

Evaluation of Drug Resistance from Sputum Specimens of Suspected Tuberculosis Patients attending a District Hospital, Abuja

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Research article

Keywords: Drug resistance, M. tuberculosis complex, antimicrobial susceptibility, Abuja, sputum, first-line drugs

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Abstract

Background: This study evaluated the prevalence of drug resistant tuberculosis infection among suspected tuberculosis patients attending Asokoro District Hospital (ADH), Abuja, Nigeria. **Methods:** A total of 301 AFB+/- sputum specimens from suspected TB patients were collected for the study following study approval from Asokoro District Hospital Ethic Committee. Eighty-nine (89) identified *Mycobacterium tuberculosis* complex were isolated after morphological and biochemical testing. Sputum specimens collected from the patients were processed, cultured on Lowenstein-Jensen (LJ) media and subjected to in-vitro antimicrobial susceptibility testing. The eighty-nine (89) identified *M. tuberculosis* complex isolates were challenged with Rifampicin (RIF), Isoniazid (INH), Ethambutol (EMB) and Streptomycin (SM) drugs respectively. **Results:** Out of the total 89 samples analyzed, 13 (14.6%) showed resistance to the first-line drugs while 76 (85.4%) were susceptible. Drug resistance was identified in 10 (11.8%) of the new tuberculosis case (primary drug resistance cases) and 3 (75%) in re-treatment cases (secondary or acquired resistance). Prevalence of mono-resistant, double resistant and triple resistant patterns were 5 (5.7%), 6 (6.7%) and 2 (2.2%) respectively. Multi-drug resistant (resistant to both RIF and INH, the two most potent anti-tuberculosis drugs, with or without resistant to other drugs) was 1.1%. No isolate was resistant to all the four drugs. **Conclusion:** Drug resistance were observed in the cultures of *M. tuberculosis* complex, however no isolate showed resistance to all the four first-line drugs used. This study therefore recommends strict adherence to medication for tuberculosis patients as poor compliance or inappropriate use of drugs could induce resistance. **Keywords:** Drug resistance, *M. tuberculosis* complex, antimicrobial susceptibility, Abuja, sputum, first-line drugs.

1. Introduction

Nigeria is one of the leading countries in the high burden countries for TB/HIV, DR-TB, MDR-TB and XDR-TB with an estimated rate of 322 per 100 000 population with only 15% of the total burden of the disease in the country being reformed in 2015 (WHO, 2017). According to WHO (2017), out of the global rate of 10.4 million incident cases of TB, 3.9% were estimated to have had rifampicin-or Drug resistant tuberculosis whereas 21% of previously treated TB cases were estimated to have had MDR/RR-TB in the same year. Nigeria is one of the leading countries in the high burden countries for TB/HIV, DR-TB, MDR-TB and XDR-TB with an estimated rate of 322 per 100 000 population with only 15% of the total burden of the disease in the country being reformed in 2015 (WHO, 2017). MDR-TB is caused by strains of *M. tuberculosis* that is resistant to both isoniazid and rifampicin. Drug-resistant TB (DR-TB) patients require prolonged and expensive treatment using second-line medications that are less effective and more toxic (WHO, 2016). Anzaku *et al* (2017), reported that the control efforts and the burden of drug resistant tuberculosis (TB) is poorly comprehended in resource-limited settings.

Multi-drug resistant tuberculosis (MDR-TB) (resistant to rifampicin and isoniazid, the two most powerful first-line TB drugs) could be worse, and the emergence of more potent extensively drug-resistant (XDR) *M. tuberculosis* (defined as resistant to at least isoniazid, rifampin, any fluoroquinolone, and either aminoglycosides [amikacin, kanamycin] or streptomycin or both) in Africa and worldwide has been a

major challenge in tuberculosis control worldwide (WHO, 2012). As part of the strategies to trash tuberculosis, the Nigerian government established the National TB and Leprosy Control Programme (NTBLCP) in 1991 and subsequently adopted the WHO-recommended Directly Observed Treatments (DOTs) strategy in 1993 to checkmate the scourge of TB (PHW, 2006). DOTs has since expanded from its previous 47% coverage areas of 1995 to the present 75% (WHO, 2008) with little impact on TB spread as Nigeria stands shoulder high among the 22 high burden countries with new cases. The current cases detection rate of 20% and treatment success of 75% (WHO, 2008) has not fully meet up with the universally recommended 70% new sputum smear-positive case detection arising per year and 85% successful treatment of such cases (Dye *et al.*, 2007). Between 1995 and 2006 the case detection rate has increased from 11 percent to 20 percent while the treatment success rate slipped from 49% in 1995 to 32% in 1996 and picked in 1997 to 73% (WHO, 2015). The treatment success rate has maintained the above 70% since then. The 2004 incidence figure of tuberculosis was 290/100,000 persons per year or 373, 682 new TB cases of which 33,755 (126/100,000) were smear positive (WHO, 2016). However, the new WHO report (WHO, 2015) put the incidence case at 311/100,000 person or estimated 450,000 new cases of which 137/100000 or 198, 300 persons are smear positive.

Although the true level of drug resistance tuberculosis in the world today is unknown, studies have shown that it has been increasing (Espinal *et al.*, 2011). Drug resistant surveillance commenced in the developed world in the early 1990s but the true incidence remained unclear in the developing world where there is neither no or limited access to testing for drug susceptibility (Cohn *et al.*, 2010). An estimated 4% of the world's tuberculosis cases are resistant to at least one of the current first-line drugs (Moran, 2014). WHO reported global burden of drug resistant tuberculosis data in order to determine the global magnitude of resistance to the first-line antituberculosis drugs and by 2003, the third round of the global project (WHO, 2004). Despite strategies to curb emergence of drug resistance tuberculosis, most TB drugs are increasingly becoming resistance (WHO, 2009). This study was conducted to determine the prevalence of anti-tuberculosis drug resistance in a selected district hospital in Abuja, a section of Nigeria.

2.0 Materials And Methods

De-identified sputum specimens obtained from suspected TB patients attending Asokoro District Hospital (ADH), Abuja collected from the laboratory between February 2015 and July 2016 were studied in the Research Laboratory of Zankli Medical Centre in Abuja.

2.1 Ethical clearance and informed consent form

Approval for the study was obtained from Asokoro District Hospital Ethic Committee and sputum from patients with no reported history of prior antituberculosis treatment and those that have previously accessed therapy but not on TB treatment as at the start of this work were used. Patients were properly counselled on the importance of the study and Informed consent was obtained from all participants. Those below 18 years had their parents or guidance endorsed the consent in proxy. Both patients and the

hospital management were also informed that the study would not interfere with the patients' management.

2.2 Sputum sample processing

Sputum specimens were processed according to standard mycobacteriological culture method while *Mycobacterium tuberculosis* complex were identified by microscopy, morphology and biochemical tests respectively (WHO, 2015). Sputum specimens were digested and decontaminated using the modified Petroff's method (WHO, 1998). 100 µl of sediments (decontaminant) from each specimen was cultured on LJ media and incubated at 37°C for 30 days to observe for growth. The isolates were confirmed as *M. tuberculosis* complex (MTBC) by cultural characteristics, nitrate reduction test, 68°C catalase test and Ziehl Neelsen smear to observe the serpentine cords typical of MTBC.

Drug susceptibility of the isolates to Rifampicin, Isoniazid, Ethambutol and Streptomycin was done by Proportion method (Kehinde, 2012). The recommended critical concentrations for the drugs were 4µg/ml for SM, 0.2µg/ml for INH, 40µg/ml for RIF and 2µg/ml for EMB respectively. The drug resistant was determined by the ratio of number of colonies growing in drug-containing medium and on drug-free medium and more than 1% increase was considered to be resistant (Vareldzis *et al.*, 1994; Canetti *et al.*, 1969; Canetti *et al.*, 1963).

2.3 Primary resistance

Primary resistance was classified as resistance to at least one of the drugs tested on the isolates from patient without prior history of anti-tuberculosis therapy while acquired resistant was classified as resistance of isolate obtained from patient that has previously being treated for tuberculosis. Multidrug resistant tuberculosis (MDR-TB) was classified as resistant to at least both the rifampicin and isoniazid.

Statistical analysis was done using OpenEpi version 2.2 software packages with variables subjected to Pearson's Chi-squared tests or Fisher exact tests when numbers were small.

3.0 Results And Discussion

The growth response of the sputum specimens on LJ media is summarized below. Of three hundred and one (301) AFB+ and – cultures studied, ninety-seven (97) mycobacteria isolates grew, 190 did not grow and the remaining 14 were contaminated. Of the 97 isolates, 89 were MTB complex while 8 were identified as non-tuberculous mycobacteria (NTM) (Table 1).

Table 1: Culture status of AFB+/- sputum specimens on LJ media

The result of anti-tuberculosis of the drug resistance tuberculosis to both the first line drugs and second line drugs is presented in table 2 below. The prevalence of drug resistance in this study was 14.6% while

85.4% were susceptible. Primary drug resistance was 11.8% (10/85) while secondary or acquired resistance was 5% (3/4) respectively. The overall prevalence of MDR-TB was 1.1%. Mono-resistant TB case was 5.7% with the highest occurring from streptomycin resistant 3.4% follow by ethambutol 2.3%. Double resistant TB case was 6.7% with combination of rifampicin-streptomycin (1.1%) and isoniazid-streptomycin combination (5.6%). Triple resistant tuberculosis case prevalence was 2.2%. Rifampicin-isoniazid-streptomycin combination and isoniazid-ethambutol-streptomycin combination were the only two identified cases in this category. The prevalence of rifampicin-isoniazid-streptomycin resistance was 1.1% and that of isoniazid-ethambutol-streptomycin was also 1.1%. From this study, double resistance had the highest prevalence rate (6.7%) follow by mono-resistant (5.7%) and triple resistant (2.2%) which had the lowest rate. The figure below showed the percentage profile of the resistance prevalent.

Table 2: Prevalence of drug resistance tuberculosis= (14.6%)

Table 3. Drug Resistant profile of *M. tuberculosis* complex isolates from Asokoro District Hospital, Abuja.

Figure 1 below showed total tested isolates, resistance isolates and susceptible isolates to antituberculosis agents.

2.2 Discussion

The prevalence of drug resistance in this study was 14.6%. Levels of primary and secondary drug resistance are 11.8 % and 75% respectively among suspected tuberculosis patients attending the district hospital in Abuja. The level of acquired resistant in this study is significantly higher than the primary resistant ($p=0.016$). Meanwhile, the primary and acquired drug resistance fall below the acceptable limit for country with well implemented national tuberculosis control programme. Level of acquired drug resistance is between 50%-80% where the national tuberculosis control programme is poorly implemented (Crofton *et al.*, 2012). As acquired drug resistance determines the occurrence of primary resistance, the latter is expected to be lower than the former (Chaulet *et al.*, 2015). Okodua *et al.* (2012), asserted that primary drug resistant tuberculosis is 5% or less and acquired drug resistant to decrease to between 10%-20% where DOTS program is well implemented. This study shows 1.1% rate of multi-drug resistant tuberculosis (MDR-TB) which was in contrast to Lawson *et al.*, (2011) that reported 8% cases of MDRTB. This could be as a result of three (3) cities covered for their study and a larger sample size as compared to one district hospital for this present study. The prevalence of MDR-TB among the re-treatment cases in this study was 25%. This was about similar to nationwide survey report of 25.6% in China (WHO, 2010) and contrary to another study from Jos (a North central city in Nigeria) that reported 18% of retreatment cases (Ani *et al.*, 2009). This could be because most patients accessing the DOTS may not have enough information on importance of drug adherence as it is often noticed that they stop their regimen without completing it once they get relief (PHW, 2006). MDR-TB is a public health concern as it accounts for TB treatment failure worldwide (WHO, 2014). Identifying patients with MDR-TB earlier enables rapid treatment which increases their chances of survival and minimizes risk of transmission (Breathnach *et al.*, 2008). However, treatment of MDR-TB is complicated because it requires the use of second-line drugs

for ≥ 24 months which are more costly, toxic, and less effective than the first-line drugs used for regular tuberculosis therapy (Shah. *et al.*, 2007). The results of mono-resistant pattern showed 5.7% prevalence. Resistant to specific drug indicates that Streptomycin and ethambutol are observed with prevalence of 3.4% and 2.3% respectively. The range of resistant to these two drugs is also consistent with the world report resistant range of 0-4.9% for Streptomycin and 0-4.2% for ethambutol respectively found in countries with cases of mono-resistant tuberculosis challenge (WHO, 2004).

Double resistant pattern in this study show resistant MTB isolates to: (1) 5.6% prevalence in Isoniazid and streptomycin combination. (2) 1.1% prevalence in Rifampicin and streptomycin combination. The Isoniazid and streptomycin combination prevalence could be because they are among the first few anti-TB in existence since middle of nineteenth century, hence resistant to these two old drugs may have developed over the years (Bello, 2014). Of concern is the isolate resistant to both rifampicin and streptomycin (1.1%). Although MDR-TB is resistant to at least rifampin and isoniazid, the two most powerful and commonly used anti-TB drugs WHO (2014), resistant to RIF alone can be a useful surrogate marker for MDR-TB (Sam *et al.*, 2006; WHO, 2004a; Somoskovi *et al.*, 2001). MDR-TB threatens the effectiveness of chemotherapy for both treatment and control of TB and require the use of second-line drugs that are more expensive, less effective than the first-line drugs, toxic and require longer administration periods (18-24 months) (Prammananan *et al.*, 2005; Moran, 2004). Mortality among cases of MDR-TB is high and this is worrisome because of its high treatment failure rate. Idigbe *et al.* (2002), 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. Triple resistant pattern of the MTB in this study show: (1) 1.1% prevalence of Rifampicin, isoniazid and streptomycin combination. (2) 1.1% prevalence of Isoniazid, ethambutol and streptomycin combination. Isolate showing resistant to rifampicin and isoniazid with or without other first line drug is classified to be a MDR-TB (Sam *et al.*, 2006; WHO, 2004a; Somoskovi *et al.*, 2001), often identified with high mortality among the victims and threat to TB treatment and control. The second triple resistant case may be because these drugs were among the first anti-tuberculosis drugs (especially for isoniazid and streptomycin) (Johnson *et al.*, 2007; Crofton and Mitchison, 1948), and it being abused or inappropriately used over the years. However, EMB resistant in this triple resistant may not be categorical because phenotypic determination of true resistant to EMB is still unclear (Johnson *et al.*, 2007; Johnson *et al.*, 2006).

The overall drug resistant TB rate of 14.6% found in this study is attributable to poor compliance with the DOTS guidelines common in low-income countries (Jones-Lopez and Ellner, 2005), irrational use of drugs as common in countries that sell antimicrobial drugs without prescription (i.e., over-the-counter) (Stratchounski *et al.*, 2013; Okumura *et al.*, 2012), lack of the DOTS in parts of the remote areas in the country (PHW, 2006), proliferation of unregistered drug distributors in resource poor settings like Nigeria, inadequate awareness about tuberculosis (its mode of infection and treatment), poor socio-economic condition, HIV/AIDS as well as illiteracy.

4.0 Conclusion And Recommendation

Drug resistance were observed in the identified cultures of *M. tuberculosis* complex, however no isolate showed resistance to all the four first-line drugs used. This study therefore recommends strict adherent to medication for tuberculosis patients as poor compliance or inappropriate use of drugs could induce resistance.

Strengthening Laboratory capacity that include drug resistance surveillance in Nigeria should be encouraged. This could be done through the provision of faster, automated culture and DST facilities or automated polymerase chain reaction (PCR) technologies that are emerging elsewhere. Future studies should investigate if extensively drug resistant TB (XDR-TB) strains are also affecting newly diagnosed patients with TB in Nigeria and if strains are still sensitive to fluoroquinolones and other alternative agents.

Declarations

Competing interest

All authors have declared that, no conflict of interest exist in this manuscript.

Ethical clearance:

The ethical clearance for this study was obtained from the Ethic Committee of Asokoro District Hospital, Abuja, Nigeria. Participants for this study were allowed to voluntarily participate after obtaining informed consent forms.

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Tables

Table 1: **Culture status of AFB+/- sputum specimens on LJ media**

Status	Isolates	Percentage occurrence
MTB complex	89	29.6
NMTB	8	2.7
Contaminated	14	4.7
No growth	190	63.1
Total	301	100%

Key: MTB=Mycobacterium tuberculosis; NMTB= Non Mycobacterium tuberculosis

Table 2: Prevalence of drug resistance tuberculosis= (14.6%)

Anti-TB agent	Type of resistance				Percentage occurrence
	MDR-TB	Mono resistance	Double resistance	Triple resistance	
Ethambutol		2.3%			5.7%
Streptomycin		3.4%			
RIF-SM			1.1%		6.7%
INH-SM			5.6%		
RIF-INH-SM				1.1%	2.2%
INH-EMB-SM				1.1%	
Total	1.1%	5.7%	6.7%	2.2%	14.6%

Keys: SM=Streptomycin; INH= Isoniazid; EMB=Ethambutol; RIF = Rifampicin

Table 3. Drug Resistant profile of *M. tuberculosis* complex isolates from Asokoro District Hospital, Abuja.

Resistant Pattern	AFB+		OR	95% CI	P- value
	(N=89)	(%)			

Any Drug (N) *	10	11.8 (10/85)	0.8	0.3-1.9	0.591
Any Drug (RE) *	3	75 (3/4)	16.7	1.7-466.4	0.016
Any Drug (N+RE) *	13	14.6		Reference	

MDR-TB (N)	0 ⁰	0.0	1.0	0.0-41.3	0.977
MDR-TB (RE)	1	25 (1/4)	29.3	1.5-589.8	0.001
MDR-TB (N+RE)	1	1.1		Reference	

Monoresistant $\perp\perp$

Rifampicin	0 ⁰	0.0	0.5	0.0-6.6	1.000
Isoniazid	0 ⁰	0.0	0.5	0.0-6.6	1.000
Ethambutol	2	2.3		Reference	
Streptomycin	3	3.4	1.5	0.2-13.0	0.684

Double resistant $\perp\perp$

Rifampicin + Streptomycin	1	1.1		Reference	
Isoniazid + Streptomycin	5	5.6	5.2	0.7-125.9	0.120

Triple resistant $\perp\perp$

Rifampicin + Isoniazid + Streptomycin	1	1.1	1.0	0.0-39.4	1.000
Isoniazid + Ethambutol + Streptomycin	1	1.1		Reference	

Monoresistant $\perp\perp$	5	5.7		Reference	
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Double resistant $\perp\perp$	6	6.7	1.2	0.3-4.5	0.768
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Triple resistant $\perp\perp$	2	2.2	0.4	0.1-2.0	0.281
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Any Rifampicin resistance*	2	2.2	0.3	0.0-1.3	0.101
Any Isoniazid resistance*	7	7.9		Reference	
Any Ethambutol resistance*	3	3.4	0.4	0.1-1.6	0.215
Any Streptomycin resistance*	11	12.4	1.6	0.6-4.7	0.335

*=Resistance to drug in question, either alone or in combination with resistance to others; N=New cases; RE=Re-treatment cases;

⊥= Resistance to the specified drug; MDR-TB= Multidrug resistant tuberculosis; OR=odds ratio; CI= confidence interval.

⊞ = calculated by adding 0.5 to numerator and denominator (reference).

Figures

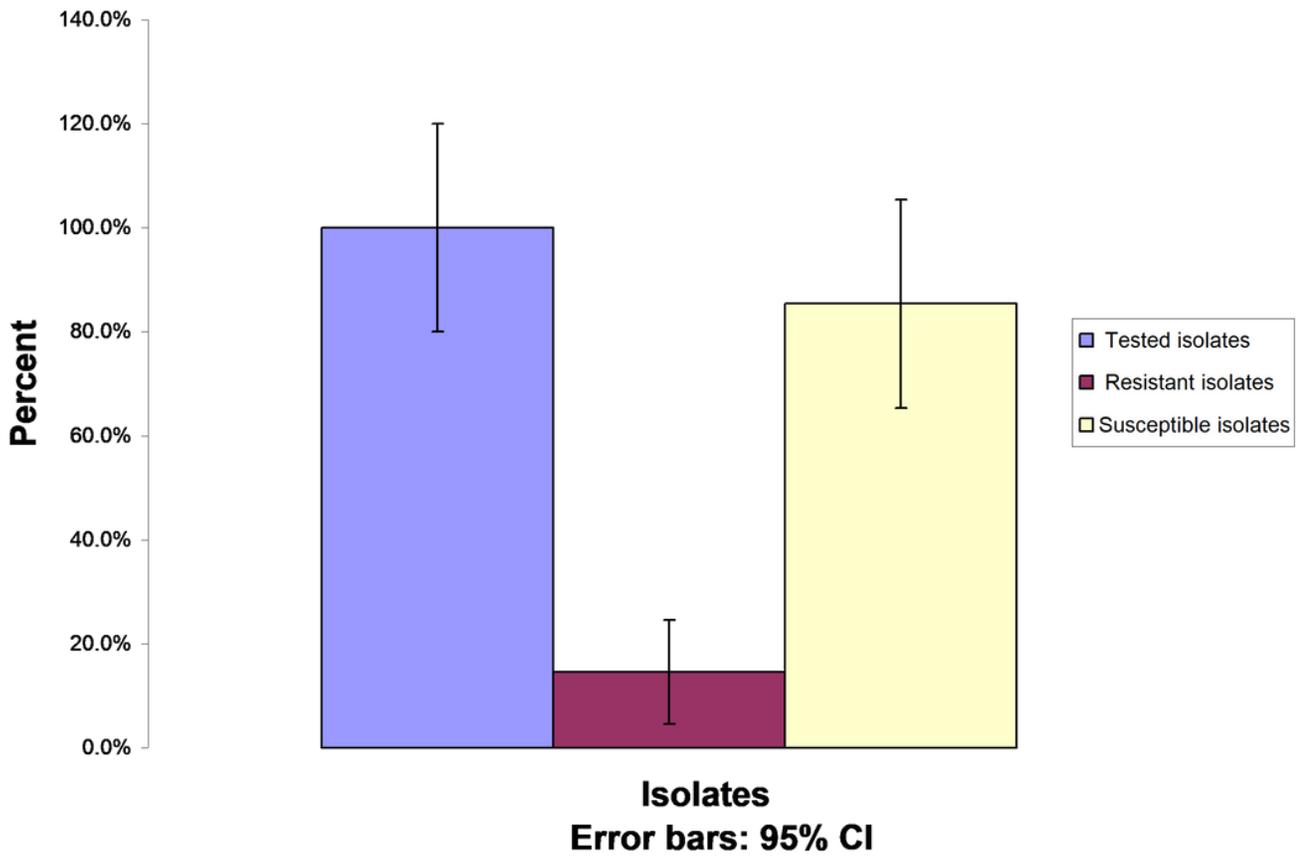


Figure 1: Isolates' response to the first-line drugs

Figure 1

Showed total tested isolates, resistance isolates and susceptible isolates to antituberculosis agents.