East African Medical Journal Vol. 94 No 10 October 2017
DRUG RESISTANT TUBERCULOSIS IN KENYA: TRENDS, CHARACTERISTICS AND TREATMENT OUTCOMES, 2008 – 2016
Jacqueline.C Louis,RCO, HnD, Narok County Referral Hospital, Narok County, Kenya. Eunice Omesa,MBChB,MSc (Epi) National Tuberculosis and Lung Diseases, Nairobi, Kenya. Murima Ng'ang'a,BCHD,BSc, MSc, Ministry of Health, Neglected Tropical Diseases Unit, Nairobi, Kenya. Omanwa Kireki, MD,Ph.D Department of Obstetrics and Gynaecology, University of Nairobi, Kenya. Maureen Kamene,MB ChB, Dip Epidem, MPH, Department of Obstetrics and Gynaecology, University of Nairobi, Kenya. Enos Masini, MBChB, National Tuberculosis and Lung Diseases, Nairobi, Kenya. Francis Kiio, MBChB, MPH (Epi), Narok County Referral Hospital, Narok County, Kenya. Norah Maore, B.Pharm., M.Pharm, Ministry of Health, Embakasi East Sub – County, Nairobi County, Kenya. Japhet Chelimo, RCO, HnD, Narok County Referral Hospital, Narok County, Kenya. Omondi Ogutu,MBChB, Mmed, Department of Obstetrics and Gynaecology, University of Nairobi, Kenya. Nicholas Kirui,MBChB, MMed, Department of Medicine, Moi Teaching and Referral Hospital, Eldoret, Kenya. Jacqueline C. Louis, P.O Box 11-2500 Narok

DRUG RESISTANT TUBERCULOSIS IN KENYA: TRENDS, CHARACTERISTICS AND TREATMENT OUTCOMES, 2008 – 2016

JACQUELINE C LOUIS, EUNICE OMESA, MURIMA NG'ANG'A, OMANWA KIREKI, MAUREEN KAMENE, ENOS MASINI, FRANCIS KII, NORAH MAORE, JAPHET CHELIMO, OMONDI OGUTU and NICHOLAS KIRUI.

ABSTRACT

Background: **Drug resistant (DR) tuberculosis (TB) remains a major public health concern. Failure to treat patients with TB adequately increases the risk of transmission of infection to the general population. Treatment of DR TB is characterized by lengthy treatment duration, use of toxic and less effective drugs and high likelihood of adverse treatment outcomes that include adverse drug reactions, high mortality and loss to follow up.**

Objective: **To determine the trends, characteristics and treatment outcomes of patients >15 years notified with DR-TB in Kenya from 2008 to 2016**

Design: **Retrospective descriptive cross-sectional study**

Setting: **Tuberculosis treatment centers in Kenya**

Subjects: **Persons above 15 years notified with DR TB**

Results: **We reviewed records of 1903 DR-TB patients who were notified between 2008 and 2016. The public sector made the highest contribution of the notified cases (80%). Most of the cases were male (62.3%). The HIV testing rate was 99.5%, with the TB/HIV co-infection being 36%. Initiation of antiretroviral therapy among those who tested positive for HIV was 94.6%. Co-trimoxazole preventive therapy uptake was 99.3%. Most patients had secondary DRTB (77.3%). Multi-drug resistant TB accounted for 78.4% of the DR TB cases while mono drug resistance was observed in 26% of the cases. Treatment success was achieved in 79% of the cases. Mortality and treatment failure during the study period was 11% and 0.2% respectively.**

Conclusion: **An upward trend in notified DR-TB cases was observed during the period under review. The public sector gave the most contribution. Active surveillance on patients lost to follow up while on treatment and poor drug adherence will be of importance to reduce the potential of development of drug resistance.**

INTRODUCTION

Drug resistant (DR) tuberculosis (TB) is a form of TB whose strains are resistant to the most effective first-line anti-TB drugs(1). Treatment of DR-TB requires second-line drugs (fluroquinolones, aminoglycosides, and others), which are generally less effective, more toxic and much more expensive than first-line drugs (2).

If these second-line drugs are not prescribed well or are taken incorrectly, further resistance can develop leading to extensively drug resistance (XDR) TB. In 2015, the World Health organization (WHO) estimated that, globally, DR-TB caused an estimated 480,000 new TB cases and 250,000 deaths. Multidrug-resistant (MDR) TB accounts for 3.3% of all new TB cases worldwide. Drug resistance surveillance data shows that 3.9% of newly and 21% of previously treated TB cases were estimated to have had rifampicin or multidrug resistance. Thirty percent (132,000) of TB patients notified globally were tested for drug resistance TB, up from 22 % (122000) in 2014(3). Drug resistance surveillance data show that 3.9% of new and 21% of previously treated TB cases were estimated to have had rifampicin or multidrug-resistant tuberculosis (MDR/RR-TB) in 2015. In 2014, MDR-TB accounted for 3.3% of new TB cases (4).

Approximately 9.0% (7000) of the half a million DR-TB cases diagnosed globally have XDR TB which is characterized by additional resistance to fluoroquinolones and at least one injectable anti-TB drug (3). Previous studies from sub-Saharan Africa (SSA) indicated that the proportion of DR TB was lower than that of Asian countries and that of Eastern Europe (5). According to WHO report in 2015 the estimated DR-TB rate was 4.3/100000 whereas the TB/HIV incidence was 233/100000 population(6). Twenty three countries in Africa and Asia have introduced shorter regimens to treat DR-TB. These shorter regimens have been evident to give higher treatment success rate of about 80 to 90 percent. Standardized shorter DR-TB regimens is not recommended for XDR TB (4).

Kenya was previously among the 22 high TB burden countries, it is currently listed in the new WHO 2016-2020 reclassification with 13 other countries facing high drug susceptible TB, Multi Drug resistance (MDR) TB and TB/HIV burdens.

In 2015, 81518 people were notified with TB out of whom 8.5% were children under 14 years. WHO also estimates that there are 2,750 (children and adults) cases of DR-TB in Kenya (7).

Somalia has the highest levels of DR-TB in Africa and the Middle East region with 5.2% and 40.8% of patients with new and previously treated TB(8). Diagnostic capacity exists in Somalia with no treatment capacity therefore patients diagnosed with DR TB cross the border to Kenya seeking treatment. In 2013, Daadab in Kenya reported a large increase in cases with DR-TB.

In July and August of 2013, DR- TB drugs ran out of stock in Dadaab Somalia and no new patients were started on treatment. Patients migrated from Somalia to Kenya seeking treatment with the results of a GeneXpert test in hand showing rifampin-resistant tuberculosis (3).

This indicates that resistant strains of TB are present in the population with new transmissions of DR-TB to previously uninfected persons leading to primary DR-TB (9). Acquired MDR-TB develops when a person with a non-resistant strain of TB is treated inadequately, resulting in the development of antibiotic resistance in the TB bacteria infecting them. These people can in turn infect other people with DR-TB directly.

Programmatic Management of Drug-Resistant TB (PMDT) in Kenya was initiated in 2007. In 2013, 254 cases of multi-drug resistant TB (MDR-TB) were identified and started on treatment compared to 60 in 2007.

Twenty eight percent of notified MDR-TB cases occurred among refugees residing in Kenya (7). Drug resistant tuberculosis monitoring in Kenya is a passive surveillance system that targets high risk groups that include: 1) all previously

treated TB patients – treatment failures, relapses, patients lost to follow up; 2) DR TB contacts who present with signs and symptoms of TB, 3) health care workers with TB symptoms, 4) patients who develop TB symptoms while on Isoniazid prophylaxis treatment, 5) refugees with TB symptoms, 6) smear positive patients at 2 months of treatment, and 7) prisoners with TB.

The current study aimed at documenting the trends, characteristics and treatment outcomes in DR TB cases notified in Kenya between 2008 and 2016.

MATERIALS AND METHODS

Study Design: This study involved a retrospective analysis of secondary data of patients above 15 years diagnosed with DR-TB in Kenya between 2008 and 2016.

Study Setting:

General setting: Kenya is a sub-Saharan lower middle-income country that borders Somalia to the East and North East. Somalia has a high DR-TB burden. It has an approximate population of 44.4 million, 30% of whom reside in the urban areas (10). Kenya has 278 Basic Management TB Zones, 3320 diagnostic sites and 1920 treatment units. There is a central national TB reference laboratory that does conventional drug susceptibility test (DST) as well as molecular DST with Lipo-Protein Assay (LPA) for 1st and 2nd Line drugs. There are 146 Gene Xpert machines (detects only rifampicin resistance) distributed in the country with a robust sample referral and networking for reference sites (11).

Study population: The study population comprised of all patients >= 15 years diagnosed with DR-TB and notified in Kenya from January 2008 to December 2016.It was done on retrospective data of patients initiated on DRTB in all the 290 TB control zones distributed within the 47 counties in Kenya.

Data collection: Tuberculosis Program utilizes TIBU data management as central database of the NTLD-P which is a web based solution integrated with mobile/tablet technology developed and introduced in Kenya in the year 2012 with inter-sectorial support. Patients with drug resistant TB upon diagnosis, are notified, treated and followed up with primary record capture obtained from patient records and MDR log book entered into registers as a summary of the data entered in the registers. This data is subsequently uploaded at Sub–County level into TIBU by sub-county TB coordinators electronically via mobile computer tablet. The data set for DR- TB was then exported from the TIBU database onto Microsoft Excel 2008 (Microsoft corporation, Seattle .USA) for cleaning, validation and analysis.

Data Analysis: Descriptive analysis was undertaken with mean (standard deviation) being reported for normally distributed data while median (interquartile range) is reported for non-normally distributed data. For categorical variables, proportions and accompanying absolute numbers were reported. We reported annual trends of the notification rates of DR-TB over time for the period 2008 -2016. However, we restricted the analysis on the outcomes of DR –TB cases notified to the period 2008-2014 since cases notified after this period have not completed the 2 year follow-up required for DR-TB cases. Analysis was done using Stata version 14.

Variables and data source: The study variables included demographic data (age, sex, sector) and year of diagnosis. Clinical variables included treatment outcomes, HIV status and type of DR-TB. We subsequently conducted a descriptive analysis. Categorical variables were summarized by frequencies and proportions while continuous variables were summarized using means and SD.

Ethical approvals: This study was approved by the Moi University College of Health Sciences (MU/CHS) and Moi Teaching & Referral Hospital (MT&RH) Institutional Review Board (IREC).

RESULTS

The total number of DR-TB cases among persons above 15 years notified between 2008 and 2016 was 1903, with males accounting for 63% of these cases. The mean age for the cases was 35 (SD 12) years with the majority of cases being in the age group of 25 to 50 years. Patients who were malnourished (BMI<18.5) at the time of diagnosis were 54%. Of the 1893 cases, 99.5% tested for HIV with, 36% being HIV positive, 10 patients declined testing. Majority of the TB/HIV co-infected cases were started on anti-retroviral therapy (99.5%) and co-trimoxazole preventive therapy (96%). Secondary DR-TB cases (retreatment cases) accounted for 77.3% of all cases while primary DR TB cases (new cases) accounted for 24.7% of the cases. Transfer in constituted 1.3% of the cases. Health facilities in the public sector contributed 80% of the notified cases. Analysis of the resistance pattern showed that MDR TB accounted for 63% of all the notified cases. Prevalence of mono drug resistance was 26%. The proportion of cases that were diagnosed with Poly Drug Resistance (PDR) was 4%. Rifampicin resistance was reported in 5.6% of the cases while Extensively Drug Resistance (XDR) TB was noted in 0.4% of the cases as shown in Table 1.

Table1.

Demographic and clinical characteristics of the notified DR TB cases in Kenya, 2008-2016

Characteristic	Number	%
Age (years) (n=1903)		
15-19	128	6.7
20-24	242	12.7
25-29	302	15.6
30-34	366	20.0
35-39	270	14.0
40-50	367	19.0
>50	228	12.0
Sex (n=1903)		
Female	707	37.2
Male	1196	62.8
BMI group (n=1903)		
<15	271	14.2
15-18.4	765	40.2
18.5-24	604	31.7
>25	56	3.0
*Not Recorded	207	10.9

HIV Test (n=1903)		
Done	1893	99.5
Not Done/Declined	10	0.5
HIV test result (n=1893)		
Positive	683	36.1
Negative	1210	63.9
Cotrimoxazole uptake (n=683)		
Yes	678	99.3
No	5	0.7
Antiretroviral uptake (n=683)		
Yes	652	94.6
No	31	5.4
Registration Group		
LTFU/RAD/RETREAT/O/R/FRT/FFT (Secondary drug resistance)	1408	77.3
New(primary drug resistance)	470	24.7
TRANSFER IN	25	1.3
Sector (n=1903)		
Prisons	18	0.9
Private	363	19.1
Public	1522	80.0
Type of TB (n=1903)		
Pulmonary	1869	98.2
Extra-pulmonary	34	1.8
Resistance pattern		
Multidrug resistance	1206	63.4
Mono-drug resistance	497	26.1
Rifampicin-resistant TB	106	5.6
Poly drug resistance	84	4.4
Pre-Extensive drug resistance	1	0.1
Extensively drug resistance	7	0.4

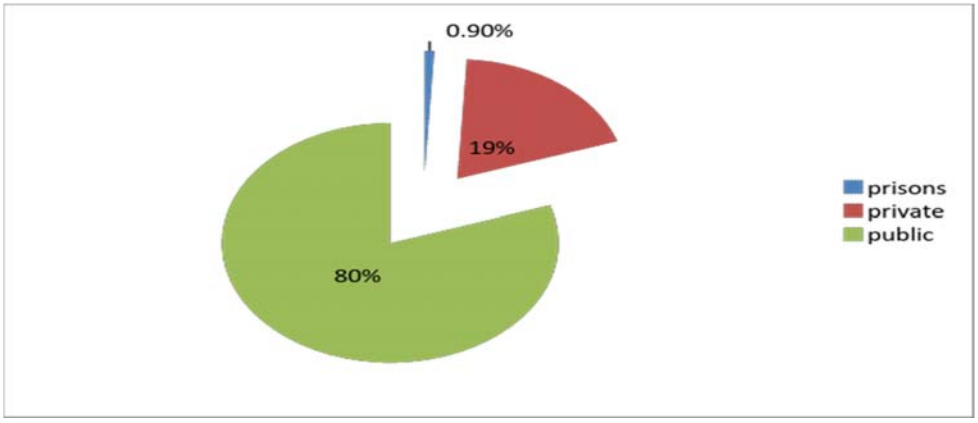
**LTFU – loss to follow-up/ RAD – return after default/ R – retreatment/ O – out of control/ FRT – failure retreatment/ FFT – failure first line treatment.*

****BMI – Not recoded: Patients whose BMIs were not recorded by the healthcare workers***

Health facilities in the public sector contributed the highest number of DR-TB cases (80%), while those in the private sector contributed 19.1% and prison facilities contributed 0.9% of the case as shown in Figure 1 below.

Figure 1:

Drug resistant TB cases per sector in patients above 15 years of age

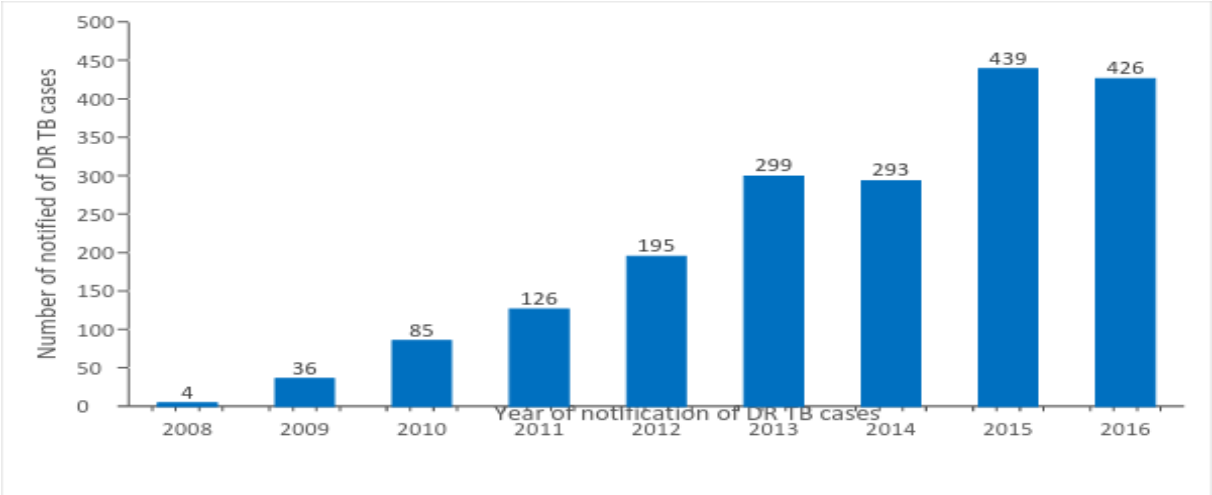


DR-TB cases notified over the period increased from 4 in 2008 to 439 in 2015.

The highest number of DR-TB cases was notified in 2015 as shown in Figure 2.

Figure 2:

Trends of notified Drug Resistant Tuberculosis Cases (>15yrs) in Kenya, 2008-2016



The number of DR-TB cases whose treatment outcomes were documented was 1037(54.49%). Fifty six cases notified in 2015 and 2016 were still on treatment. A treatment success rate of 79% was observed with mortality rate of 11%, loss to follow up at 6%, those who never completed treatment were 1% and treatment failure was 0.2% for the period between 2008 and 2014.. Globally in 2013, the treatment outcomes were a treatment success rate of 52%, 17% of the patients died and 9% of the patients had treatment failure. Approximately 22% were lost to follow-up or were not evaluated (4).

Table 3:

**Treatment Outcomes for Drug Resistant TB patients (<15years) 2008- 2014.*

	All patient N=1037	**(%)**
Cured	567	54
Died	122	11
Failure	3	0.2
Loss to follow/ OOC	67	6
Not completed	13	1
Treatment completed	254	24
Transfer out	11	1
***Treatment Success Rate**	**821**	**79**

**Treatment Success Rate=Cured +Treatment Completed*

**OOC-Out of control*

**for the period 2015-2016, the 866 patients are still on their treatment and therefore the outcome is yet to be evaluated*

DISCUSSION

This study demonstrated a gradual increase in the number of patients notified with DR TB between 2008(4 cases) and 2016(426), with the highest number of notified cases being in 2015(439). The probable reasons for the observed increase include: 1) decentralization of TB control measures to community health care workers, hence greater social awareness of TB, 2) increased training and sensitization of health care workers, 3) introduction and accessibility of superior testing tools like gene expert machines to the rural areas and 4) support to the already affected patients (12). In addition, there was cross border immigration of patients from Somalia who had already been diagnosed with DRTB with no medication (3). A previous study by Weiss et al. found no association between age and successful treatment outcomes, in line with our findings (13).

Most of the DR TB patients were HIV negative. This indicates that though HIV is a major risk factor for drug sensitive TB, there are other risk factors that predispose to DR-TB (14). This is further supported by the fact that most patient with DR-TB had been previously treated for drug sensitive TB and had been on re-treatment regimens. Poor drug adherence with patients having to be put on re-treatment regimens is a major risk factor for DR-TB.

This has also been demonstrated in a study by Sindani et al in Somalia that showed history of previous anti-TB treatment was the strongest independent risk factor for MDR TB (odds ratio [OR] 23.0, 95% CI 9.4–56.1, p<0.001),(8). In the same study, most patients who had DR-TB were male who have poor health seeking behaviour, social life and nomadic ways of life leading to poor drug adherence. All these factors contribute to the increased cases of DR TB.

Approximately 78% of all DR TB patients had favourable treatment outcomes. This is slightly higher than the WHO recommended accepted rates of 75%(7). Some of the factors that contribute to poor treatment outcomes include: 1) long duration of treatment, 2) drug related toxicities, 3) border immigrations, 4) associated co-morbidities (diabetes, renal failures, HIV) and 4) patient ignorance. In addition, most patients were malnourished and therefore at risk of poor treatment outcomes. The poor treatment outcomes included DR-TB treatment failure with the development of XDR TB which is more difficult, more costly and more challenging to manage. XDR TB is a big potential long term problem to the healthy Kenyan population and the NLTLD program.

The study had a number of limitations. Firstly, use of routine program data did not include a comprehensive assessment of other patient risk factors e.g. comorbidities, smoking, alcohol, substance abuse and pregnancy. Secondly, the data collecting tool could not pick out socio-economic characteristics of the patient which have an impact on the risk factors and DR TB treatment outcomes. Despite these limitations, this study had several strengths.

DISCUSSION

First, the study utilized national drug resistance data thus accurate data. Secondly, the study had an adequate sample size and data capture was done by trained personnel with data validation being done every three months, to clean the Data and make it more accurate.

CONCLUSION

This study highlighted the substantial burden of DR-TB in Kenya with an upward trend in notified DR-TB cases being observed during the period under review. Health facilities in the public sector had the highest number of DR-TB cases with the pulmonary type of DR-TB being the most common type of TB. There is need for enhanced infection prevention practices in the public health facilities. Health facilities in the private sector need to be capacitated to handle DR-TB cases. There is no systemic information capturing adverse Drug reactions for patients on treatment and other co-morbidities and thus, active surveillance of patients lost to follow up while on treatment and poor drug adherence will be of importance to reduce the potential of development of drug resistance.

Conflict of Interest: None

FUNDING/ ACKNOWLEDGEMENT STATEMENT

This research was conducted through the Structured Operational Research and Training Initiative (SORT IT), a global partnership led by UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) based at the World Health Organization The model is based on a course developed jointly by the International Union Against Tuberculosis and Lung Disease (The Union) and Médecins sans Frontières (MSFOCB). The specific SORT IT programme which resulted in this publication was led by the Department of Obstetrics and Gynaecology, University of Nairobi and the National Tuberculosis, Leprosy and Lung Disease Program's (NTLD-P).

REFERENCES

1. http://blogs.worldbank.org/opendata/new-country-classifications. New country clasification. Indian J Tuberc [Internet]. 2010;57(4):180–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21141336(Accessed 19th June, 2017)
2. Africa S. Multi-drug-resistant tuberculosis. 2015. p. 1–11.
3. Cain KP, Marano N, Kamene M, Sitienei J, Mukherjee S, Galev Aleksandar; Burton, John; Nasibov, Orkhan; Kioko, Jackson; De Cock, Kevin M.(2015)The Movement of Multidrug-Resistant Tuberculosis across Borders in East Africa Needs a Regional and Global Solution. PLoS Med. 2015;12(2):1
4. WHO. Mdr-Tb. Burden, Glob Treat Enroll O N Mdr-tb Outcomes, Treat. (2016);2015–6.
5. The WHO/IUATLD (1997). Global Project on Anti tuberculosis Drug Resistance Surveillance. Anti-Tuberculosis drug resistance in the world [Internet]. Available from:http://apps.who.int/iris/bitstream/10665/43889/1/WHO_HTM_TB_2008.394_eng.pdf?ua=1&ua=1(Accessed 20th June, 2017)
6. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis. Geneva, Switz. 2016;
7. On Charter, Rights the Republic of Kenya. 2007.
8. Sindani I, Fitzpatrick C, Falzon D, Suleiman B, Arube P, AdamIsmail Baghdadi, SamihaBassili, Amal Zignol, Matteo (2013). Multidrug-Resistant. 19(3):1–3.
9. Nathanson E, Nunn P, Uplekar M, Floyd K, Jaramillo E, Lonnroth KnutWeil, DianaRaviglione, Mario (2010) M 1050. N Engl J Med. 2010;1050–8
10. Kenya National Bureau of Statistics. Kenya economic survey [Internet]. Vol. 1, Kenya National Bureau of Statistics. 2015. p. 1689–99. Available from: www.knbs.or.ke/index.php?...economic..%5Cn
11. MOH. Programmatic Management of Drug Resistant Tuberculosis (PMDT) - Kenya. 2014;(Third Edition). Available from: http://apps.who.int/medicinedocs/documents/s21976en/s21976en.pdf
12. Omale N. 3 rd End TB Strategy Meeting
13. 13.Mibei DJ, Kiarie JW, Wairia A, Kamene M, Okumu ME. Treatment outcomes of drug-resistant tuberculosis patients in Kenya. 2016;20(November 2015):1477–82.
14. WHO, Geneva 2016. Global Tuberculosis Report 2016 [Internet]. Available from: http://www.who.int/tb/publications/global_report/en/