

Prevalence of multidrug resistant tuberculosis among previously treated TB patients in Nairobi county, Kenya

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Abstract

Background: The emergence of multidrug resistant Tuberculosis (MDR TB) continues to pose a public health threat globally, and complicates patients' clinical management, especially in resource-poor settings that depend on donor funding for drug supply. The present study evaluated the prevalence of MDR TB among previously treated TB patients in Nairobi County, Kenya.

Methods: A cross-sectional study was conducted on 120 previously treated TB patients, recruited from selected healthcare facilities in Nairobi (Mbagathi, Rhodes, Dandora, Kangemi, Riruta and Kayole Clinics), between August 2014 and February 2015. TB positive cases were confirmed microscopically by Ziehl Neelsen staining of sputum samples, plus the use of Capilia™ TB-Neo Assay. Briefly, TB positive samples were cultured on slopes of Lowenstein Jensen (LJ) media, and their antimicrobial susceptibility patterns determined against four first line anti-TB drugs, including isoniazid (H), rifampicin (R), streptomycin (S) and Ethambutol (E), using the BD BACTEC™ Mycobacterium Growth Indicator Tube (MGIT) 960 system. In addition, in suspect MDR TB smear positive Mycobacterium complex isolates, drug resistance to isoniazid and rifampicin was confirmed by LPA.

Results: Drug sensitivity testing performed on a total 86 Mycobacterium tuberculosis isolates, revealed resistance of 5.8 % to any one of the four first line anti-TB drugs, 2.3% to two drugs, 5.8% to three drugs, and 4.7% to four drugs. Sensitivity to all four drugs was observed in 81.4% of isolates tested. The rate of resistance to Isoniazid was 12.5%, rifampicin 9.2%, streptomycin 6.7% and ethambutol 5.0%, while prevalence of multidrug resistance was 11.6%. Age, gender or previous treatment were not significant risk factors for development of multidrug resistance.

Conclusion: This study confirms the high prevalence of resistance to first line anti-TB drugs, and suggests the risk of emergence and spread of MDR TB across Nairobi County. These results emphasize the importance of re-establishing and restructuring robust TB prevention and control programs, as well as the need for constant surveillance for drug resistance and drug adherence.

Keywords: tuberculosis, multidrug resistance, isoniazid, rifampicin

Abbreviations: TB: Tuberculosis, MDR: multidrug:resistance, DOTS: direct observation treatment, XDR: extensively drug-resistant, INH: isoniazid, RIF: rifampicin

Background

Tuberculosis (TB), an ancient scourge, remains one of the most prevalent infectious diseases globally, and most clinically significant of the mycobacterial infections [1]. For the past few years, TB has been ranked ninth after HIV and AIDS among the leading causes of mortality in the world [2]. The increasing infection rate of TB and impacted population could be associated with its infectious nature of transmission, co-morbidities with other infections, as well as emergence of drug resistance. In most resource-poor settings, the inflated cost and technical complexity in drug susceptibility testing has precluded its use among patients with newly detected smear positive for tuberculosis [3].

MDR TB is defined as resistance to rifampicin (RIF) and isoniazid (INH). Worldwide prevalence of MDR TB among new cases and previously treated cases is estimated as 3.6% (95% CI: 2.1-5.1%) and 20.2% (95% CI: 13.3-27.2%) respectively (WHO, 2013). In Kenya, the levels of MDR-TB have been increasing since 2005 (0.04%) and 2011 (0.16%) [4]. The increasing rates of MDR TB pose a great challenge in TB control, especially in resource-

limited countries whose only choice for patient management is usually more expensive than preliminary management. Those who end up into second line treatment option, most of these cases 10-30% may result into total treatment failure and eventually death.

As much as recent data on TB, MDR TB and HIV-associated notification rates are shown to have increased, progress in filling the detection and treatment gaps are sluggish and big gaps remain, hence making this a challenge. In Kenya alone, close to 40% of all incident TB cases go unnoticed or undetected, hence reflecting a mixture of under reporting or misdiagnoses of these cases. Confounding factors in global collection of incidence and prevalence data includes; non-effective treatment, difficulties in identifying extra pulmonary disease and those associated with tuberculin testing [5].

Despite vaccination, populations vulnerable to TB infections still exist. Therefore, lack of all-inclusive national drug resistance surveillance data from all countries is a hurdle to understanding the intensity of prevalence and incidence of MDR. In addition to the existing threat of extensively drug-resistant tuberculosis (XDR

TB) and HIV co-infection, a rigorous assessment of TB drug resistance and evaluation of data specific deficiencies is urgently needed.

Levels and trends of drug resistance vary by location (WHO, 1997). Additionally, drug resistance serves as an epidemiological indicator, which allows investigators to assess the extent of resistant bacterial transmission in the community [6]. Therefore, drug resistance surveillance (DRS) is considered a useful tool to assess the drug susceptibility profile among newly diagnosed and previously treated patients, as well as to determine the effective functioning of TB control programs (WHO, 1997). Early identification of drug-resistant strains, particularly MDR strains, is crucial to permit the timely administration of appropriate drug regimens and minimize transmission of these strains. Considering the above facts, the present study was purposed to evaluate the prevalence of MDR TB and drug resistance associated mutations among treated individuals in Nairobi, Kenya.

Methods

Study Design

A descriptive cross-sectional study was carried out among consented, TB-infected individuals (n=120), previously treated with first-line anti-TB drugs, and seeking clinical care at selected TB Healthcare Centres in Nairobi, Kenya, including the Rhodes Chest Clinic, Dandora, Kangemi, Riruta, Kayole II Health Centres, and Mbagathi County Referral Hospital. Sputum samples were collected from all 120 study participants, between August 2014 and February 2015. Questionnaires were administered, with consent from study participants, to obtain basic demographics including gender and age. The ethics approval for the study was obtained from Kenyatta National Hospital and University of Nairobi prior to commencement of the study.

Inoculum was picked and cultured from collected sputum samples, and the remnants were used to make smears. Air-dried smears were stained with auramine and microscopically examined for acid-fast bacilli (AFBs). Samples for microbial culture, were first decontaminated/digested using 4% sodium hydroxide, according to modified Petroff's procedure before inoculation in liquid media (MGIT), as previously described [7].

Line Probe Assay

Bacterial DNA was extracted from decontaminated smear-positive samples using the GenoLyse® Kit (Hain Lifescience GmbH, Nehren, Germany), according to manufacturer's instructions. The DNA samples were then processed using the GenoType®MTBDRplus version 2.0 (Hain Lifescience GmbH, Nehren, Germany) for detection of MTB complex and rifampicin and/or INH resistance, according to the manufacturer's instructions.

BACTEC MGIT 960 Culture

The auramine stained smear-positive samples were cultured on slopes of Lowenstein Jensen (LJ) media, and their antimicrobial susceptibility patterns determined against first line drugs (isoniazid, rifampicin, streptomycin, and ethambutol), using the BD BACTEC™ MGIT 960 system. Briefly, colonies of confirmed Mycobacterium tuberculosis isolates were scrapped from the LJ slopes and used to make McFarland standard suspensions. Thereafter, the clean suspension and drug dilutions were placed into liquid medium and loaded into the BACTEC MGIT 960 system (Becton Dickinson, Franklin Lakes, NJ, USA) and incubated at 37 °C overnight [8].

Capilia™ TB-Neo Assay

All the positive culture isolates were subjected to Capilia™ TB-Neo Assay to confirm mycobacterium complex according to manufacturer's instructions [9]. Briefly, the Capilia™ test was performed by adding 0.1 ml of liquid culture into each sample well, and incubating test cassettes strips for 15-30 minutes at room temperature (RT). The pink band in the 'C' region confirmed the test's validity. An additional pink band in the 'T' region was interpreted as positive for the MPT64 antigen. The presence of only the pink band in the 'C' region and no band in the 'T' region was considered as negative for the MPT64 antigen. However, no band in 'C' region was interpreted as an invalid test. H37Rv was used as a positive control for each new kit [10].

Data Analysis

Statistical analysis was performed using SPSS (version 22). Demographic characteristics including age and gender were summarized as means and percentages. The Pearson Chi-Square analysis was performed to test for significance of association between age, sex, patient category and drug resistance. P-values < 0.05 were considered as statistically significant.

Results

Demographic characteristics of study participants

A total of 120 TB-infected patients who had completed treatment on first line anti-TB drugs were recruited for the study. They were selected from six health facilities within Nairobi County, and comprised 88 (73%) males and 32 (27%) females, aged between 18 and 61 years. Majority of the patients (29.2%) were between 30-35 years, the least (4.2%) were above 54 years. Initial TB screening by auramine staining confirmed that all samples (n=120) collected from study participants were positive for TB (Table 1). Gender and age had no significant effects on treatment response and TB infection (p= 0.524 and p = 0.310, respectively).

Among samples (n=120) cultured on slopes of LJ media, 86 (72%) were positive for TB, confirming that majority of study participants were still infected with Mycobacterium tuberculosis despite completing their first-line treatment. To confirm Mycobacterium complex, the TB-positive isolates were processed for ZN smear microscopy, sero-detected using Capilia™ TB-Neo Assay, and the purity check done by sub culturing on Brain Heart Infusion Media (BHI) (Table 2). However, 34 (28%) samples were contaminated and excluded from subsequent analysis (Table 2).

Prevalence of multi drug resistance tuberculosis

Antimicrobial susceptibility tests were conducted on 86 confirmed positive TB isolates cultured in LJ liquid media. Only 16 (19%) isolates were resistant to first line drugs, with 10 (11.6%) being MDR TB strains. The MDR TB strains were those resistant to at least isoniazid and rifampicin drugs. These M. tuberculosis isolates were mainly resistant to isoniazid 15 (17%), compared to 11 (13%) resistant to rifampicin, 8 (9%) to streptomycin, and 6 (7.0%) to ethambutol. However, majority (n=70;81%) of the analyzed strains were susceptible to all first-line drugs. There was no significant association between resistance patterns of MDR TB and the sampling areas (p = 0.333) (Table 3).

Pattern of Mycobacterium tuberculosis to first-line TB drugs

Sputum smear-positive samples (n=120), were tested by LPA for presence of M. tuberculosis complex, as well as resistance to isoniazid and rifampicin, as mandated for accredited diagnostic reference laboratories. Among samples tested (n=120), 104 (87%) were susceptible to all drugs, while 10 (8%) were MDR TB strains. From the ten (10) MDR TB strains that were resistant to both isoniazid and rifampicin; fifteen (15) were resistant to isoniazid (Both low- and high-level resistance to isoniazid), ten (10) were resistant to Rifampicin. In the case of mono-resistance, one isolate was resistant to rifampicin, and five to isoniazid (Table 4).

Age Group	Males (n=88)		Females (32)		TB-ve	Total No. of Cases Sampled
	TB+ve*	MDR-TB +ve	TB+ve*	MDR-TB+ve		
18-23	4	0 (0 %)	4	2 (50.0 %)	5	13
24-29	10	2 (20 %)	8	1 (12.5 %)	3	21
30-35	19	3 (15.8 %)	3	0 (0 %)	13	35
36-41	13	2 (15.4 %)	4	0 (0 %)	10	27
42-47	8	0 (0 %)	4	0 (0 %)	1	13
48-53	3	0 (0 %)	2	0 (0 %)	1	6
54-59	2	0 (0 %)	0	0	0	2
>60	2	0 (0 %)	0	0	1	3
Total	61	7	25	3	34	120
Gender		($\chi^2 = 0.074$, df=1, P=0.524)				
Age		($\chi^2 = 1.457$, df = 1, P =0.310)				

*Liquid culture using BACTEC MGIT 960 system; Abbreviations: MDR TB - Multidrug resistant tuberculosis

Table 1. Demographic Characteristics and TB Status of Study Participants (n=120).

Test	No. Tested	No. Positive	No. Negative
Zn staining	120	86 (78 %)	34 (22 %)
BHI	120	34 (22 %)	86 (78 %)
Capilia	120	86 (78 %)	34 (22 %)

Abbreviations: BHI- Brain heart infusion agar, Zn-Zielh-Neelsen

Table 2. Confirmation of *Mycobacterium tuberculosis* complex.

Resistance	No. of Resistant MTB Isolates	Drugs Patterns	Healthcare Centre
All drugs	4 (4.2 %)	S+I+R+E	Dandora Mbagathi Rhodes Kangemi
One drug	5 (5.2 %)	S I	Kangemi Rhodes, Riruta
Two drugs	2 (2.1 %)	R+I	Rhodes
Three drugs	5 (5.2 %)	I+R+E	Dandora
			Kayole
		S+I+R	Kayole
			Rhodes
Susceptibly to all drugs	70 (72.9 %)		All
Resistant strains	16 (16.7%)		p = 0.333

Abbreviations: No-Number, E-ethambutol, R-rifampicin, I-isoniazid, S-streptomycin

Table 3. Resistance Patterns to Four First Line Anti-TB Drugs (DST).

rpoB	katG inhA	Number of MTBC strains
S	S S	104 (86.6 %)
R	R R	5 (4.2 %)
R	R S	3 (2.5 %)
R	S R	2 (1.7 %)
S	R R	1 (0.8 %)
S	R S	2 (1.7 %)
S	S R	2 (1.7 %)
R	S S	1 (0.8 %)

Abbreviations: rpoB - Genes associated with rifampicin resistant, inhA and katG - Genes associated with resistance to isoniazid, S-Sensitive, R-Resistant

Table 4. Line Probe Assay of Smear-Positive Samples (n=120).

Discussion

MDR TB refers to Mycobacterium tuberculosis infection that fails to respond to treatment by both rifampicin and isoniazid drugs. The burden of MDR TB has become increasingly alarming, especially in poor resource settings that depend on donor funding for supply of these drugs. This challenge is aggravated by the inadequate availability of prompt diagnostic and treatment options.

In countries with effective TB control programmes, the proportion of previously treated patients infected drug resistant TB should be low [11]. However, in the present study the overall proportion of MDR-TB prevalence was 11.6%. This level of resistance confirms treatment failure that poses grave public health concern in the region. These findings are comparable with previous studies that have been conducted here in Kenya [12], as well as Ethiopia [13,14], and China [15]. However, these findings were found to be higher than those previously reported in the country, including 9.4% prevalence reported by the WHO in 2016. This shows an increasing trend of resistance that could be associated with interrupted or suboptimal treatment, including political instability during the study period. Previous studies have indicated that development of MDR TB is associated with history of TB treatment [15]. In addition, emergence of new cases of MDR TB is frequently associated with close contact to known cases, facilitated by overcrowding [16] (Biadglegne et al., 2014), leading to TB infection and transfer. Likewise, in this study, all participants resided in informal settlements that are often overcrowded, with poorly ventilated housing, conditions that facilitate spread of TB infection.

In this study, genotyping by GenoType®MTBDRplus version 2.0 assay was performed simultaneously to detect M. tuberculosis and common mutations in rpoB and katG genes that are associated with resistance rifampicin and isoniazid (Table 4). As reported widely elsewhere, rifampicin resistance is highly associated with mutations in the 81 base pair regions of the rpoB gene [17]. In addition, occurrence of gene mutation associated with low-level drug resistance induced by the mutations in the promoter region of inhA gene with or without concurrent katG mutation occurred in 5%. This varied across strains with mono occurrence being high (7.6%). Several reports have examined relative elevated levels of katG and inhA promoter mutations in INH-resistant isolates. For instance, in Ethiopia 0.8% inhA (without katG) mutation have been reported, (4%) in Poland and (9.6%) China [18].

Reports on high levels and provision of specific gene mutations associated with rifampicin and isoniazid resistance, can allow clinicians to adjust a patient's treatment regimen and maximize its effectiveness. Isoniazid is a highly potent drug against Mycobacterium tuberculosis. Studies have confirmed that various mutations could cause diverse levels of resistance to isoniazid that could pose a challenge to clinical management of patients infected with MDR TB or XDR TB strains. However, other studies have indicated that patients could be managed with higher doses of isoniazid in cases where the bacterial strains could have exhibited low-level resistance due to low or suboptimal isoniazid treatment for MDR TB or XDR TB [18].

The major limitation of the present study is the small sample size, since it is not representative of the population at large. In fact, this limitation was also observed many previous studies on MDR TB. The countrywide surveillance data on the prevalence of MDR-TB is crucial to enable effective empirical regimens, to monitor functioning and progress of the national TB control programme. In conclusion, the increasing prevalence of MDR TB among previously treated pulmonary TB patients is worrisome, and emphasizes the need for constant surveillance for TB drug resistance [19-37].

Conclusion

We report that only 16 (19%) strains were resistant to first line drugs, with 10 (11.6%) being MDR TB. This confirms that MDR TB remains a major public health problem, especially in sub-Saharan Africa where HIV is endemic. This finding depicts that the prevalence of MDR TB is increasing over time, posing a threat to implementation of TB control programmes in Nairobi County and the rest of the country. There is need for continuous improvement in diagnostic approaches, access to healthcare, and supervision of drug adherence, as well as constant surveillance for TB drug resistance.

Declarations

Ethics approval and consent to participate. This study approved by Kenyatta National Hospital/University of Nairobi scientific ethical committee and consent to participate in the study by the participants.

Availability of data and material

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

JKK collected the samples and did laboratory analysis and drafting of the manuscript. AKN designed and guided the study, coordinated all research activities and reviewing of the manuscript. JM co-supervised the research and reviewed the manuscript. COO was involved in interpretation of mutations and drafting of the manuscript. All the listed authors took part in reading, revising and approving of the manuscript.

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