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Research Article

Multi Drug Resistant Tuberculosis an Emerging Concern a Study at Tertiary Health Center in Nigeria

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Abstract

Background: The emergence and spread of drug-resistant tuberculosis (DR-TB) has become the major concern in global TB control nowadays due to its limited therapy options and high mortality. An evaluation of the epidemiological trends of DR-TB in Abubakar Tafawa Balewa University Teaching Hospital (ATBUTH), Bauchi, of which TB incidences is remarkable, is essential but lacking.

Aim: There has been a steady rise in MDR-TB in Nigeria between 2009 and 2014 and the number of patient enrolled is still well below the estimated 21,000 cases of MDR-TB. Few studies on the trends of MDR-TB was done in Nigeria. This study is center based survey to understand the burden and dynamics of DR-TB for effective planning and positioning of the health care centers in order to mitigate, treat and reduce the burden of DR-TB.

Method: This study is cross sectional study which looked into the presumptive DR-Tb register at the Bacteriology laboratory of ATBUTH for a period of 24 months, between November 2014 to October 2016, patient data for acid fast bacilli (AFB) smear and Xpert MTB/RIF assays were obtained. Socio demographic data including age, sex, were collected and clinical data including treatment history, prior TB contact, cavity, and bilateral disease on chest radiology were available.

Results: Multidrug-resistant TB (MDR-TB) was found to be on the increase with more males (15%) affected compared to female (8%), Majority of the positive cases 8% were among those age 26 - 35 yrs and 2% among the elderly patient age ≥ 55 yrs. 2.3% of the study subject had MDR-TB/HIV co infection. There were more male co infected patients 5.9% compared to female co infected patient 2.6% among the MDR-TB positive subject (P = 0.619). It is essentially an acquired condition, 17% among retreatment compared to 5% among new cases (P = 0.000).

Conclusion: MDR-TB is on the increase it is essentially an acquired condition with mal preponderance, its association with HIV disease is still on the lower side compared to studies in advanced countries poor diagnostic technique for immunocompromised host with pauci bacillary disease could be a factors for low levels noticed in poor countries.

Keywords: *MDR-TB; Age; Sex; HIV Co-Morbidity*

Abbreviations

TB: Tuberculosis; MDR-TB: Multi Drug Resistant Tuberculosis; XDR-TB: Extensively Drug Resistant Tuberculosis; XPERT/MTB RIF ASSAY: Expert/Mycobacterium Rifampicin Assay; ATBUTH: Abubakar Tafawa Balewa University Teaching Hospital; DST: Drug Sensitivity

Testing; DOTS: Direct Observation Therapy Short Course; RFP: Rifampicin; INH: Isoniazide; RR-TB: Rifampicin Resistant Tuberculosis; MTB: *Mycobacterium tuberculosis*; ADR: Adverse Drug Reaction; HIV: Human Immuno deficiency Virus; WHO: World Health Organisation; AFB: Acid Fast Bacilli; LJ: Lowenstein-Jensen; EMB: Ethambutol; Z: Pyrazinamide; NCs: New Cases; PTCs: Previously Treated Cases; CI: Confidence Interval; Th: T Helper Cells; TNF-α: Tumor Necrosis Factor Alfa; AIDS: Acquired Immuno Deficiency Virus; UNAIDS: United Nation Program on AIDS

Introduction

In the year 2016, 87% of new Tuberculosis (TB) cases occurred in the 30 high TB burden countries. Seven countries accounted for 64% of the new TB cases: India, Indonesia, China, Philippines, Pakistan, Nigeria, and South Africa. Global progress depends on advances in TB prevention and care in these countries. Anti-TB medicines have been used for decades and strains that are resistant to 1 or more of the medicines have been documented in every country surveyed. Drug resistance emerges when anti-TB medicines are used inappropriately, through incorrect prescription by health care providers, poor quality drugs, and patients stopping treatment prematurely [1].

Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, the 2 most powerful, first-line anti-TB drugs. MDR-TB is treatable and curable by using second-line drugs. However, second-line treatment options are limited and require extensive chemotherapy (up to 2 years of treatment) with medicines that are expensive and toxic. In some cases, more severe drug resistance can develop extensively drug-resistant TB (XDR-TB), it is a more serious form of MDR-TB caused by bacteria that do not respond to the most effective second-line anti-TB drugs, often leaving patients without any further treatment options [1].

The emergence of DRTB, and particularly multi drug resistance Tuberculosis (MDR-TB) has become a significant public health problem in a number of countries and an obstacle to effective global TB control [1] with the increasing accessibility to Xpert MTB/Rif assay there has been steady increase in cases of Drug Resistant Tb (DR-TB) across the states in Nigeria [1]. Abubakar Tafawa Balewa Teaching Hospital (ATBUTH) Bauchi, which is tertiary health centre in Bauchi, North eastern Nigeria has observed similar trend and this study sort to highlight such surge in the number of suspected DR-TB cases that were confirmed positive with a Gene Xpert machine. This increase in incidence could be attributable to lack of well trained personnel, lack of well-equipped facilities for diagnosis and treatment of drug susceptible Tb (DST), recurrent drug stock out, lack of awareness among the populace and poor application of Direct Observation Therapy Short course (DOTS) strategy in most of the facilities across the country [2].

Mycobacterium tuberculosis (MTB) strain that are resistant to two or more of the most powerful anti-Tuberculosis drugs Rifampicin (RFP) and Isoniazid (INH) is increasing globally [1]. Mycobacterium drug resistance Tuberculosis (MDR-TB) occurs mostly due to in adequate drug treatment which emanates from sub optimal or substandard drugs and spoor application of DOTS, Stop Tb strategy as a result of lack of or bad government policies, inefficient system, lack of patient Education, counseling and close monitoring of patients on Tb treatment [3].

Treatment naïve patient are also at risk of developing MDR TB as a result of spontaneous mutation or transmission of resistant strain of MTB ab initio [1].

In 2015, there were an estimated 480 000 new cases of MDR-TB and an additional, 100,000 people with Rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR-TB treatment [1] worldwide majority of these cases are in Eastern Asia, India, China and the Russian Federation accounted for 45% of the combined total of 580,000 cases [1]. There has been 0.25 million reported death as a result of DR-TB. There were 4.3% (3.2 - 5.4) among new cases and 25% (19 - 31) among previously treated cases with MDR/RR. 1 case of Extremely Drug resistant (XDR-TB) was confirmed and started on treatment, about 50,274 patient were notified and tested for Rifampicin resistance 40% among new cases 64% among previously treated cases with a median prevalence of 7%, thus reflecting the failure of the programmed designed to ensure complete cure of patient with Tb [1]. Drug resistance in *M. tuberculosis* isolates arises from spontaneous genetic mutations and can be enhanced by poor adherence of patients to anti-TB drugs [3]. MDR-TB portrays a great challenge to treatment interventions while XDR-TB is more much difficult to treat with treatment associated adverse drug reaction (ADR) [4].

Nigeria moved from 4th position in 2007 to 10th in 2012 among the 22 high Tb burden countries in the world and from 1st to 4th highest TB burden in Africa [1]. About 4,700 MDR-TB cases estimated which constitute 3 - 5% of all cases of Tb with estimated 4.3% among new cases and about 23% among retreatment Tb cases [4].

Effectively run Tb control program based on the policy DOTS is essential for preventing the emergence of MDR-TB [5]. Nigeria is the third highest burden of Human Immunodeficiency Virus (HIV) infection in the world with 4.4% prevalence rate and an estimated rate of 3 million individuals are infected with 21% TB/HIV co-infection. The implementation of DOTs strategy in Nigeria since 1993 has achieved a case detection rate of 30% and treatment success rate of 79% which is still below the global target of 70% detection and 85% cure rate respectively [6].

The management of MDR Tb should be undertaken by an experienced clinician at centers equipped with reliable laboratory services mycobacterium culture and *in vitro* sensitivity testing as it requires prolonged treatment period with potential drug toxicity in addition to the high cost of the second line anti Tb drugs [7].

Another dreadful outcome of drug resistant Tb is the emergence of yet an extensively resistant strain of MDR-Tb [7]. In early 2005, physicians at a rural hospital in KwaZulu-Natal, a province of South Africa, were concerned by a high rate of rapid death among patients infected with the HIV who also had tuberculosis [7]. A study revealed the presence not only of MDR-Tb but also what came to be called XDR-TB. It is caused by a strain of *Mycobacterium tuberculosis* resistant to isoniazid and rifampin (which defines MDR tuberculosis) in addition to any fluoroquinolone and at least one of the three following injectable drugs: capreomycin, kanamycin, and amikacin [7] these alarming findings attracted much attention at the International AIDS Society conference in Toronto in August 2006. But this was not the first time that XDR tuberculosis had been identified. The March 2006 report by the Centers for Disease Control and Prevention and the World Health Organization (WHO) documented the presence of XDR tuberculosis in about 17 countries [8] though not representative, the data showed that 10% of MDR tuberculosis isolates were in fact XDR tuberculosis. More representative data from the United States, the Republic of Korea, and Latvia showed that 4%, 15%, and 19%, respectively, of MDR tuberculosis isolates were XDR strains [8,9].

There has been a steady rise in MDR-TB in Nigeria between 2009 and 2014 and the number of patient enrolled is still well below the estimated 21,000 cases of MDR-TB [10] only one pilot study on prevalence of MDR-Tb done in Nigeria done in 2010 [11] and very few studies done at tertiary hospitals in Nigeria [11]. Therefore there is need to carry out center based and state based survey in order to understand the burden and dynamics of DR-TB effective planning and positioning of the health care centers in order to mitigate, treat and reduce the burden of DR-Tb among populace.

Methods

This study is cross sectional study which looked into the presumptive DR-Tb register at the Bacteriology laboratory of ATBUTH for a period of 24 months, between November 2014 to October 2016, patient data for acid fast bacilli (AFB) smear and Xpert MTB/RIF assays were obtained. Socio demographic data including age, sex, were collected and clinical data including treatment history, prior TB contact, cavity, and bilateral disease on chest radiology were available. AFB smear results and genotypic result based on Xpert MTB/RIF molecular assay was obtained from the National DR-TB reference laboratory in Zaria, Kaduna state and HIV status of each patient was obtained from the baseline investigation record of each patient admitted at the treatment center. Patient sputum with positive XPert/MTB RIF assay were subjected to Drug susceptible test (DST) and data was collected for the first-line drugs isoniazid, Rifampicin, ethambutol (EMB), and pyrazinamide (Z).

DST was performed using the proportion method on acid-buffer Lowenstein-Jensen (L-J) medium. Specimens were digested and de-contaminated with 4% sodium hydroxide for 15 minutes and then inoculated to L-J media. Susceptibility testing for INH, RFP, EMB, and Z was performed on L-J medium at the following concentrations 0.2, 40, 2.0, and 4.0 μg/mL, respectively. The isolates were considered to be resistant if there was more than 1% growth on medium containing anti-TB drugs as compared with the growth on drug-free medium. The laboratory at study sites is subjected to external quality assessment through TB National Reference Laboratory Network.

Subjects

A total of about 270 patients data for MDR-Tb using the AFB and Gene Expert Machine, Patient are normally screened for MTB/DR-TB based on previous history of Tb treatment, symptomatic contact with DR-Tb, current history Productive cough, progressive weight loss, drenching night sweat, with or without AFB positivity and HIV positive patients that presented with cough all patients. Sample contaminations, machine and human error were considered as possible confounders to this study.

All the TB cases that had a positive *Mycobacterium tuberculosis* culture with DST results as well as demographic and clinical information were included. Patients' HIV status was considered in this study. We excluded patients with non-tuberculous mycobacteria.

Drug-susceptible TB was defined as TB susceptible to both INH and RFP. MDR-TB was defined as TB with resistance to at least INH and RFP. A new TB case is defined as a patient who has never been treated for TB or has taken anti-TB drugs for less than 1 month; a previously treated TB case means that the case has received TB treatment before the current TB episode for 1 month or more [12]. Accordingly, primary drug resistance was defined as drug resistance in a new TB case, and acquired resistance was defined as drug resistance in a previously treated TB case.

Ethical approval was obtained from the ethical committee of the ATBUTH Bauchi, Nigeria.

Statistical Analysis

Data collected from Presumptive MDR-TB register was entered into the excel spread sheet, coded and exported into the SPSS software for analysis. Access to the data stored in the computer was limited through a secured password The SPSS version 24 was used for statistical analysis.

Continuous variables which were normal or fairly normal in distribution were expressed as means (standard deviation). These included such variables as age, Sex, weight. Student unpaired t test was used for comparison of continuous variables; while chi square test was used for comparison of nominal data. P values less than 0.05 were considered significant.

Results

In Nigeria there has been a steady rise in presumptive DR-TB and Rifampicin resistant cases since between 2010 and 2016 with the highest number of these cases recorded in 2016, with about 50% cases not enrolled for treatment presenting a huge gap of unmated need in DR-TB treatment program in Nigeria (Table 1) this might have been due to increase number of gene expert machine in the country which increase the diagnosis of DR-TB in country.

Indicator	2010	2011	2012	2013	2014	2015	2016
Presumptive cases	126	129	1647	3531	24313	51566	82771
Rif Resistant cases	23	25	185	554	703	1279	1686
Enrolment	23	24	156	345	410	665	1251

Table 1: *DR-TB case notification In Nigeria.*

A total of about 270 presumptive DR-TB patients that were screened for MDR-Tb using the sputum smear AFB and Xpert MTB/RIF molecular assay obtained from the DRTB register were analyzed for the purpose of this study. There were more male cases 154 (57%) screened for MDR-TB within the period under review compared to the female patients 116 (43%), (mean age ± standard deviation: overall (35.84) [1.06] years for males and (28.16) [1.35] years for females) (Table 1). There were 36% of the presumptive cases between the ages of 26 to 35yrs and 10% were 55yrs and above (Table 2). There were total of 64 (23.7%) patient that tested positive by XPERT/MTB RIF molecular assay (Figure 1), there were 42 (15%) MDR-TB positive male patient compared to 22 (8%) positive female cases, (p = 0.7657), majority of the positive cases 21 (8%) were among those age 26 - 35 yrs and 5 (2%) among the elderly patient age 55yrs and above (Figure 2). About 23(2.3%) of the study subject had MDR-TB/ HIV co infection (Figure 3). There were more male co infected patients 16 (5.9%) compared to female co infected patient 7 (2.6%) among the MDR-TB positive subject (p = 0.619) (Table 3). The incidence of MDR-TB was observed to be higher among the retreatment cases 46 (17%) compared to the new cases 16 (5%) P = 0.000*.

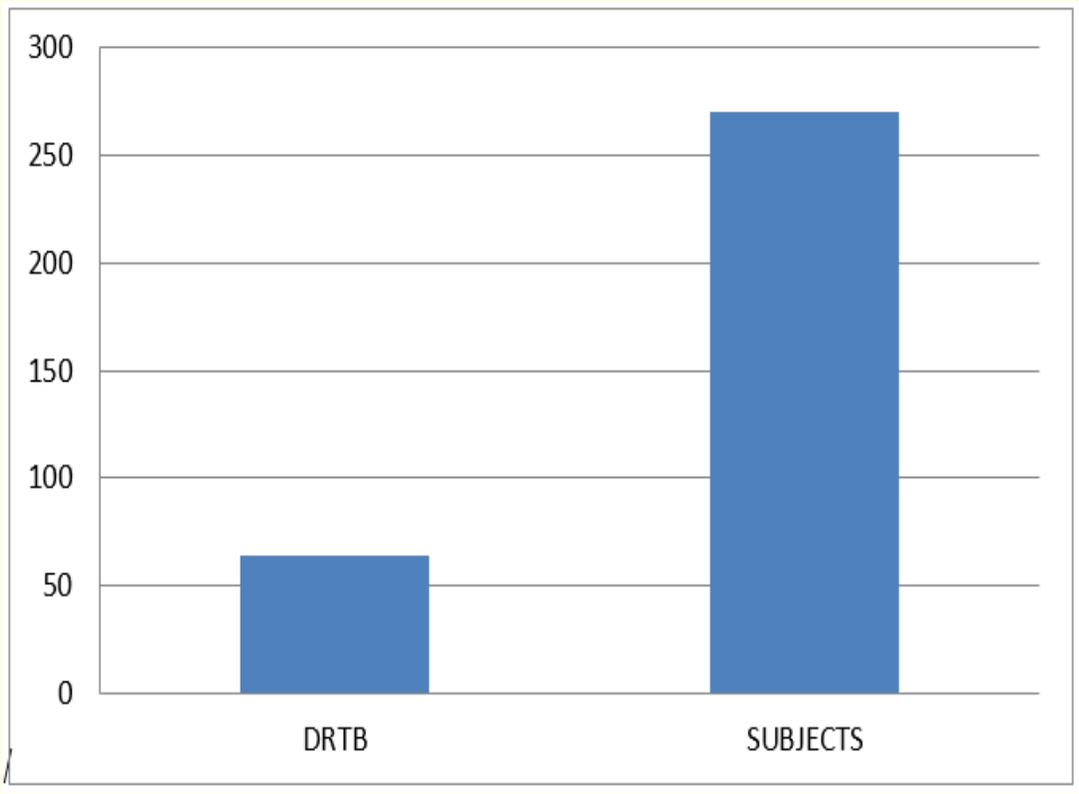

Figure 1: *DR-TB among presumptive cases.*

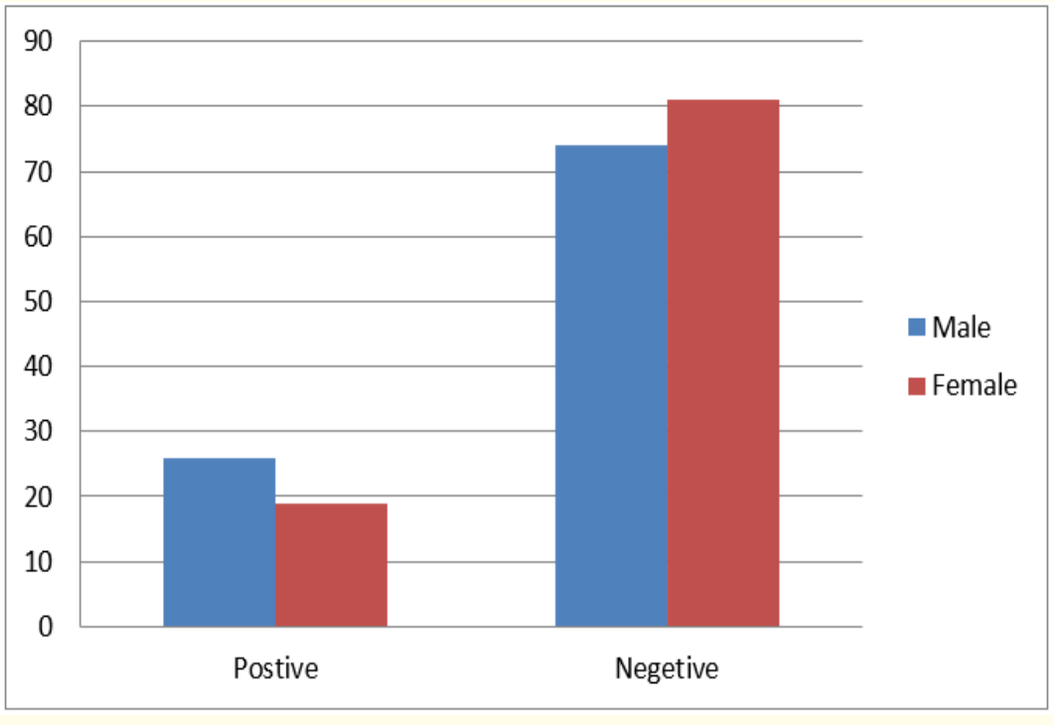

Figure 2: *DR-TB among presumptive cases.*

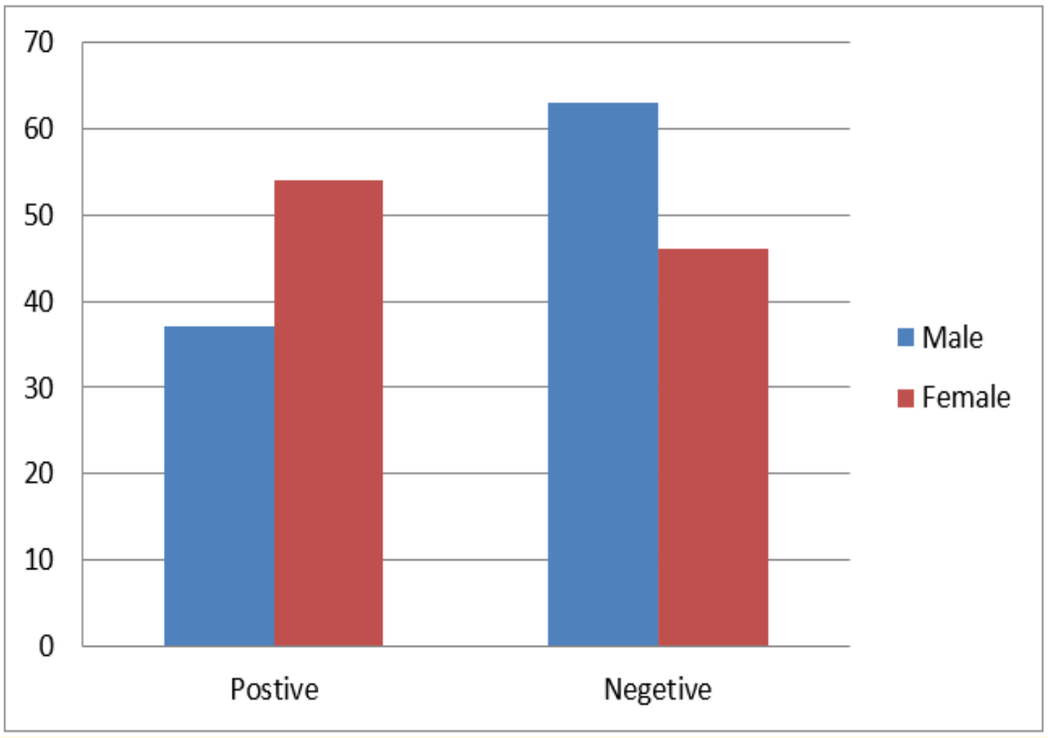

Figure 3: *HIV Co-infection among MDR cases.*

	Sex			
Age (years)	**Males'**	**Females'**	**Total**	**Percentage (%)**
1 - 25	13	31	44	16.3
26 - 35	54	43	97	36
36 - 45	36	27	63	23.3
46 - 55	30	9	39	14.4
> 55	21	6	27	10
Total (%)	154 (57.0)	116 (43.4)	270 (100)	100

Table 2: *Demography.*

	Frequency		
Sex	**MDR-TB Suspect (%)**	**MDR-TB +VE (%)**	**HIV/MDR**
Males	154 (57.0)	42 (15.6)	16 (5.9)
Females	116 (43.0)	22 (8.0)	7 (2.6)
Total (%)	270 (100%)	64 (23.7)	23 (2.3)

Table 3: *Sex related MDR-TB/HIV co infection.*

Discussion

Despite efforts to control the TB epidemic, there were an estimated 10.4 million incident cases of TB with 1.8 million mortality worldwide by 2015 and 10% estimate of this total will develop drug resistant Tb [1]. MDR-TB remains a public health crisis and a health security threat. WHO estimates that there were 600 000 new cases with resistance to rifampicin - the most effective first-line drug, of which 490 000 had MDR-TB [8]. Globally The HIV epidemic and the emergence of anti-TB drug resistance represent serious threats for achieving the Stop TB Partnership's goal of eliminating TB as a public health problem by 2050 [8].

In ATBUTH 23.7% of the presumptive Tb cases tested positive for drug resistant Tb, this is almost higher than the national average predicted for Nigeria by WHO (3.2 -5.4%) [10,11]. This prevalence appears to be among the highest MDR TB prevalence reported in an African countries thus. In countries, like South Africa, the estimated MDR TB prevalence was 1.8% (95% CI 1.5 - 2.3) in new case-patients (NCs) and 6.7% (95% CI 5.5 - 8.1) in previously treated case-patients (PTCs) in 2002 [13] where as in Mozambique, 3.5% (95% CI 2.5 - 4.7) of NCs and 11.2% (95% CI 4.2 - 30.0) of PTCs had MDR TB in 2006 [13]. In Ethiopia there has been an average of about 46.3% of MDRTB cases found [14]. This increase in prevalence may be due to improvement in case detection and diagnosis through Xpert/MTB RIF molecular assay lack of appropriated DOTS services, TB/HIV co infection, poor infection control could also be a positive contributory factor [13]. The correlation between HIV infection and anti-TB drug resistance remains controversial; there were more frequent associations reported in studies in North America than in studies in Africa [15]. Several factors have been proposed to explain such an association. Malabsorption of anti-TB drugs has been documented for HIV-positive patients, which could increase the risk for acquired rifampin resistance [15].

Certain specific phylogenetic lineage named Beijing *M. tuberculosis* genotype has been identified as a particularly prevalent strain independently associated with MDR TB and transmission, indicating a potential role of this pathogen in the epidemiology of drug resistance in some regions of the world like eastern Europe, this might also be a factor contributing to the increase in cases of MDR-TB in our environment [16].

In some Asian countries like India WHO has estimated that India has 79,000 cases of MDR-TB.

Countrywide prevalence of MDR-TB also increased from decade 1 (14.9%) to decade 2 (27.9%), with an overall prevalence of 23.3% for the study period. Prevalence of pre-XDR-TB and XDR-TB were 7.9% and 1.9%, respectively, over the study 20-year study period [1].

There were more male cases 154 (57%) screened for MDR-TB within the period under review compared to the female patients 116 (43%), this study also reconfirms the predominance of males compared to females with MDR-TB as reported in most studies [17]. This could be probably due less access to diagnostic facilities by female in some cultural settings which limits female movements, this could also reflect epidemiological difference between male and female folks in terms of exposure, susceptibility and transmission dynamics of the diseases [17,18]. The degree of male bias varies by geographic location and by year, but the overall trend is clear, and of the 20 high-burden countries for which data are available, the median male-to-female ratio is 1.8:1, with only Afghanistan reporting a ratio of < 1:1 (WHO report 2013). Smoking, alcohol and mine related silicosis which is more among males could also be a factor [19,20]. In general, testosterone is thought to down regulate the Th1 response, whereas estrogen is believed to enhance it. In reality, the effects of sex hormones on the Th1/Th2 balance are more nuanced. Low levels of 17B-estradiol, for example, promote Th1 differentiation and production of cytokines such as TNF-α, while high levels promote Th2 polarization, with a consequent effect on cytokines [21].

There were 36% of the presumptive cases between the ages of 26 to 35 yrs and 10% were ≥ 55 yrs (Table 1). This shows increase in prevalence among the most productive age bracket in the society, this is similar to studies conducted elsewhere [22,23].

This study shows that there are more cases of MDR-Tb among the retreatment Tb cases compared to the Tb treatment naïve patients, 17% vs 5% (P = 0.000). This is almost similar to the national average of 23% vs 4.3% among retreatment and new cases respectively [10,11]. A systemic review and meta-analysis done in the country also showed 32% cases among retreatment cases compared to 6% among new cases [24]. Similarly there was 47% vs 23% MDR-Tb cases among retreatment and new Tb cases in Vladimir region in Russia [25]. This trend could possibly be as a result ineffective DOT and poor quality anti Tb medications [4].

MDR-TB can primarily affect HIV-infected persons, delay diagnosis, inadequate initial treatment, and prolonged infectiousness led to extraordinary attack rates and case-fatality rates among HIV-infected persons [26]. In this study 2.3% of the study subject had MDR-TB/HIV co infection (Table 2) there were more male co infected patients (5.9%) compared to female co infected patient (2.6%) among the MDR-TB positive subject (p = 0.619). HIV infection may lead to Malabsorption of anti-TB drugs and acquired rifamycin resistance. HIV-infected patients with MDR-TB have associated high mortality; both antiretroviral and anti-mycobacterial treatment are necessary to prevent this [26]. Co-infection with HIV presents a number of additional challenges in DR TB management including shared drug toxicities between TB and HIV drugs, potential for increased drug toxicity due to underlying HIV-related organ disease such as nephropathy, pharmacokinetic drug-drug interactions and immune reconstitution inflammatory syndrome including manifestations at extra pulmonary sites [27].

Further disaggregation showed that there were more male co infected patients 16 (5.9%) compared to female co infected patient 7 (2.6%) among the MDR-TB positive subject (p = 0.619). Figure 3 the convergence of the HIV infection and MDR-TB epidemics is evident from recent WHO estimates of the MDR-TB and HIV-associated TB burden, as well as from the 2006 report by UNAIDS on the global AIDS epidemic [1].

Conclusion

MDR-TB is on the increase it is essentially an acquired condition. Its association with HIV disease is at present still on the lower side compared to studies in advanced countries. This could be in part due to poor yield in diagnosis due to pauci bacillary nature of TB/HIV co infection and low level hi-tech diagnostic methods available in developing world.

Lack of line probe assay and DST for other first line and second line drugs might have limited our diagnostic accuracy for other forms of drug resistant Tb other than using only Xpert/MTB RIF assay as a surrogate for isoniazid resistance.

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