB in 100 fields                              | Report the exact number |
| 10-99 AFB in 100 fields                            | +                       |
| 1-10 AFB per fields in at least 50 fields          | ++                      |
| Greater than 10AFB per field in at least 20 fields |                         |

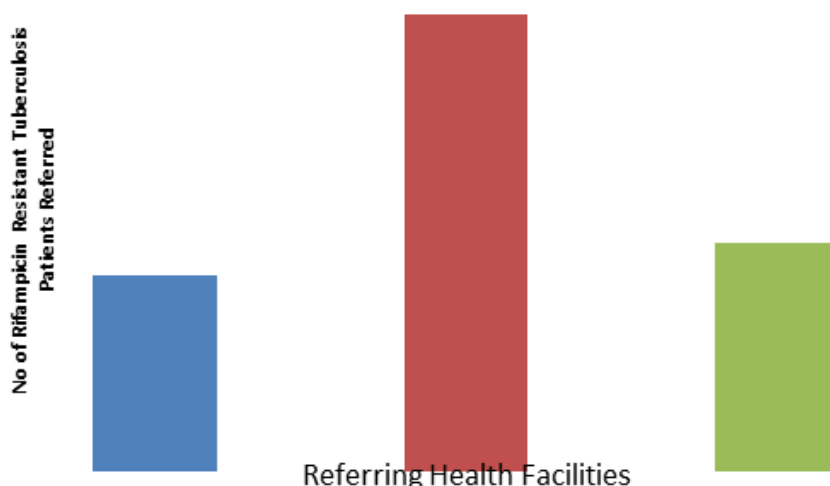


**Figure 1: Pattern of Referral of Suspected Rifampicin Resistant Tuberculosis Patients**

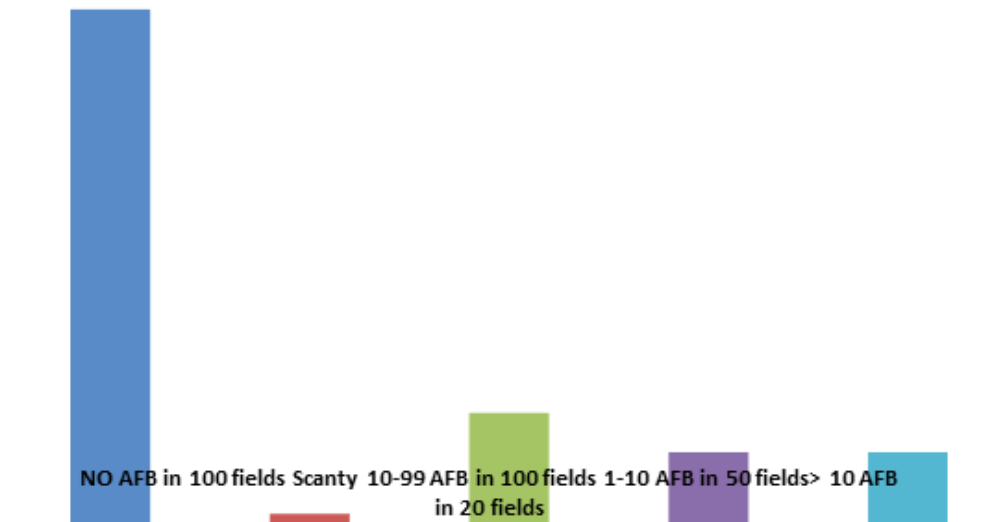


Figure 2: Sputum Scoring Among the Respondents

GeneXpert was used to diagnose TB and to test for rifampicin (RIF) resistance which was used as proxy for MDR-TB. The specimen for GeneXpert was collected in an open field fresh. The patient was instructed to inhale deeply 2-3 times, breathe out each time, cough deeply from the chest, place the open container close the mouth to collect the specimen. Appropriate specimen used for GeneXpert was sputum, minimum of 1ml without food particles and stored at 4°C for max, minimum 10 days. Results were as follows: MTB detected, MTB not detected, RIF resistance detected, RIF resistance not detected, RIF resistance indeterminate and Error/invalid.

Completed questionnaire and measurements were entered into a computer data base. The data were analyzed using the epidemiological information (Epi-info) 2005 software package of Centers for Disease Control and Prevention (CDC). The 2 by 2 contingency tables were used to carry out Chi-square test and to find out the level of significance and values less than 0.05 were regarded as statistically significant.

## RESULTS

One hundred and forty patients consisting of 84 males, and 56 females with cough of more than two weeks duration were investigated during the study period. The minimum age of respondents was 18 years, while the maximum was 83 years. The mean age was  $38.39 \pm 13.75$ .

Figure 1 shows the pattern of referral of the TB suspects with the secondary health facility making

the highest referral, while the primary health centers made the least.

## DISCUSSION

Demographic characteristics analysis showed that the age group 31-40 had the highest drug resistance TB. This was comparable to the previous study in Nigeria<sup>16</sup>, but differed from that of Imam and Oyeyi<sup>17</sup> in Nigeria, where 15.29 age group had the highest percent distribution.

There was male preponderance, 84 (60%) as against 56 (40%) female; this was also in agreement with the previous studies<sup>16-18</sup>, and in concord with the work of Taura et al.<sup>19</sup>, where male subjects had a prevalence of 61.5% as against 38.5% of females. This disparity could be due to the fact that male subjects were more exposed to the risk factors of TB infection such as smoking, which usually makes them more susceptible.

Forty eight (34.3%) of the respondents had smear-positive TB. This is comparable to 31 (18.2%) obtained in the study by Lawson<sup>20</sup> et al. but lower than 8%) smear-positivity reported by Boyer et al.<sup>21</sup>. For TB diagnosis in sputum smear-positive samples, studies showed sensitivities ranging from 93% to 98% and specificities of 83% to 99%<sup>22,23</sup>. Sputum smear microscopy has some limitations because it can only be used to diagnose TB when sputum has sufficient TB often goes undetected because people living with HIV (PLHIV), especially those with severe immune suppression generally have very low number of bacilli<sup>24</sup>. A more sensitive approach to

diagnosis is to culture sputum samples, which can include testing for drug resistance. However, such techniques require expensive and sophisticated laboratory equipment and staff, and it takes weeks or months to obtain such results. Realistically, most people who need culture tests to diagnose their TB will not have access to the test results on time in order to commence medication on time thereby preventing complications and spread of disease to others. In this regard, GeneXpert assay is more sensitive than sputum smear microscopy in detecting TB, and it has similar accuracy as culture (Figure 2).

Eighteen (12.9%) of the respondents were HIV positive and it was commoner among males than females. Age group 31-40 (33.57%) had the highest prevalence of multi resistant TB. This could be attributed to the social life style in the study area. Many of them lived a polygamous way of life, as well as the culture of wife inheritance as influenced by their religion. Alcohol use and misuse was another contributing factor. Social class-V, constituting 8(12.9%) of the respondents were generally unemployed. Majority of them were full time house wives, and some of them were subsistence farmers. They were found to be statistically significant (Table 2).

**Table 2:** Socio-Demographic Characteristics of the Respondents

| <b>Variables</b>          | <b>Frequency</b> | <b>(%)</b> |
|---------------------------|------------------|------------|
| <b>Age</b>                |                  |            |
| <21                       | 9                | 6.4        |
| 21 – 30                   | 38               | 27.1       |
| 31 – 40                   | 47               | 33.6       |
| 41 – 50                   | 27               | 19.3       |
| 51 – 60                   | 8                | 5.7        |
| >60                       | 11               | 7.9        |
| <b>Sex</b>                |                  |            |
| Male                      | 84               | 60         |
| Female                    | 56               | 40         |
| <b>Marital Status</b>     |                  |            |
| Single                    | 9                | 6.4        |
| Married                   | 85               | 60.8       |
| Divorced                  | 8                | 5.8        |
| Separated                 | 11               | 7.8        |
| Widow                     | 17               | 12.1       |
| Widower                   | 10               | 7.1        |
| <b>Level of Education</b> |                  |            |
| Non-formal                | 84               | 60         |
| Primary                   | 40               | 28.6       |
| Secondary                 | 11               | 7.8        |
| Tertiary                  | 5                | 3.6        |
| <b>Religion</b>           |                  |            |
| Christianity              | 48               | 34.2       |
| Islam                     | 85               | 60.8       |
| Traditional               | 5                | 3.5        |
| Others                    | 2                | 1.5        |
| <b>Occupation</b>         |                  |            |
| Business person           | 58               | 41.4       |
| Civil servant             | 7                | 5          |
| Retired workers           | 11               | 7.8        |
| Farmers                   | 12               | 8.6        |
| House wives               | 17               | 12.2       |
| Unemployed                | 29               | 20.7       |
| Students                  | 6                | 4.3        |
| <b>Social Class</b>       |                  |            |
| I                         | 0                | 0          |
| II                        | 5                | 3.8        |
| III                       | 19               | 13.5       |
| IV                        | 40               | 28.5       |
| V                         | 76               | 54.2       |
| <b>HIV Status</b>         |                  |            |
| Non-reactive              | 122              | 87.1       |
| Reactive                  | 18               | 12.9       |

**Table 3:** Rifampicin Sensitivity Pattern

| Variables    | RIFAMPICIN        |                      |                      | Total            | p-value |
|--------------|-------------------|----------------------|----------------------|------------------|---------|
|              | Not on Rifampicin | Rifampicin Resistant | Rifampicin Sensitive |                  |         |
| Sex          |                   |                      |                      |                  |         |
| Male         | 46 (54.8)         | 6 (7.1)              | 32 (38.1)            | 84 (100)         | 0.076   |
| Female       | 40(71.5)          | 4 (7.1)              | 12 (21.4)            | 56 (100)         |         |
| <b>Total</b> | <b>86 (61.4)</b>  | <b>10 (7.2)</b>      | <b>44 (31.4)</b>     | <b>140 (100)</b> |         |

Table 3 shows that 32 (38.1%) male out of 84 and 12 (21.4%) female out of 56 were sensitive to rifampicin, while 6(7.1%) male out of 84 and 4 (7.1%) female out of 56 were resistant to it.

**Table 4:** Prevalence of Multi Resistant Tuberculosis MDR-TB and Rifampicin Resistant (RIF)

| Sex          | MDR-TB          |                 |                         |                 | Total            | p-value |
|--------------|-----------------|-----------------|-------------------------|-----------------|------------------|---------|
|              | Negative        | Positive        | Positive RIF resistance | Invalid Results |                  |         |
| Male         | 40(47.6)        | 32(38.2)        | 6(7.1)                  | 6(7.1)          | 84 (100)         | 0.031   |
| Female       | 39(69.7)        | 12(21.4)        | 4(7.1)                  | 1(1.8)          | 56 (100)         |         |
| <b>Total</b> | <b>79(56.4)</b> | <b>44(31.4)</b> | <b>10(7.2)</b>          | <b>7(5.1)</b>   | <b>140 (100)</b> |         |

Table 4 shows the prevalence of MDR-TB and RIF resistance. Forty four (31.4%) were MDR-TB positive with a prevalence of 31.4%. Ten (7.2%) were Rifampicin resistant; this included 6 males and 4 females. This is statistically significant.

In this study HIV co-infection was not found to be statistically significant with anti-TB drug resistance as found in other studies<sup>25,16</sup>. The current meta-analysis provides strong evidence to affirm that HIV co-infection may not have an influence on the development of anti-TB drug resistance. Additionally, with the exception of a report from Latvia and Ukraine, several reports from different parts of the world had shown that HIV infection had no statistically significant association with multidrug resistant TB<sup>27</sup>. This was however in contrast to findings in studies done about two decades ago, which showed that 90% of cases of multidrug resistant TB occurred in HIV-co-infected individuals<sup>28</sup>. Similarly, in the United States, it was reported that HIV infection was associated with the emergence of MDR-TB<sup>29</sup>. Anastasis et al. expressed concern regarding the development of drug-resistant TB as the HIV epidemic progressed in the United States<sup>30</sup>.

In this study, 44(31.4%) of the respondents were rifampicin sensitive, while 10(7.2%) were

rifampicin resistant (Table 3). This agrees with the findings of Olusoji et al<sup>16</sup>, where (8.6%) were resistant to rifampicin, but lower than that of the study by Lawson et al.<sup>20</sup> where (19%) isolates were resistant to rifampicin. This level of resistance was in keeping with the findings of Idigbe et al.<sup>31</sup> who reported 2% resistance to rifampicin in Lagos, Nigeria, but contrary to the findings in the study by Akaninyene and co-workers<sup>18</sup> where no strain of rifampicin resistance was reported. Mycobacterium TB is more liable to undergo mutation when it is exposed to rifampicin than to many of the second line anti-TB drugs<sup>32</sup>.

Forty four (31.4%) of the respondents were positive and this was comparable to rates published in previous studies from India<sup>33,34</sup>, but much lower than 77.4% reported by Olusoji et al<sup>16</sup>. Not many studies had documented the presence of MDR-TB in Nigeria, with prevalent rates ranging from 4%-76.3%<sup>6-9</sup>. According to the World Health Organization, 650,000 people are infected worldwide by MDR-TB and 12 million people suffer from tuberculosis. In Africa, 1.99% of new cases and 9.4% of diagnosed and treated patients are infected by MDR strain<sup>2</sup>. The 2002-2007 global survey conducted by WHO also showed that the highest prevalence of MDR-TB among newly diagnosed and previously treated TB cases were 22% and 60%

respectively<sup>35</sup>. The World Health Organization (WHO), without an actual survey, estimated a much lower burden of 1.9 and 9.3% for new and previously treated patients, respectively<sup>1</sup>. This could be attributed to poor record keeping. It is probable that WHO has underestimated Nigeria's burden. This echoes the dire need for good clinical management practices and a prospective countrywide survey and adequate record keeping. Idigbe et al.<sup>31</sup> reported that 56% of the strains recovered from 96 patients not responding to anti-TB treatment were resistant to one or more of the drugs used, with 38% being resistant to Isoniazid, although only 2% were resistant to rifampicin at that time<sup>9</sup> and did they did not find an association with HIV infection<sup>10</sup>. There is a need to establish more National Reference Laboratories in Nigeria for technical support, quality assurance and surveillance. Several factors might be responsible for the development of MDR-TB and these include patient factors such as poor adherence of patients to first line anti TB drugs, inappropriate treatment regimens, dosage and duration of treatment and non-compliance to national guidelines of TB treatment protocol by clinicians.

Since drug-resistance is a dynamic phenomenon, it is pertinent to monitor the trend of drug-resistance periodically among patients presenting with TB symptoms. Adequate enlightenment should be given to patients for proper drug compliance, because inadequate dosage or non-compliance on the part of the patients is common and clinicians should be encouraged to abide with the National Tuberculosis Protocol (NTP).

## CONCLUSION

Rifampicin resistant TB is factor to be considered in refractory cases, hence the need for continuous monitoring of drug resistance trends, in order to assess the efficacy of current interventions and their impact on the TB epidemic.

## STRENGTHS

GeneXpert has the potential to significantly increase TB case detection where traditional diagnostic method are inadequate, such as in people with suspected HIV-associated TB and MDR-TB.

## LIMITATIONS

First of all, this was a hospital-based study, hence

there could have been significant referral bias involved in patients selection. GeneXpert machine is recommended to test for rifampicin resistance, which is used as proxy for other anti TB drug. Every RIF-resistant case should also have culture done to determine resistance against other first and second line drugs. GeneXpert however is not a panacea and its implementation presents major challenges, particularly related to the cost of infrastructure, which calls for a thoughtfully phased and careful introduction of the machine.

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## Conflict of Interest Statement

The authors declare that we had no financial or personal relationship(s) which may have inappropriately influenced us in the conduct of this study.

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