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DIAGNOSTIC METHODS AND TREATMENT OUTCOMES FOR TB IN CHILDREN UNDER 15 YEARS IN KISII COUNTY, 2012-2016
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DIAGNOSTIC METHODS AND TREATMENT OUTCOMES FOR TB IN CHILDREN UNDER 15 YEARS IN KISII COUNTY, 2012-2016

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ABSTRACT

Background: **Diagnosis of TB in children poses a challenge due to the paucibacillairy nature of TB and difficulties in making a bacteriological confirmation. Globally, the TB burden in children is unknown with WHO estimating that they account for 10-15% of all cases. In Kenya, children contributed to 8.5% of all notified TB cases in 2016.**
Objective: **To describe the diagnostic methods and treatment outcomes among children aged<15 years in Kisii County, 2012-2016.**
Design: **A descriptive analysis of children aged <15 years in Kisii County diagnosed and notified of TB to the National TB program.**
Results: **We abstracted 825 records of children:217 in 2012,156 in 2013,164 in 2014,136 in 2015 and 152 in 2016.The median age was 8(IQR 2-13) years with a male: female of ratio 1:1. The 10-15 years age-group accounted for 43% (351) while those aged<1year accounted for 10% (81). HIV testing was done among 806 (98%) with a TB/HIV co-infection of 31% and 96% ART initiation rate. Bacteriological and clinical diagnosis was done for 129/825 (16%) and 696/825(84 %). Gene Xpert was done for 28/825 (3%) in 2016 and 1/825 in 2012. Overall, for the period 2012-2015, the treatment success rate (TSR) was 96%**
Conclusion: **There has been a decline in notification rates over time, however, it was not clear whether this was due to absence of disease or improved use of diagnostics which requires further research. Older children accounted for majority of the cases diagnosed for TB. Most of the children in the younger age groups <5 years were initiated on treatment based on clinical diagnosis or a chest X-ray and hence a need to support health workers and health system in general on acquisition of sputum specimen in this younger age group.**

INTRODUCTION

Tuberculosis (TB) in children is a reflection of on-going transmission of TB in the community. Children acquire TB from an infectious individual in close contact with them, usually an adolescentor adult (1).

Childhood TB is believed to be under-diagnosed, in part due to the difficulties in obtaining microbiological confirmation (2). Each year, approximately 9.6 million people develop TB. Globally, children less than 15 years account for 15% of the total TB burden(3).Kenya ranks 15 among 22 high-burden countries that collectively account for 80% of TB cases. In 2015, 81,518 TB cases were notified in Kenya, out of which 6968 (8.5%) were in children less than 15 years(4), suggesting an under estimate in the TB burden in children. The risk factors for infection are closeness, duration of contact with the source, smear positivity of the source case, living in high TB endemic communities, overcrowding, young age(especially 0-2 years),HIV infection, malnutrition, post measles, and not having BCG vaccination(5).Often, children are paucibacillary and they do not present with classical signs and symptoms of TB making diagnosis difficult.(6).This leads to under diagnosis and under reporting. There is need to explore how successful the available diagnostics methods being utilized in diagnosis of TB.

The diagnosis of TB in children relies on comprehensive history, careful physical examination and relevant investigations like tuberculin skin test, chest radiograph (CXR) and bacteriological evaluation of specimens (7-8).Bacteriological evaluation through smear microscopy, culture or histology can be made from sputum, gastric aspirate or fine needle aspirate from enlarged lymph node(7)(8). Over the past decade a transition in the diagnostic approaches for TB has occurred including the introduction of GeneXpert in 2012 in Kenya. This evaluation sort to explore the diagnostic methods and treatment outcomes for children aged less than 15 years enrolled in TB care in Kisii County to better understand the trend and potential gap in TB detection.

MATERIALS AND METHODS

Study Design: This is a descriptive analysis of routine data of children aged less than 15 years notified to the National TB Program between 2012 to 2016 in Kisii County.

Setting: Kisii County is one of the 47 Counties in Western part Kenya. It has a population of 1,152,282 of which 41% are children. About 60%of the population predominantly lives in rural areas with the main economic activity being subsistence farming, as such,56% of the population in poverty(9) About 6% of children less than 15 years are HIV infected (10).TB services are provided by 70% of health facilities in the county public 68%, private 23% and faith based 9% (11).In 2015 ,1,661 cases of TB were reported of which 136 (8%) were children aged less than 15 years(12). The National Tuberculosis Leprosy and Lung Disease Program (NTLD-P) estimates that 10-15% of cases will be in children less than 15 years. Based on this national estimate there may be 30 – 114 undiagnosed or unreported childhood TB cases in Kisii.

Surveillance system of TB in children: Health workers are provided with guidelines by the National TB Program for the diagnosis and management of TB. Passive case finding of TB in children occurs when children who have signs and symptoms of TB are screened at health facilities. Additionally, active case finding through contact tracing is carried out to identify children who live in close contact with a person who has been diagnosed with smear positive TB. Notification of TB is made following a positive test result based on either of the following methods; clinical diagnosis (symptom screening, physical examination and CXR) or bacteriological confirmation (smear microscopy, cultures, Gene expert or biopsy). Largely though, high index of suspicions used to diagnose TB in children.

Study population: The study population included all children aged less than 15 years in Kisii County diagnosed and notified to the National Tuberculosis Program between 2012-2016.

Data Collection: The national TB Program in Kenya utilizes TIBU (Tuberculosis Basic Unit) data management as central database. The TIBU system is a web based solution integrated with mobile/tablet technology developed and introduced in Kenya in the year 2012. Patients with TB upon diagnosis, are notified, treated and followed up with primary information captured from patient records and drug resistance TB (DR TB) 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 bi-annually at the national level to review and address data quality issues within the database.

Data analysis: Descriptive analysis was undertaken, for continuous data, mean and median were calculated for normally distributed and non-normally distributed data respectively. Frequencies and percentages were calculated for categorical variables. To describe trends over time, a line chart was used. Data was summarised in tables and charts. Data cleaning and analysis were undertaken in Stata version 14.

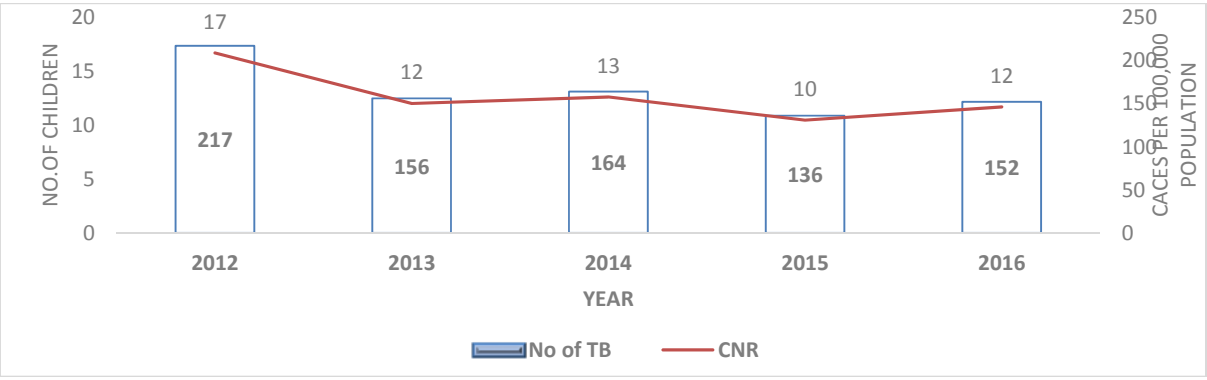
Ethical consideration: This study was approved by the Moi University College of Health Sciences (MU/CHS) and Moi Teaching & Referral Hospital (MT&RH) Institutional Review Board (IREC).

RESULTS

The total number of children diagnosed with TB in Kisii County between 2012 and 2016 was 825.Thenumber of children diagnosed with TB varied overtime with the highest reported being in 2012 (217 cases) while the lowest was in 2015 (136 cases). Overall, there was a decline in the TB notification rates for children 17/100,000 in 2012 compared to12/100,000 in 2016 (Figure 1).

Figure 1:

Trend of childhood TB cases and notification Rates per 100 000 pop.in Kisii County, between 2012 and 2016



CNR-Case Notification Rate

Table 1 shows the demographic and clinical characteristics of children diagnosed with TB. The median age was 8(IQR 2-13) years with majority of the children being in the age group 10-14 years 351(43%).Based on the site affected by TB, Pulmonary TB accounted for 710(86%) cases across the 5 year period. HIV testing was done for 806(98%) children and the TB/HIV co-infection rate was258/806 (32%). Of the TB-HIV co-infected children, ART was initiated in246 (96%) children.

Table 1:

Demographic and clinical characteristics of children aged less than 15 years in Kisii County, 2012-2016

Variable	**N=825** **n (%)**
Age group	
0-1	81 (10)
2-4	220 (27)
5-9	173 (21)
10-14	351 (43)
Sex	
Female	408 (50)
Male	417 (51)
Sector	
Publicfacilities	725 (88)
Private facilities	95 (12)
Othe Faith Based facilities*	
Type of TB	
Extra-pulmonary	115 (14)
Pulmonary	710 (86)
HIV Status	
Not done	19(2)
Negative	548 (67)
Positive	258 (31)
Anti-Retroviral Therapy Yes/No**N=258**	
No	11 (4)
Yes	246 (96)
Cotrimoxazole Preventive Therapy **N=258**	
No	1(0)
Yes	257(100)

**These are faith based facilities that have not been captured in the public facilities as in the recording and classification system*

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Of the childhood TB cases notified in Kisii County within TIBU, 22% had either two or three diagnostic methods/tests used in the diagnostic process and initiation of treatment (data not shown). Among the younger age groups (0-1 years), chest X-ray and clinician diagnosis were the commonly utilised diagnostics for 51(63%) and 25(31%) of the children respectively. Similarly, CXR 46(40%) and clinician 58(50%) were also the commonly utilised diagnostics during the diagnostic process for informing initiation of treatment for extra-pulmonary TB cases. A detailed description of the diagnostic methods used (including when more than one method was used) to inform initiation of treatment is presented in table 2.

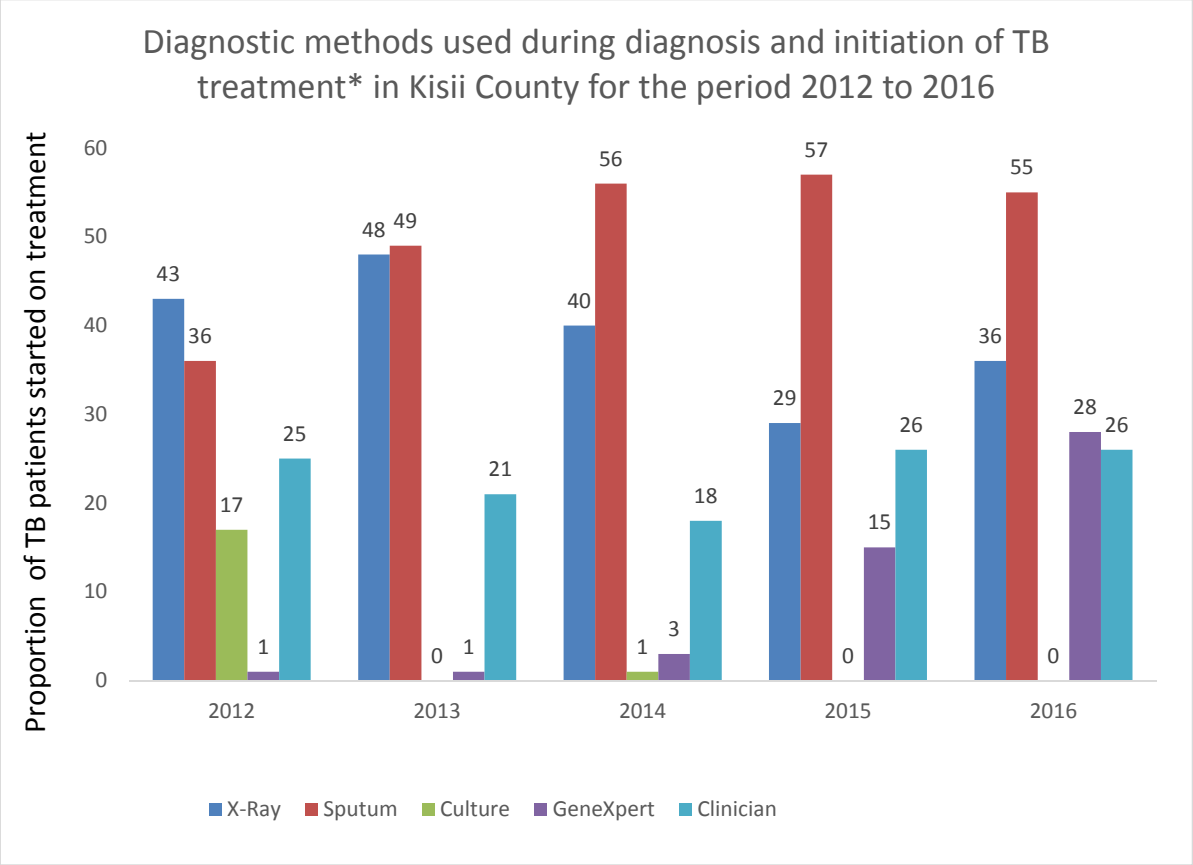
Table 2:

Diagnostic methods used alongside others for informing initiation of treatment among children aged less than 15 years.

		X-Ray	Smear	Culture	GeneXpert	Clinical
Sector						
	Private	57(60)	37(39)	1(1)	10(11)	19(20)
	Public	272(37)	369(51)	37(5)	61(8)	172(24)
Age group						
	0-1	51(63)	9(11)	2(3)	2(3)	25(31)
	1-4	105(48)	42(19)	10(5)	20(9)	83(38)
	5-9	73(42)	81(47)	13(8)	18(10)	43(25)
	10-15	100(29)	274(78)	13(4)	31(9)	40(11)
Sex						
	Female	163(40)	220(54)	15(4)	38(9)	78(19)
	Male	166(40)	186(45)	23(6)	33(8)	113(27)
Type of TB P/EP						
	Extra Pulmonary	46(40)	7(6)	3(3)	5(4)	58(50)
	Pulmonary	283(40)	399(56)	35(5)	66(9)	133(19)

Reviewing the trends over time for the use of diagnostic methods (including when multiple methods were used), there was an increasing trend in the use of sputum and GeneXpert (from 2014 onwards). Although there was a declining trend in the use of clinician suspicion and CXR in the diagnosis in the periods 2012 to 2014 and increase in the utilization of these methods was observed in the 2015 and 2016 periods (figure2)

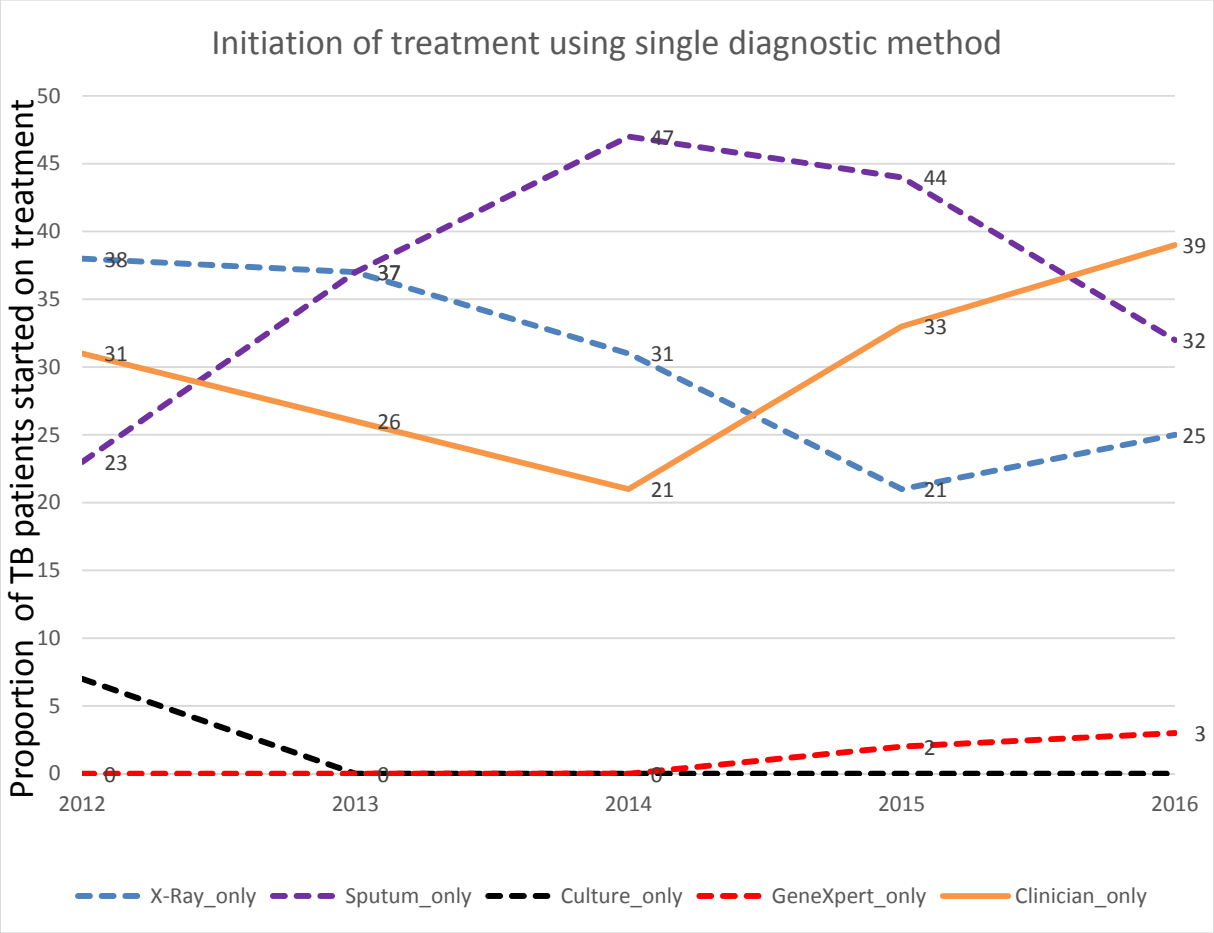
Figure 2:
Types of TB Diagnostic methods used among children in Kisii County 2012-2016.



**More than one method was used in one quarter of patients.*

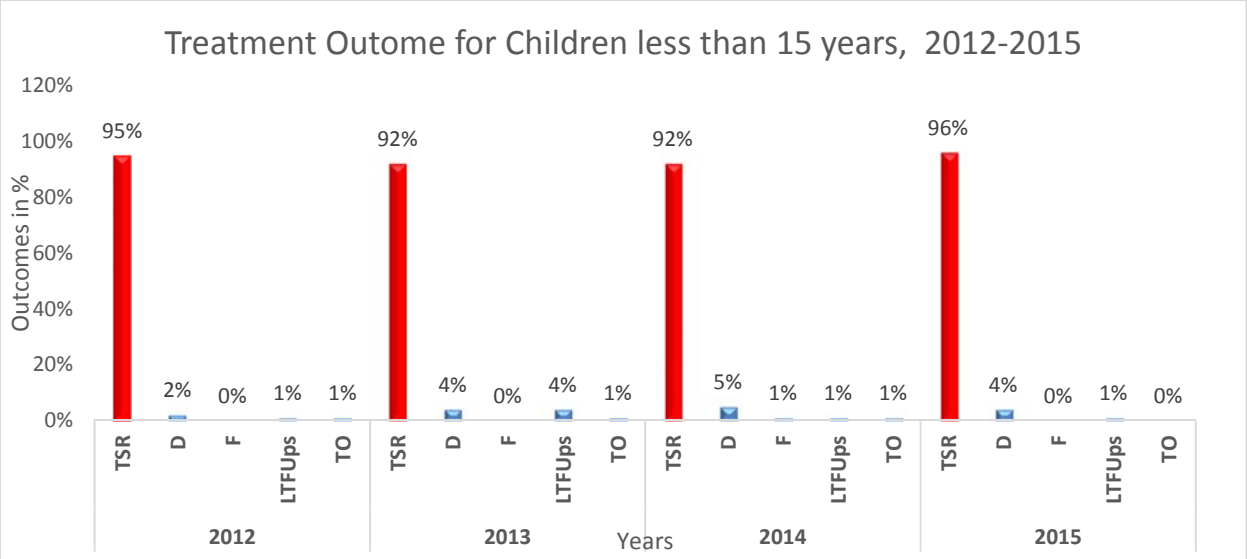
Comparing trends of when one or more than one diagnostic test was used to initiate TB treatment in children to when only one diagnostic test was used, lower proportions of patients were started on one diagnostic test only. Sputum smear was still the most utilised method. However, overtime, as the use of Gene Xpert increased starting 2014, there was a decline in the use of sputum smear and diagnosis and CXR while the use of clinician diagnosis seems to be increasing (figure 3). A comparison of single versus multiple diagnostic tests used for initiation of treatment is presented in supplementary figure 1.

Figure 3:
Initiation of treatment using single diagnostic method



Overall, there was a high treatment success rate (>90%) for children over time. Similarly, all-cause mortality relatively constant at 4%-5% with the exception of 2012 when the all-cause mortality was reported as 2% (2/217). Figure 4 illustrates the outcomes of children age less than 15 years.

Figure 4:
Treatment outcomes for children aged less than 15 years in Kisii County



*TSR= Treatment success Rate,D=Dead=treatment failure ,LFTUps=Lost to follow ups,T0=Transfer out. *2016 were not included in the outcome because patients who started treatment in late 4th quarter were still on treatment.*

Comparing the treatment success rate by the demographic and clinical characteristics of children, there were relatively lower treatment success rates over time for the age group 5-9 years. Treatment success rate for HIV negative children was consistently higher across to time when compared to HIV positive (97 vs 92%) in 2012 and (97 vs 93%) in 2015.

Over time almost all HIV positive children were initiated on ART. Only one child was not initiated on treatment in 2015 compared to four in 2012.

Table 3:
Compares the Treatment Success Rate by Demographic and clinical among children under 15 years in Kisii County between 2012- 2015

Variable	n(%)			
Year	2012	2013	2014	2015
Age group				
0-1	26 (90)	15 (94)	11 (85)	12 (100)
1-4	75 (97)	32 (91)	29 (97)	29 (91)
5-9	34 (94)	30 (86)	36 (88)	27 (90)
10-15	71 (95)	66 (94)	74 (93)	62 (100)
Sex				
Female	100 (94)	71 (91)	79 (91)	65 (96)
Male	106 (96)	72 (92)	71 (91)	65 (96)
Sector				
Private	20 (100)	25 (93)	17 (94)	17 (100)
Public	186 (94)	118 (92)	133 (91)	113 (95)
HIV Status				
ND	8 (83)	5 (83)	4 (100)	0 (0)
Negative	138 (97)	105 (94)	102 (94)	89 (97)
Positive	60 (92)	33 (87)	44 (85)	41 (93)
ART				
No	4 (100)	2 (67)	0 (0)	1 (100)
Yes	56 (92)	31 (89)	44 (90)	40 (93)

DISCUSSION

The overall aim of this study was to determine the diagnostic approaches used to inform initiation of TB treatment in children. Overall, 78% of the children were initiated on treatment based on a single diagnostic test. The commonly used diagnostic test in the younger age groups (<5 years) was CXR and clinical diagnosis (high index of suspicion for TB infection) while in the older age groups, sputum for microscopy was used. These findings could be linked to the difficulty in obtaining sputum in younger children as they cannot voluntarily expectorate. Sputum induction is the gold standard for getting sputum in children. It is rarely done with anecdotal evidence suggesting lack of skill from clinicians or well aerated rooms to conduct the procedure as some of the reasons these approaches are not used. However, studies from LIC settings and high HIV burden have demonstrated that sputum induction is safe and tolerable in younger age groups(13,14). The alternative is a gastric aspirate specimen first thing in the morning, however, this might require hospitalisation but has also been associated with poor yield in cultures and positive results(15) and where available the results are often not considered convincing since the specimen is not from the lungs.

Similar challenges in diagnosing was reported in a study done by Nadia Rahmanin paediatric departments at Danish university hospitals which showed that the diagnosis of TB in childhood still suffers from considerable uncertainty(16)Reviewing the trends in the use of diagnostic tests over-time in patients where a single diagnostic test was used to inform initiation of treatment, there is an increase in the use of clinical diagnosis with a decline in the use of CXR and sputum for microscopy. This may be linked to the introduction of a new diagnostic algorithmin 2015 where the diagnosis is mainly based on compatible clinical symptoms and signs, radiological findings suggestive of TB, a positive TST and a history of exposure.(17).The study also demonstrates a steady increase in the use of gene Xpert and decline in culture. Gene Xpert is accessible, highly specific &sensitive to mycobacterium tuberculosis. It enables the diagnosis of TB in children to improve because it is highly sensitive and specific to mycobacterium tuberculosis but also gives results in two hours. In addition, it detects resistance to Rifampicin.(18). Culture results thus, policy makers at the National TB program should give higher priority for childhood TB case management. Going by the recent prevalence survey, which estimates the missing TB cases to be 40%, finding childhood TB could bridge this gap. Childhood TB needs continuous attention with a special focus on risk groups. Emphasis on improving early TB case detection, contact tracing and further implementation of preventive treatment is necessary at all health service delivery points. provided after 4-8 weeks and may therefore not guide immediate treatment initiation (19).The study demonstrates that it is possible to achieve favourable treatment outcomes in children including children who are HIV positive. With the recent Ministry of Health policy of test and treat, children who are HIV positive are started on ART immediately. Similar recommendations have been proposed and shown to improve outcomes elsewhere (20) with delay in initiating ART being linked to a high mortality. A study done in south India indicated that non-initiation of ART emerged as a high risk factor for unfavourable TB treatment outcome and mortality(21)**.** Immunity in children is not well developed and often they present with a typical signs of TB like wheeze or acute pneumonia, therefore, the associated difficulty in obtaining sputum increases the risk of miss-diagnosis of TB in children. In a recent review by Oliwa and colleagues on tuberculosis as a comorbidity in of childhood pneumonia, 7.5% of children presenting with acute respiratory symptoms had a positive culture for TB(22). Additionally, given the high burden of TB in the adult population, it is likely that there are a lot of missed cases in the population due to the weak follow-up structures for active tracing of potential children in the households of sputum positive TB adults. Therefore, there is need to not only improve capacity for health workers on diagnosis through laboratory supported results hence the ability to undertake sputum induction but also strengthening of the TB program in follow-up and routine screening of children with respiratory symptoms. The program should strengthen diagnostic methods, specimen collection, and management of children. The data we report should be interpreted in the light of the limitations. Firstly, it is not possible to accurately determine from TIBU which diagnostic method was used to initiate treatment. However, given that the difficulty in making a diagnosis of TB in children, this could in part explain the use of multiple diagnostic approaches.

Secondly, the data used in this analysis was routinely collected and therefore additional data on important factors that might further explain use and choice of diagnostic methods like comorbidities, nutritional data, history of contact with a suspected or confirmed case were not available.

Lastly, we have only presented data from one of the 47 counties in Kenya although, we feel the data presented is likely to be representative of the status on the use of diagnostics as the challenges presented are more generic. However, by demonstrating the value of routinely collected data to inform policy and by reviewing data on children – a vulnerable population, whose management is not often reviewed, findings from this work will inform future updates of TIBU and will inform other programmatic activities like monitoring and evaluation of TB diagnostics in Kenya.

CONCLUSION

There has been a decline in the notification rates for children over time. Understanding whether this is due to absence of disease or improved use of diagnostics requires further research. Older children comprised the majority of cases diagnosed for TB suggesting under-diagnosis in the younger population.

There is need to train and support health workers on techniques for sputum acquisition especially in the younger age groups for whom most of the diagnostic test used for whom initiation was not supported by laboratory results. HIV contributes substantially to the childhood TB burden in the county.

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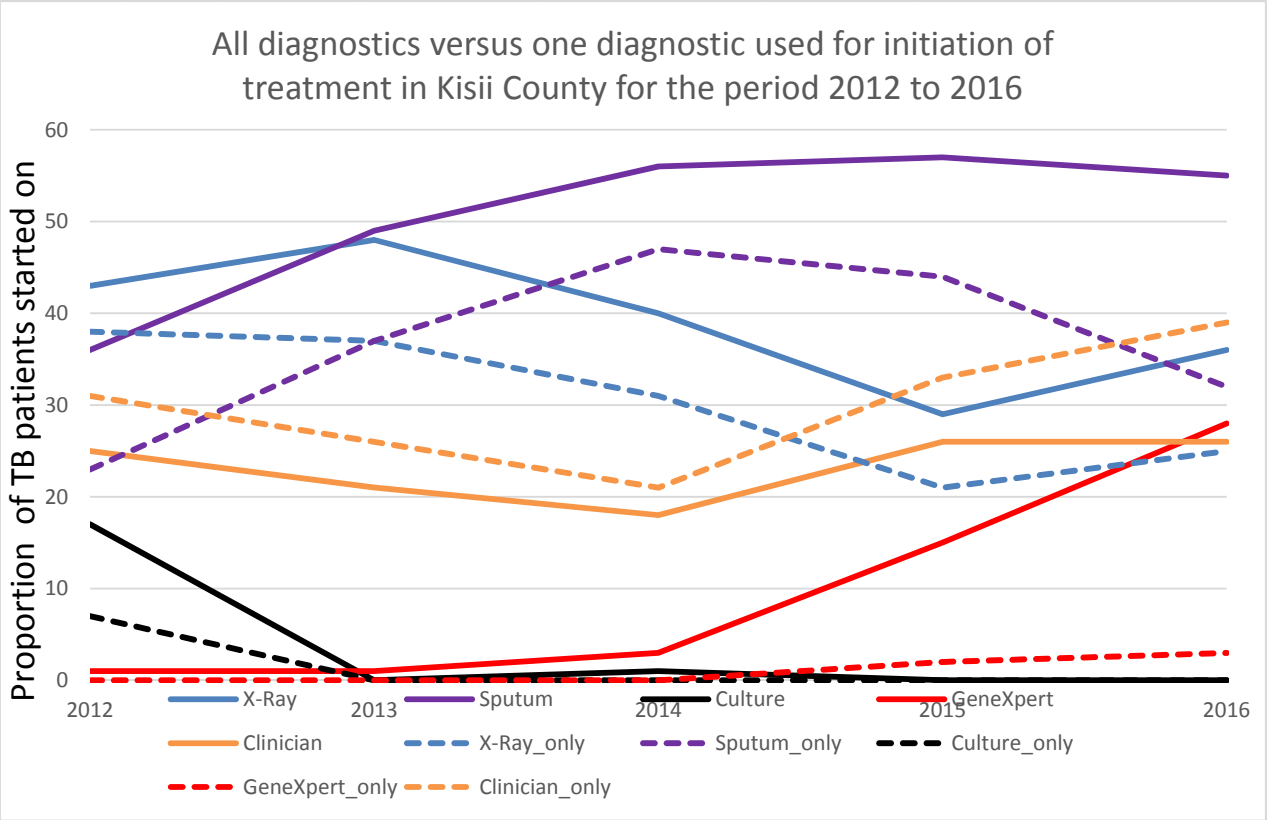
Supplementary figure1:

Comparison of utilization of one or more diagnostic methods used for initiation of treatment over time



**Dotted lines represent when only that diagnostic test was used; continuous line is for when the diagnostic test was used alongside other tests.*

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