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TREATMENT OUTCOMES FOR DRUG RESISTANT TUBERCULOSIS AMONG CHILDREN BELOW 15 YEARS IN KENYA, 2010-2016

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ABSTRACT

***Background*: Tuberculosis is a common cause of morbidity and mortality in children. Children are less likely to acquire resistance during the treatment of tuberculosis (TB). Most of the drug resistant TB infection in children is transmitted from adults.**
***Objective:* To determine the characteristics and treatment outcomes among children below 15 years managed for drug resistant TB in Kenya, 2010 – 2016.**
***Design:* Retrospective descriptive study.**
***Setting:* All health facilities managing drug resistant TB in Kenya**
***Subjects:* Children below 15 years treated for drug resistant TB between 2010 and 2016.**
***Results:* Sixty three children were notified with DR TB between 2010 and 2016. The median (IQR) age was11 (10-13) years with a female to male ratio of 1:1. With 32 (52%) and 31 (51%) with smear and culture positive laboratory results respectively. Primary drug resistance was present in 25 (40%) of the children All the sputum and culture converted negative at month three of treatment. HIV testing uptake was 100% with a positivity rate of 26 (41%) and 100% anti-retroviral therapy uptake. The treatment success rate for the cases was 31(91%) with a mortality rate of 2(5%) and lost-to-follow up 1 (3%).**
***Conclusion:* Drug-resistant tuberculosis can be successfully treated and therapy well tolerated among children. There is need for contact tracing and screening for all at risk including paediatric population.**

INTRODUCTION

Drug Resistant tuberculosis (DR TB) is a form of tuberculosis (TB) whose strains are resistant to the most effective first-line anti TB drugs. It is a global health concern that has backtracked recent successes in TB control (1). For children to develop DRTB, they must be exposed to an infectious DR-TB index case, thus a pointer towards ongoing transmission within the community (2). Globally, among adults, an estimated 480,000 new cases of multidrug-resistant TB (MDR-TB) and 100,000 rifampicin-resistant TB (RR-TB) are documented annually,

with children accounting for approximately 12-20% of the adult numbers (3). In Kenya, of the 248 MDR TB cases identified in 2013, 3% were children (4). The paucity of data on the burden of DR TB in children is a product of diagnostic challenges that include difficulty in sputum collection, paucibacillary tendency, lack of culture confirmation and making drug susceptibility testing (DST) not possible (5-7).Treatment of DR-TB in children is complex, toxic, and costly, less effective and with poor treatment outcomes compared to drug sensitive TB (8-9). In addition, where children are HIV co-infected this further complicates treatment due to drug adverse events, poor adherence, other opportunistic infections and increased risk of recurrent TB (8-9). Few studies and case series have examined outcomes for children treated for MDR-TB, and suggest that, when appropriate treatment is given within dividualized regimens and supportive supervision, treatment outcomes tend to be favorable (10-14). A better understanding of challenges associated with diagnosis and treatment of DR-TB in children, will provide useful information for better case management. We therefore set out to determine the characteristics and treatment outcomes among children below 15 years managed for drug resistant TB in Kenya, 2010 – 2016.

MATERIALS AND METHODS

Study design: This was a retrospective descriptive study using routine collected country wide data from all Health facilities in all the 47 counties in Kenya. The data was generated from the patient's records card to facility registers then to the electronic data base -Tuberculosis Information from Basic Unit (TIBU).

Setting: The study was done in Kenya which is located in the East Africa region. It has 47 semi autonomous counties, with an estimated population of 48 million with children accounting for the half of the population (15).An estimated 1.5 million infected adults live with HIV/AIDS, 950,000 of these enrolled on care (16). There are 2 refugees camp (Kakuma and Dadaab), where most of the DR TB patients are on treatment due to overcrowding and poor TB management in the war zone countries (Somalia and South Sudan).Kenya has both private and public health facilities. Public health facilities are categorized into different level, level I- community units, level II -dispensary, level III- health centres, level IV -sub county hospital, level- V county referral hospital and level VI-teaching and national referral hospital. TB services are provided by level II facilities and above.

Drug Resistant TB surveillance in Kenya: Diagnosis of DR TB in Kenya is based on a systematic algorithm that identifies patients at high risk of developing DRTB compared to the general population who present with signs or symptoms of TB. They include all previously treated TB patients, DR TB contacts, health care workers, patients who develop TB while on isonazid preventive therapy(IPT), refugees, prisoners and smear positives at month two of treatment with first line drugs. Clinical specimens are obtained and sent to the National Tuberculosis Reference Laboratory (NTRL) to determine the susceptibility of the strains to first line agents: isoniazid, rifampicin, pyrazinamide, ethambutol and second-line agents: kanamycin, capreomycin, amikacin, levofloxacin and moxifloxacin. Children who present with signs and symptoms, especially those from whom samples cannot be obtained, DR TB is suspected and a diagnosis is made based on a history of DR TB contact. Therapy for DR TB is standardized based on the resistant pattern. For children, treatment is administered based on the index case's regimen until drug susceptibility tests (DST) results are available, then they are adjusted.

Informed consent is obtained from the patient or guardian, in the case of a child below 18 years prior to initiation to treatment. The children who have DR-TB are managed with the 2nd line drugs. There is a community and facility based model of treatment. In the community based model, the health care worker observes the patient taking drugs at home while in the facility based model the patients takes the drugs in the facility.

Study population: The study population was children below 15 years who were treated for DR-TB and notified on the electronic data base to the National Tuberculosis Program between January 2010 and December 2016.Population size Sixty-three children who developed DR-TB between January 2010 and December 2016.

Sample size: All the 63 children who developed DR-TB in Kenya between 2010 and 2016 in all health facilities in Kenya. All the health facilities were used in this study since DR-TB in Kenya is rare.

Data Collection: Data was extracted from TIBU. TIBU is a real-time electronic database that ensures that case notification of TB patients and data collection is a continuous and ongoing process.

Once a patient is diagnosed with DR-TB they are registered and given a unique identifier in the facility register by the clinician. This information includes: personal information, socio-demographic information and clinical information. Once the registers are filled the information is transferred into the electronic register (TIBU) by the sub-county coordinator who visits the facility at least twice a month and immediately transmitted to the server and the national level's 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-sector support. Patients with 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 tablets TIBU has internal consistency checks to ensure that data entry errors are minimized. The TB program has quarterly data quality audits at the county level and biannually at the national level.

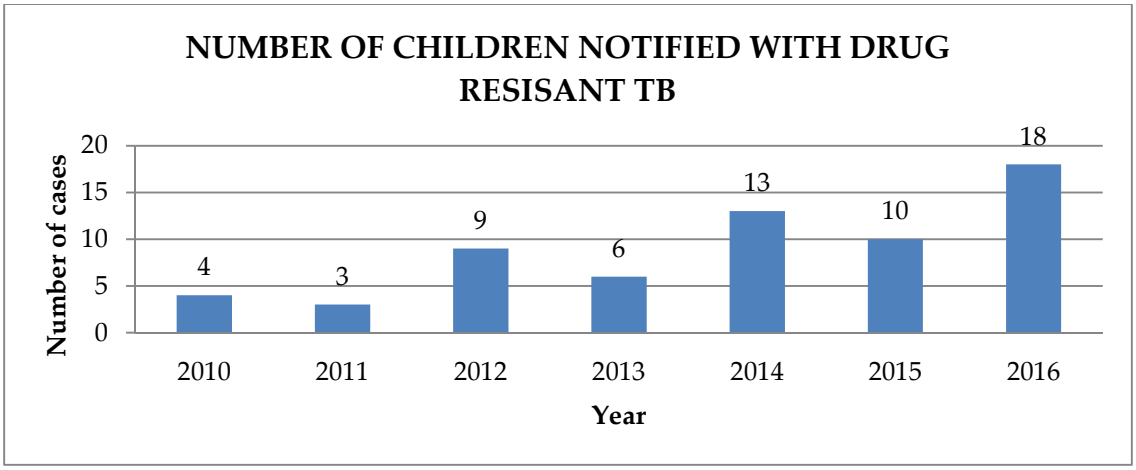
Data analysis: Data was extracted from the TIBU database, cleaned and exported to Stata v11 for analysis. Descriptive analysis undertaken. For continuous variables mean (SD) and median (IQR) were reported for normally distributed and non-normally distributed data respectively. Proportions were reported for categorical variables.

Ethical approval: 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 notified between 2010 and 2016 were 1803 with children below 15 years accounting for 63 (3.4%). The number of DR TB cases has been on an increase (as shown in figure 1.

Figure 1.
Number of the children notified with drug resistant tuberculosis in Kenya, 2010-2016



The results showed that the diagnosis and management of children with DR-TB has been on an increase but most of the children managed for DR-TB in Kenya were more than 10 years (as shown in table 1).

Table 1
Age of the participants by gender and year of children below 15years managed for drug resistant tuberculosis in Kenya, 2010-2016

Male	Year	Female
7	2010	2,11,12
10,11	2011	11
3, 8, 9, 11,11	2012	9, 9, 10, 6
	2013	14, 13, 13, 12,10, 10
9, 13, 13, 13, 13, 14, 14, 14	2014	14, 14, 13, 12,12
3, 11, 12, 14	2015	14, 14, 14, 13, 7, 7
3, 4, 5, 8, 10,10, 11, 11, 12, 12, 12, 13	2016	14, 12, 12, 8, 7, 6

Of the 63 cases of DR TB in children, 32 (51%) were male while the mean age of children notified was 9.4 (SD 3.2), median age of 11 (IQR 10-13, with 44 (70%) being aged 10-14years (as shown in table 2).

Table 2

Demographics characteristics of children below 15 years managed for drug resistant TB in Kenya, 2010 – 2016

Variable	All patient N=63 n (%)
Age group	
0-4	4 (6)
5-9	15 (24)
10-14	44 (70)
Gender	
Female	31 (49)
Male	32 (51)
Model of care	
Community based	30 (47)
Facility based	32 (51)
Isolation	1 (2)
Sputum at diagnosis smears	
Positive	33 (52)
Negative	11 (17)
Not done	10 (16)
Not documented	9 (14)

Majority of the children 59 (94%) had pulmonary tuberculosis with those reporting a resistance pattern of MDR were 43 (68%).By registration group the new patients was at 25 (40%), followed by failure first line at 19 (30%), Facility mode of care was at 28 (51%). All the DR TB patient were tested for HIV and 26 (41%) of them were HIV positive, all of them (HIV positive) were put on cotrimoxazole and antiretroviral therapy. (As shown in table 3)

Table 3:

Clinical characteristics of children below 15 years managed for drug resistant TB in Kenya, 2010 – 2016

Variable	N (%)
Type of TB	
Extra pulmonary	4 (6)
Pulmonary	59 (94)
Registration group	
Failure first line	19 (30)
Failure retreatment	11 (17)
Lost to follow up	3 (5)
New	25 (40)
Retreatment	4 (6)
Transfer in	1 (2)
Resistance pattern	
Multidrug resistant	43 (68)
Monoresistant TB	15 (24)
Poly drug resistant	2 (3)
Rifampicin resistant	3 (5)
Genexpert	
[a]MTB detected, Rifampicin resistance detected	35 (56)
MTB detected, Rifampicin resistance indeterminate	1 (2)
MTB detected, Rifampicin resistance not detected	3 (5)
MTB not detected	1 (2)
Not Done	23 (37)
Z score	
3	8 (12)
2	6 (10)
1	6 (10)
-1	6 (10)
-2	0
-3	5 (7)
Not done	32 (51)
[b]HIV status	
Positive	26 (41)
Negative	37 (59)
Cotrimoxazole N=26	
Yes	26 (100.0)
[c]ART uptake N=26	
Yes	26 (100.0)

[a]MTB mycobacterial Tuberculosis, [b]HIV Human Immunodeficiency Virus, [c]ART Antiretroviral Therapsy

Most of the children were culture positive at (51%) and by the third month all had converted (as shown in table 4).

Table 4

Smear and culture conversion for children below 15 years managed for drug resistant TB in Kenya, 2010 – 2016

Variable	Month 0 (n%)	Month 1(n%)	Month 2 (n%)	Month 3 (n %)
Smear				
Positive	33(52)	10 (16)	1 (2)	0 (0)
Negative	11 (17)	22 (35)	23 (37)	24 (38)
Not done	10 (16)	23 (37)	30 (48)	29 (46)
Not documented	9 (14)	8 (13)	9 (14)	10 (16)
Culture				
Positive	32 (51)	10 (16)	2 (3)	0 (0)
Negative	4 (6)	22 (35)	20 (32)	24 (38)
Not done	14 (22)	23 (37)	26 (41)	29 (46)
Not documented	13 (21)	8 (13)	15 (24)	10 (16)

Treatment for DR-TB take about 18-24 month thus most of the clients were still on treatment, only 35 patients had a treatment outcome. Cured were 21 (60%), treatment completed at 11 (31%) making a treatment success rate of 32 (91%), with a death rate of 2 (6%) and lost-to-follow up of 1 (3%). (As shown in table 5).

Table 5:

Treatment Outcome of children below 15 years managed for drug resistant TB in Kenya, 2010 – 2014

Variables	N =35 n(%)
Treatment outcomes	
Cured	21 (60)
Died	2 (6)
Lost to follow up	1 (3)
Treatment completed	11 (31)
Treatment success rate	32 (91)

DISCUSSION

This study has shown that there is increase in the notification of children with DRTB in Kenya. This increase has been due to the roll-out and availability of molecular diagnostic testing that has led to more children being diagnosed and put on treatment which is a positive outcome as most of the children with DR-TB are diagnosed and put on treatment. The commonest age group of children affected in this study was between 10-14 years, possible reasons for this could be the fact that these children were able to produce sputum for drug susceptibility and testing. It can also suggest that younger children contacting DR-TB would be dying before adequate diagnosis and initiation of treatment thus improvements are needed to find younger children with DR-TB. The study showed that most of the children had pulmonary TB, this can be as a result of limited diagnostics equipment for the detection of extrapulmonary TB in our setting; those with extrapulmonary involvement were likely to have been missed. Most of the children with DR-TB in this study had primary resistance which was most probably acquired from adults with DR-TB in the community, rather than secondary resistance acquired as a result of suboptimal therapy. There is therefore a need for continuous paediatric DR-TB surveillance. This study also revealed ongoing transmission of DR-TB in the community and it may represent the 'tip of the iceberg' in terms of DR-TB in Kenya. This was similar to study done in china and South Africa which showed that the majority of the paediatric DR-TB cases were new cases (17-18). The results showed that most of the children were culture positive. This may indicate that health care workers wait for culture confirmation before starting DR-TB treatment or it can indicate that most of the children who would benefit from empirical treatment are left out 'missing of DR-TB in children. The results demonstrate that, it is possible to achieve favorable outcomes among children treated for DR-TB; this is similar to the study done in South Africa which examined outcomes in 111 children with MDR-TB, 82% of patients achieved favorable outcomes (19). This can be attributed to excellent treatment adherence produced by daily supervised therapy. The results of the study showed that all the DR-TB patients were tested for HIV and for those who were HIV positive were put on cotrimaxozole preventive therapy and antiretroviral drugs. This can be due to the policy that state that all those patients diagnose with Tuberculosis should be tested for HIV and those found to be HIV positive to be put on ARV immediately.

The limitation of this study was the use of routine programmatic records that may have inaccuracies, inconsistencies and missing data-though data validation is normally conducted on quarterly basis. The strength of this study is the use of country data and the reporting was in accordance with STROBE guidelines (20). This study is among the first studies in Kenya on outcome of children managed for DRTB. Implication of the study: contact tracing is important in identification of children with DRTB and nutritional assessment of all children put on treatment is important.

Conclusion: Drug-resistant tuberculosis can be successfully treated and therapy well tolerated among children in Kenya. Adverse events seem to be less common among children than among adults and rarely compromise treatment when managed appropriately. There is a need to ensure that contact tracing for intensified case finding among children is done.

Conflict of Interest: None

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