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COMPARISON OF DEMOGRAPHIC AND CLINICAL CHARACTERISTICS BETWEEN PULMONARY AND EXTRA-PULMONARY TUBERCULOSIS PATIENTS IN KIAMBU COUNTY, 2012-2015

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ABSTRACT

Background: Tuberculosis (TB) continues to be a public health challenge globally. The most common organ to be involved is the lung although it can affect any organ in the body. The diagnosis of extra-pulmonary TB (EPTB) has faced many challenges mainly due to inadequate expertise to diagnose or lack of equipment for diagnosis.

Objective: To compare the demographic and clinical characteristics between pulmonary and extra-pulmonary tuberculosis in Kiambu County

Design: Retrospective cross-sectional study

Setting: Kiambu County, Kenya

Subjects: Tuberculosis patients notified in TIBU surveillance system

Results: Of the 15, 833 patients analyzed, 2,704 (17%) had extra-pulmonary tuberculosis. Male to female ratio was 1:1.7 in PTB and 1:1.3 in EPTB patients. There was declining trend of TB cases notified over the years for both PTB and EPTB. Pleural TB accounted for 38% with TB lymphadenitis accounting for 14% of the EPTB subtypes. TB-HIV co-infection was higher among EPTB (36%) compared to PTB (30%). The treatment success rate was 85% and 86% among PTB and EPTB cases respectively. The mortality was 10% among EPTB and 5% in PTB cases. The 5-14 age category were more likely to developing EPTB compared to PTB (AOR 4.67 95% CI (1.5-13.99). Kabete zone was most affected with EPTB (AOR 2.11(1.19-2.74) while a protective factor was observed among the HIV positive clients (AOR 0.58 (0.43 - 0.78)

Conclusion: There was a general decline in cases for both EPTB and PTB. However, the age category most affected was 5-14 years. The co-infectivity rate was higher among the EPTB patients compared to the PTB patients. High index of suspicion and appropriate diagnostic tools are needed in evaluation particularly in EPTB which will assist in early management of the patients. ART uptake could play a big role in protecting HIV positive clients from getting EPTB.

INTRODUCTION

Tuberculosis (TB) remains a public health concern worldwide and is the number one cause of morbidity and mortality globally among infectious diseases now surpassing HIV/AIDS (1). The transmission of TB is airborne. Following an infection with mycobacterium

tuberculosis, the disease mostly affects the lung parenchyma due to the nature of its transmission but can affect any organ of the body through lymphatic or hematogenous spread (2). Most patients typically present with pulmonary tuberculosis (PTB) and a lesser proportion present with extra-pulmonary tuberculosis (EPTB) (1,3–5) .

In 2015, the estimated number of persons notified globally to have tuberculosis was 6.1 million (1). Of the notified cases, EPTB contributed 915,000, HIV-TB co-infected patients contributed 500,000 while 140,000 had drug resistance tuberculosis (1). In the same year, approximately 1.5 million people succumbed to tuberculosis making it the leading killer among the infectious disease. (1). Kenya is among the 22 high TB burden countries in the world (6). Further, it is among 14 African countries that has a triple burden of tuberculosis, TB-HIV as well as multi-drug resistance TB (3). In the recently released prevalence survey results in Kenya, the burden of TB is 558 cases per 100,000 persons which is much higher than previously estimated   at 266/100,000 (1,6). In 2015, of the 81,518 persons notified with TB in Kenya, 13,690 had EPTB. (7)

The diagnosis of EPTB is more challenging than PTB. This is due to various factors which include: knowledge gaps in differentiating EPTB from other conditions which may lead to misdiagnosis, lack of expertise to obtain a specimen for diagnosis or lack of the required equipment for diagnosis depending on the anatomical site affected. Further, low bacillary load in the affected anatomical site may lead to low sensitivity during diagnosis leading to misdiagnosis and subsequently missed opportunities to treatment (8,9). Various studies, have noted an association of EPTB occurrence with the immune suppression of the host which may reactivate an existing latent infection (2,10–14). In this paper, we aim to compare the demographic and clinical characteristics of pulmonary tuberculosis and extra- pulmonary tuberculosis and look at the risk factors contributing to the occurrence of EPTB in Kiambu County.

MATERIALS AND METHODS

Study Design: A retrospective cross-sectional study using data generated in the Tuberculosis Information of Basic Unit (TIBU) at County level

Study Participants: The study participants comprised of Tuberculosis patients notified in TIBU in Kiambu County between 2012-2015.

Study site and setting: The study setting is in Kiambu County. The specifics of the study setting has being described in detail elsewhere (15).

Study site context: In regards to diagnosis, Kiambu County has smear microscopy equipment, gene-Xpert, x-ray services and Magnetic Resonance Imaging (MRI) services in public health facilities which aids in the diagnosis of tuberculosis. There are a total of 5 gene-Xpert machines which assists in the diagnosis of both PTB and forms of EPTB. In regards to microscopy, the county has both Zieln-stain and fluorescent microscopes. There are also x-ray services which are well distributed across the County which assists in the clinical diagnosis of tuberculosis. In addition, there are two MRI machines which are useful in the diagnosis of extra-pulmonary tuberculosis.

In the clinical diagnosis of tuberculosis, all the patients diagnosed with tuberculosis classified by type of tuberculosis and further by subtype in-case they have EPTB. The patients are then put on the appropriate treatment regimen based on their weight and managed with Direct Observation Therapy (DOTS) as recommended in the national guidelines (2).

Source of data: TB Program utilizes TIBU data management as central database of the National Tuberculosis and Leprosy Program (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 Multi-drug Resistance (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.
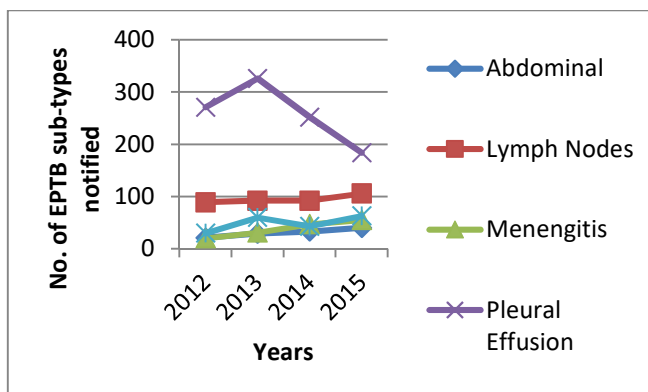TIBU has internal consistency checks to ensure that data entry errors are minimized. The TB program has quarterly data quality audits at the county level and

biannually at the national level.

Analysis and data preparation: Data was downloaded from TIBU and exported into an excel database using STATA version 13 software. All analyses were conducted using STATA. Categorical data were described using frequencies and proportions. Medians (Inter Quartile Range) and mean (Standard Deviation) were used for continuous data. Chi-Square test was used to test for the association of type of TB and other categorical variables. The strengths of associations of Type of TB with other categorical variables were presented by odds ratio (ORs) with 95% confidence intervals (CI). Variables with p-values less than 0.10 in the univariate analysis were included in the multivariate logistic regression model. All tests were two-tailed, and p-values less than 0.05 were considered statistically significant.

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).
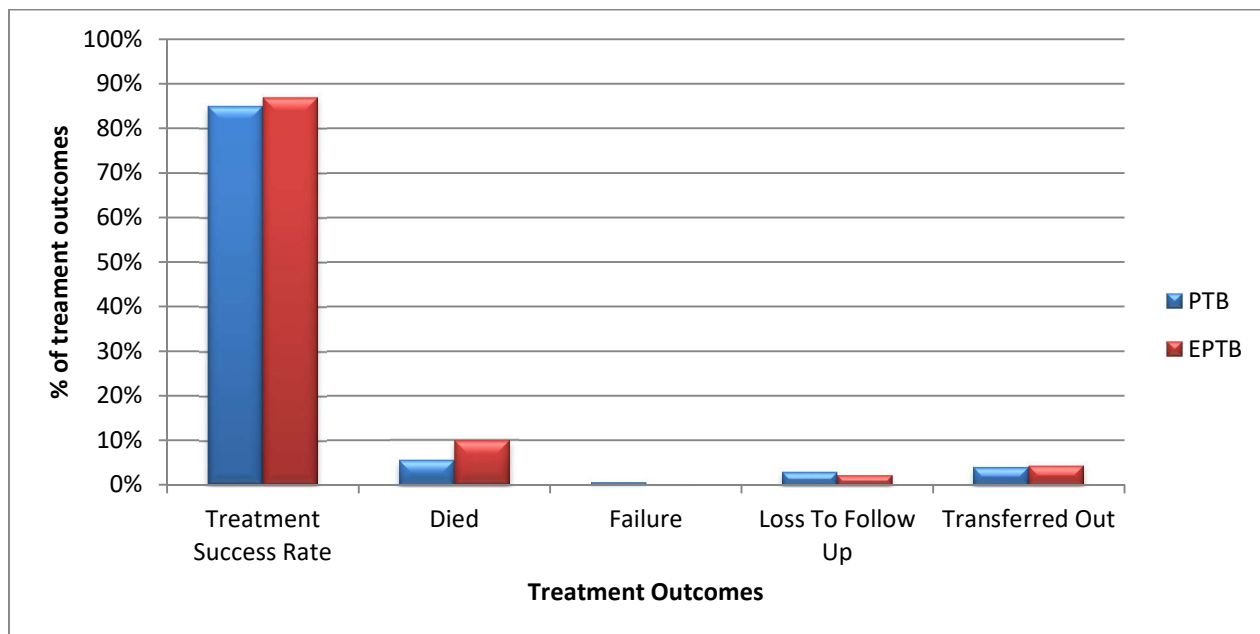
Figure 3:

Extra-pulmonary tuberculosis sub-types distribution across the years in Kiambu County, 2012-2015

The treatment success rates of PTB and EPTB were similar at 85% and 86% respectively. The mortality proportion of EPTB was much higher at 10% while that of PTB was at 5% .The patients with PTB had a slightly high proportion of lost to follow-up Vis a Vis the EPTB at 3% and 2% respectively. (Figure 4)
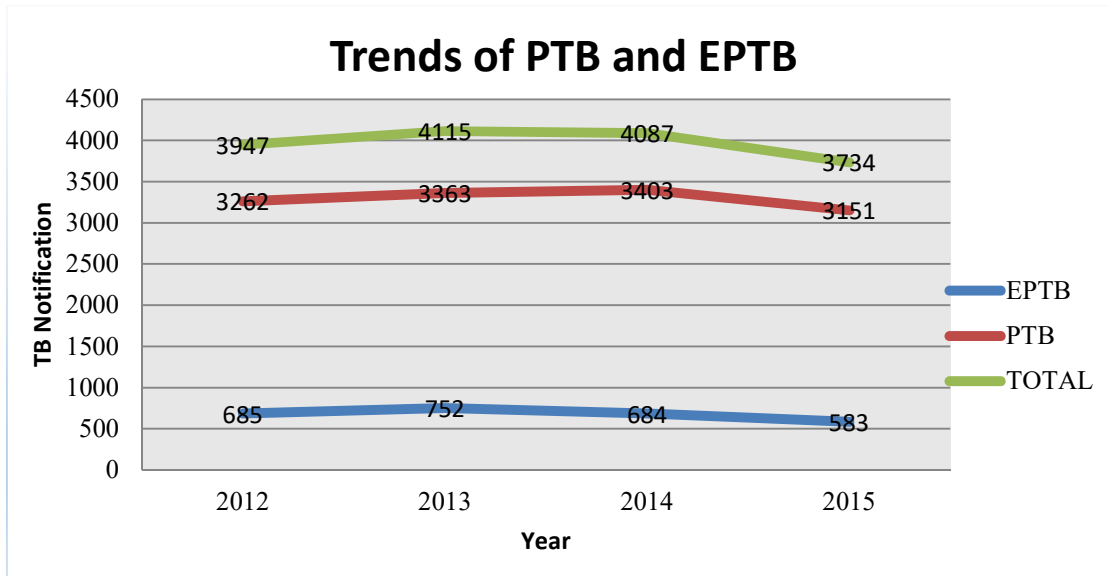
Figure 4

Treatment outcomes of Pulmonary Tuberculosis vs Extra-pulmonary Tuberculosis in Kiambu County, Kenya, 2012-2015

There has been a general decline in both pulmonary and extra-pulmonary tuberculosis cases after the year 2013 onwards Figure 5.

Figure 5

Trends of Pulmonary Tuberculosis and Extra pulmonary Tuberculosis over time in Kiambu County, Kenya, 2012-2015

Association of EPTB and various variables.

Table 2 below shows the crude and adjusted odds ratio for the association of EPTB and various variables. Upon univariate analysis, there was a similar distribution of EPTB cases across the private OR 0.99 95% CI (0.66-1.50) and public sector OR 0.76 95% CI (0.50-1.14). When compared to those in the prisons. Males are at reduced odds of developing EPTB compared to females OR 0.73 95% CI (0.67-0.80).

All the age groups seem to have higher odds of developing EPTB compared to the age group 0-4 years. Interestingly, higher BMI levels seem to predispose people to higher odds of developing EPTB. For example, the BMI category of (24.5 – 29.5) have 3 times higher odds OR 3.09 95% CI (2.5 - 3.75) compared the lowest BMI category of severe malnutrition (4 – 16). There were slightly higher odds of developing EPTB among HIV positive patients compared to HIV negative patients OR 1.34 95% CI (1.23-1.46) .Other variables are as shown in table 2 below.

Upon running a multivariate analysis, the sector where services were sought and gender don't seem to have a significant effect as being risk factors for EPTB. The age group the 5-14 age group had almost 5 times higher odds (AOR 4.67 95% CI (1.5-13.99) of having EPTB compared to the 0-4 years age category. Having a higher BMI seems to predispose one to higher odds of developing EPTB. Being Normal (BMI -18.5-24.5) the odds are about 2 times more AOR 1.58 95% CI (1.07 - 2.33). And being overweight BMI (24.5-29.5), the odds are almost 3 times more AOR 2.89 95% CI (1.63 - 5.13). The odds of acquiring EPTB were approximately 2 times higher (AOR 2.11 95% CI (1.19-2.74) among residents of Kabete zone compared to Gatundu zone. Among the HIV positive patients, the odds of developing EPTB were 42% less likely (AOR 0.58 95% CI (0.43-0.78) compared to the HIV negative clients. The other factors are as shown in table 2 below.

RESULTS

A total of 15,883 cases were analyzed of which 13,179 (83%) had PTB and 2,704 (17%) had EPTB. The public sector bore the greatest burden of disease for both pulmonary and extra-pulmonary tuberculosis at 73% and 67% respectively followed by the private sector and prisons had the least contribution.

There were more males than females for both PTB 8,432 (64%) and EPTB 1,529 (57%). Majority of patients presented with normal nutritional status with a BMI of 18.5-24.5 in both pulmonary 5,148 (45%) and extra-pulmonary tuberculosis 1,131 (50%). HIV testing was at 15,361/15,833 (97%). Of the TB-HIV co-infected patients, EPTB contributed 36% while 30% patients had PTB as shown in Table 1.

Table 1:

Demographics and clinical characteristics of PTB and EPTB in Kiambu County, 2012-2015

		PTB (n=13,179)	EPTB (n=2,704)	Total n = 15,883 (%)
Demographics				
Sector	Prisons	116 (0.9)	29 (1.1)	145(0.9)
	Private	3453 (26.2)	859 (31.8)	4312(27.1)
	Public	9610 (72.9)	1816 (67.2)	11426(71.9)
Sex	Female	4747 (36.0)	1175 (43.5)	5922(37.3)
	Male	8432 (64.0)	1529 (56.5)	9961(62.7)
BMI group	4 to 16	1749 (15.3)	260 (11.5)	2009(14.6)
	16 to 18.5	3837 (33.5)	540 (23.8)	4377(31.9)
	18.5 to 24.5	5148 (44.9)	1131 (49.9)	6279(45.7)
	Over 24.5	730 (6.4)	335 (14.8)	1065(7.8)
HIV Status	Declined	26 (0.2)	1 (0.0)	27(0.2)
	Not Done	399 (3.0)	96 (3.6)	495(3.1)
	Negative	8762 (66.5)	1618 (59.8)	10380(65.4)
	Positive	3992 (30.3)	989 (36.6)	4981(31.4)

There was a variation in the distribution of PTB and EPTB cases across the various zones in the County with Thika zone having the highest number of either PTB or EPTB cases and Lari having the least shown as shown in Figure 1. Uniquely, Thika sub-county also has the highest prevalence of HIV in the County. This can be attributed by the high rates of urbanization and settlement following the construction of the Thika Superhighway and the many tertiary institutions in the county has greatly contributed to the increase in new infections. Many studies have shown the close connection of HIV infection as a major risk factor to development of tuberculosis disease.

Figure 1:

Distribution of PTB and EPTB cases across Kiambu County, Kenya, per zone, 2012-2015.
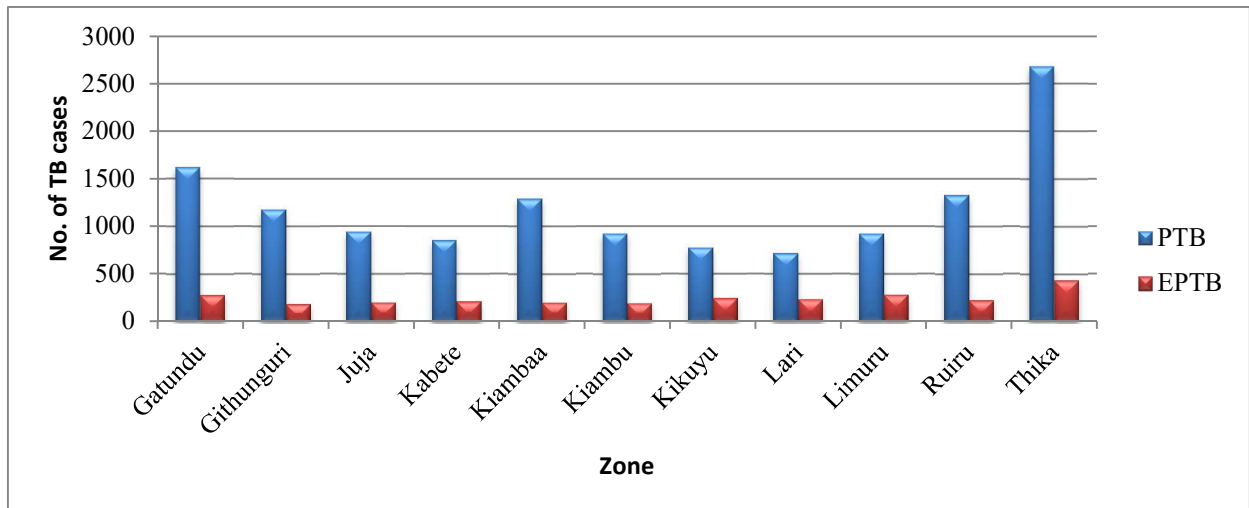
PTB and EPTB notification varied across all age groups from 0 year to over 65 years. However, the 25-44 age groups had the highest tuberculosis notification rate. Notably, from age 35 and above, there were higher numbers of cases of EPTB compared to PTB as shown in Figure 2.

Figure 2:

Comparison of PTB and EPTB across age groups in Kiambu County, 2012-2015
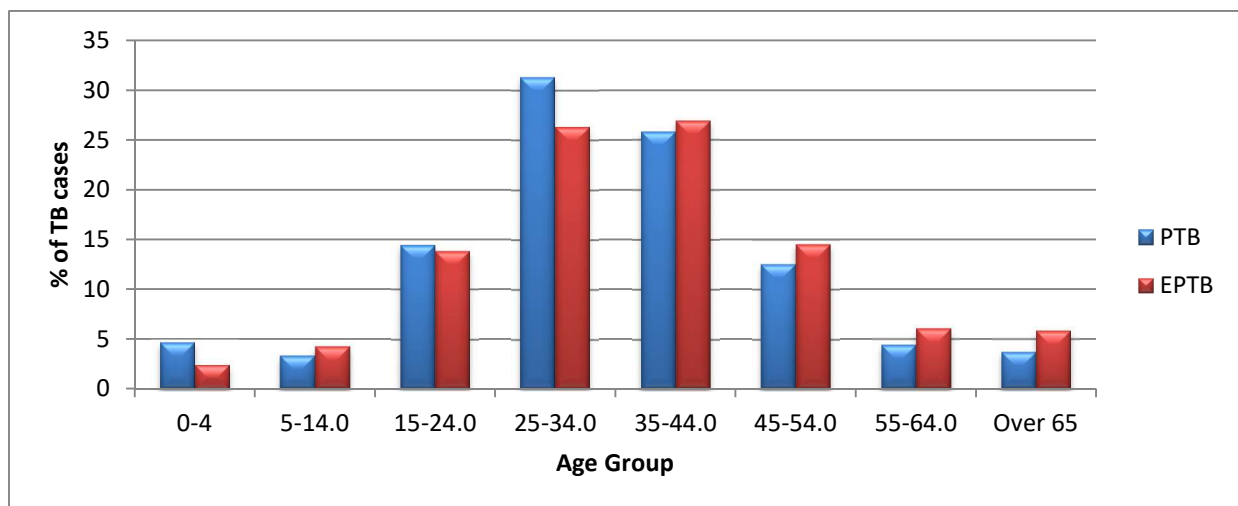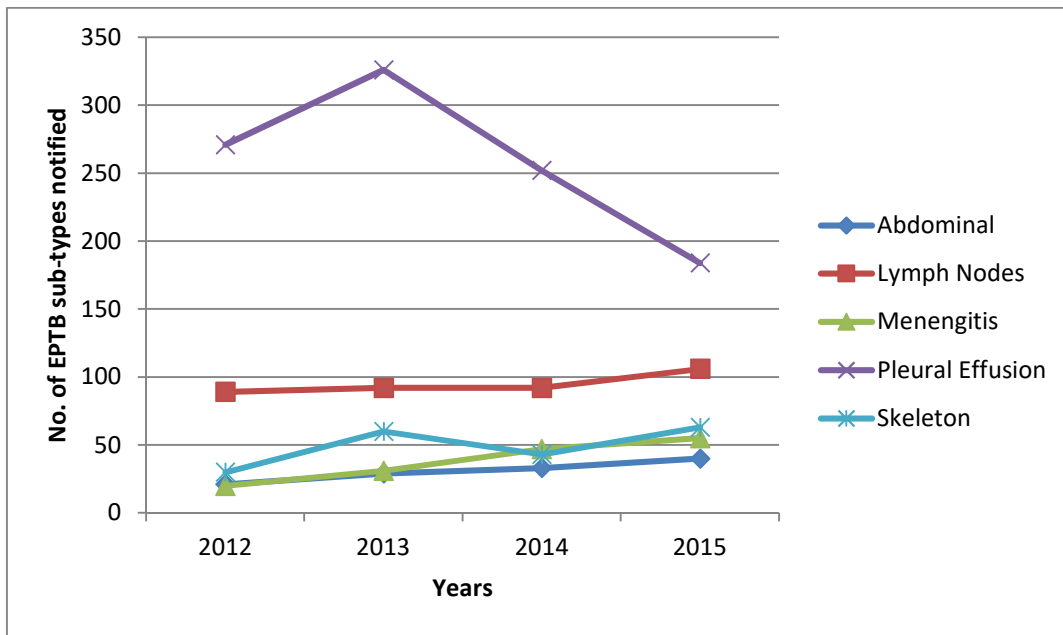

Notification of EPTB subtypes, varied across the years with TB of the pleura having the highest notified cases 38%, followed by TB of the lymph node at 14%. The least sub-type notified was abdominal tuberculosis at 5%. There has been a notable rising trend of TB meningitis and TB lymphadenitis across the years. In 2013, there was a spike in pleural, skeletal and lymph-node which was followed by a downward trend in both the TB pleuritic and abdominal tuberculosis as depicted in Figure 3:

Figure 3

Extra-pulmonary tuberculosis sub-types distribution across the years in Kiambu County, 2012-2015
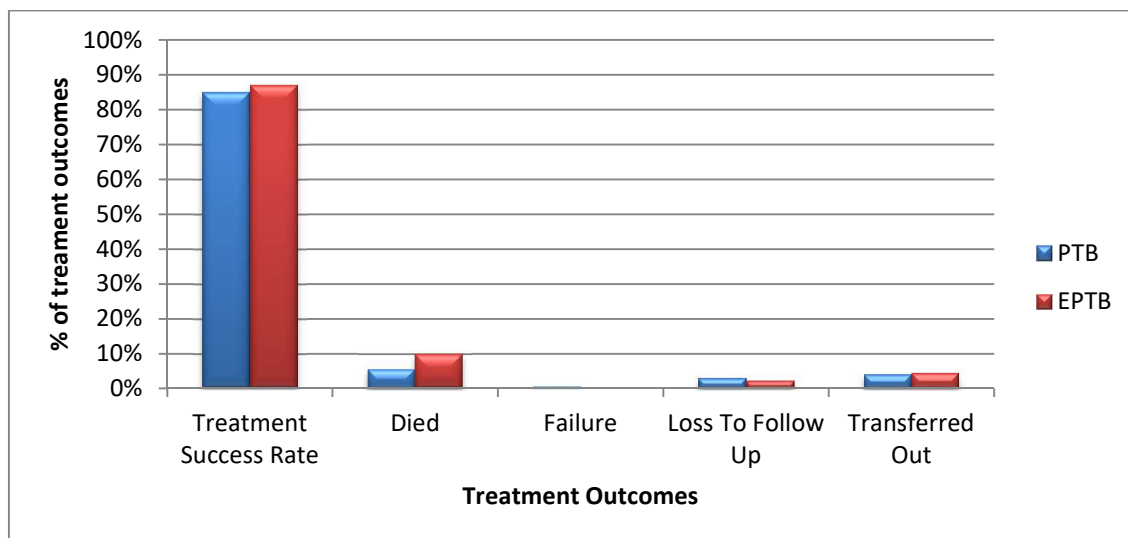

The treatment success rates of PTB and EPTB were similar at 85% and 86% respectively. The mortality proportion of EPTB was much higher at 10% while that of PTB was at 5% .The patients with PTB had a slightly high proportion of lost to follow-up Vis a Vis the EPTB at 3% and 2% respectively. (Figure 4)
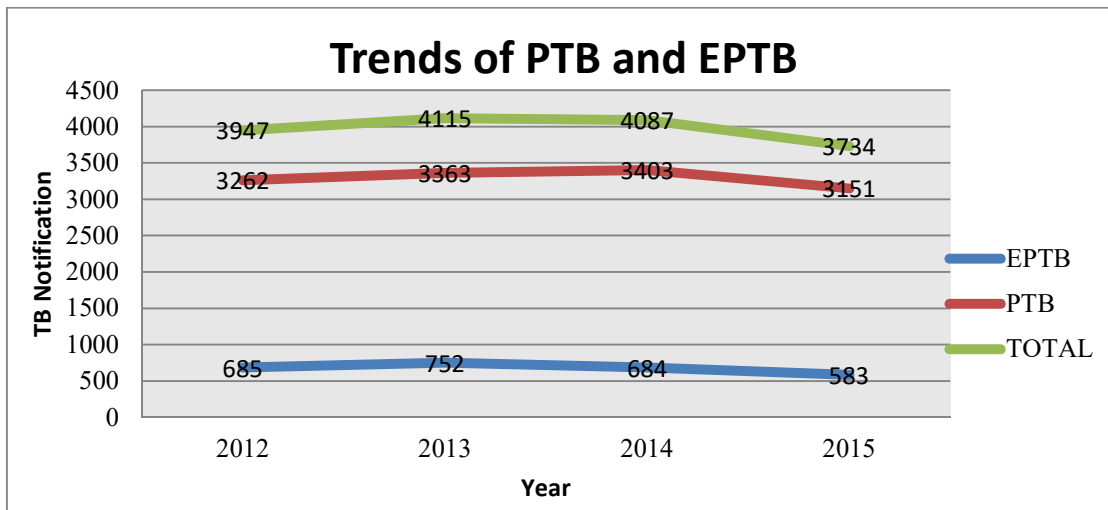
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Table 2 below shows the crude and adjusted odds ratio for the association of EPTB and various variables. Upon univariate analysis, there was a similar distribution of EPTB cases across the private OR 0.99 95% CI (0.66-1.50) and public sector OR 0.76 95% CI (0.50-1.14). When compared to those in the prisons. Males are at reduced odds of developing EPTB compared to females OR 0.73 95% CI (0.67-0.80).

All the age groups seem to have higher odds of developing EPTB compared to the age group 0-4 years. Interestingly, higher BMI levels seem to predispose people to higher odds of developing EPTB. For example, the BMI category of (24.5 – 29.5) have 3 times higher odds OR 3.09 95% CI (2.5 - 3.75) compared the lowest BMI category of severe malnutrition (4 – 16). There were slightly higher odds of developing EPTB among HIV positive patients compared to HIV negative patients OR 1.34 95% CI (1.23-1.46) .Other variables are as shown in table 2 below.

Upon running a multivariate analysis, the sector where services were sought and gender don't seem to have a significant effect as being risk factors for EPTB. The age group the 5-14 age group had almost 5 times higher odds (AOR 4.67 95% CI (1.5-13.99) of having EPTB compared to the 0-4 years age category. Having a higher BMI seems to predispose one to higher odds of developing EPTB. Being Normal (BMI -18.5-24.5) the odds are about 2 times more AOR 1.58 95% CI (1.07 - 2.33). And being overweight BMI (24.5-29.5), the odds are almost 3 times more AOR 2.89 95% CI (1.63 - 5.13). The odds of acquiring EPTB were approximately 2 times higher (AOR 2.11 95% CI (1.19-2.74) among residents of Kabete zone compared to Gatundu zone. Among the HIV positive patients, the odds of developing EPTB were 42% less likely (AOR 0.58 95% CI (0.43-0.78) compared to the HIV negative clients. The other factors are as shown in table 2 below.

Table 2:
Risk factors associated with the development of PTB Compared with EPTB among TB patients in Kiambu County, Kenya, 2012-2015

Demographics	Level	PTB	EPTB	Crude OR (95%CI)	Adjusted OR	p value
Sector						
	Prisons	116 (0.9)	29 (1.1)	1.00	1.00	<0.001
	Private	3453 (26.2)	859 (31.8)	0.99(0.66-1.50)	0.45(0.17-1.18)	
	Public	9610 (72.9)	1816 (67.2)	0.76(0.50-1.14)	0.40(0.16-1.03)	
Sex						<0.001
	Female	4747 (36.0)	1175 (43.5)	1.00	1.00	
	Male	8432 (64.0)	1529 (56.5)	0.73(0.67-0.80)	0.82 (0.62 - 1.10)	
Age group	0-4	601 (4.6)	66 (2.4)	1.00	1.00	<0.001
	5 to 14	438 (3.3)	114 (4.2)	2.37(1.71-3.29)	4.67 (1.5 - 13.99)	
	15 to 24	1901 (14.4)	372 (13.8)	1.78(1.35-2.35)	0.75 (0.39 - 1.43)	
	25 to 34	4117 (31.3)	709 (26.3)	1.57(1.20-2.05)	0.89 (0.52 - 1.52)	
	35 to 44	3395 (25.8)	727 (26.9)	1.95(1.49-2.55)	1.09 (0.65 - 1.85)	
	45 to 54	1651 (12.5)	392 (14.5)	2.16(1.64-2.85)	1.21 (0.70 - 2.09)	
	55 to 64	576 (4.4)	162 (6.0)	2.56(1.88-3.49)	1.63 (0.87 - 3.06)	
	Over 65	483 (3.7)	156 (5.8)	2.94(2.15-4.02)	NE*	
BMI group	4 to 16	1749 (15.1)	260 (11.0)	1.00	1.00	<0.001
	16 to 18.5	3837 (33.0)	540 (22.9)	0.95(0.81-1.11)	1.29 (0.85 - 1.95)	
	18.5 to 24.5	5240 (45.1)	1174 (49.9)	1.51 (1.30-1.74)	1.58 (1.07 - 2.33)	
	24.5-29.5	611 (5.3)	281 (11.9)	3.09 (2.5 - 3.75)	2.89 (1.63 - 5.13)	
	>30	174 (1.5)	100 (4.2)	3.87 (2.9 -5.11)	1.90 (0.60 - 6.04)	
Zone						<0.001
	Gatundu	1614 (12.2)	281 (10.4)	1.00	1.00	
	Githunguri	1175 (8.9)	185 (6.8)	0.90(0.74-1.10)	1.11 (0.62 - 1.97)	
	Juja	936 (7.1)	204 (7.5)	1.25(1.02-1.53)	1.40 (0.67 - 2.86)	
	Kabete	845 (6.4)	211 (7.8)	1.43(1.18-1.75)	2.11 (1.19 - 3.74)	
	Kiambaa	1286 (9.8)	203 (7.5)	0.91(0.75-1.10)	1.37 (0.79 - 2.37)	
	Kiambu	924 (7.0)	196 (7.2)	1.22(1.0-1.49)	1.55 (0.87 - 2.78)	
	Kikuyu	769 (5.8)	246 (9.1)	1.83(1.52-2.23)	1.05 (0.57 - 1.96)	
	Lari	711 (5.4)	235 (8.7)	1.90(1.56-2.31)	1.25 (0.64 - 2.45)	
	Limuru	917 (7.0)	282 (10.4)	1.77(1.47-2.12)	1.47 (0.84 - 2.59)	
	Ruiru	1324 (10.0)	227 (8.4)	0.98(0.81-1.19)	0.76 (0.38 - 1.51)	
	Thika	2678 (20.3)	434 (16.1)	0.93(0.79-1.09)	1.05 (0.63 - 1.76)	
HIV Status						<0.001
	Negative	8762 (66.5)	1618 (59.8)	1.00	1.00	
	Not Done	425 (3.2)	97 (3.6)	1.24(0.98-1.55)	0.71 (0.33 - 1.50)	
	Positive	3992 (30.3)	989 (36.6)	1.34(1.23-1.46)	0.58 (0.43 - 0.78)	
Treatment Outcome						<0.03
	Treatment Completed	522 (42.2)	117 (33.5)	1.00	1.00	
	Dead	714 (57.8)	232 (66.5)	1.45(1.13-1.86)	1.65 (1.22 - 2.25)	

not estimable

DISCUSSION

In Kiambu County, males had a higher notification for both pulmonary and extra-pulmonary tuberculosis compared to females. This could be due to males being more predisposed to the tubercle bacilli in the social gatherings, smoking lifestyle and alcohol consumption making them at a higher risk of tuberculosis. Similar findings are reported in a tuberculosis prevalence survey that was recently conducted in Kenya which revealed that TB notification cases among males were more than females at a ratio of 2.3:1 (16). Various studies that have been done have associated this to social and cultural factors as barriers to accessing health care services among women. Further, a multi-center case control study conducted in three West African countries concluded that males have gender predisposition for tuberculosis which could be due to their possible exposure to the bacilli at social gatherings (17–20).

In our study, TB-HIV co-infection rate among EPTB was higher than that of PTB. This is also consistent with various studies from developed countries which reported an association of EPTB with immunosuppression (13,14,21). Among the EPTB sub-types analyzed, TB of the pleura subtype had the highest notification of all the EPTB across the years followed by TB of the lymph nodes. This is consistent with studies that have reported pleural TB as the most common type of extra-pulmonary tuberculosis (22,23).

The other major finding was the decline of TB cases in both pulmonary and extra-pulmonary cases from the year 2012-2015. The decline in cases is in keeping with the results of the tuberculosis prevalence survey report recently done in Kenya where up to 40% of TB cases were reported to be missing (16). The reduction of TB cases could be due to passive case finding where the patient comes to the health facility when they are symptomatic Vis a Vis active TB screening for all persons presenting with respiratory symptoms. It could also be due to low level of knowledge on TB symptoms at community level coupled with stigma associated with it. The missing cases could also be as a result of limited access to diagnostic facilities since not all health facilities are equipped in TB diagnosis particularly the EPTB type .On the flip side, the reduction of cases could also be

as a result of timely initiation of treatment upon diagnosis resulting in reduced infectivity at community level.

The study established a higher likelihood of developing EPTB among school going children. This is akin to a study done in Turkey, where nearly two thirds of the children had EPTB (24). This could mean EPTB is underdiagnosed in pediatric category since the classic syndromic features of tuberculosis may be absent and requires a high acumen from the health care workers leading to an increase in EPTB cases. The residents residing in Kabete zone were found to have a higher probability of developing EPTB. This could be associated to the social lifestyle that is predominant in the area where alcohol intake and cigarette smoking is rampant making the residents vulnerable to disease acquisition at social gatherings. This finding is consistent with studies that have associated alcohol use disorder as a risk of tuberculosis through both exposures in social setups as well as suppression of the immune system due to ethanol substance (25). In addition, the zone hosts a large market promoting close interactions among the residents thus if there are persons who are infected, transmission of TB would be rampant since it is an airborne disease.

Interestingly, the HIV positive clients were less likely to develop EPTB. This could be explained by the fact that most of the HIV patients are on ART therapy and this may have played a big role in reconstituting their immune system. In addition, the roll – out of isoniazid preventive therapy (IPT) to PLWHIV has played a great role in protecting them against acquiring tuberculosis disease. Another plausible explanation could be due to the clinical challenge, pauci-bacilllary nature of EPTB and low index of suspicion for EPTB which may hamper timely diagnosis particularly in low resource limited settings. This finding is unlike some studies that have been done which showed that those who have HIV are more likely to develop EPTB due to the compromised immune system (26,27). Other studies from developed countries also reported an association of EPTB with immunosuppression showing that any form of immunosuppression poses a risk to the development of tuberculosis (13,14,21). Among the EPTB sub-types analyzed, TB of the pleura subtype had the highest notification of all the EPTB across the years followed by TB of the lymph nodes. This is consistent with

studies that have reported pleural TB as the most common type of extra-pulmonary tuberculosis (22,23).A unique finding in this study is that patients treated for PTB and EPTB were found to have normal BMI and over- nourishment. This is unlike studies that show an association of undernutrition aggravating TB(28,29). The plausible explanation maybe the patient genotype, social determinants, immune-modulation and metabolic derangement such as that associated with diabetes mellitus whose data was not available. Further studies that address nutrition will need to be conducted.

The TIBU platform provided a standardized collection method of the data base for pulmonary and extra-pulmonary TB. We adhered to the strobe guidelines. In the study, some EPTB sub-types had missing data but the numbers were not many to make a substantive change to our conclusions.

There is need to interrogate the dynamics or interactions between social cultural determinants of tuberculosis (and NCDs, diabetes and obesity in particular) in the TB Program. There is need to raise the index of suspicion amongst health care workers to predict and actively screen patients for EPTB management particularly are paramount.

CONCLUSISON

There was a general decline in cases for both EPTB and PTB. However, the age category most affected was children between 5-14 years. The HIV-TB co-infectivity rate was higher among the EPTB patients compared to the PTB patients. There is need to interrogate the interaction between tuberculosis and over-nutrition and its outcomes including diabetes mellitus. A high index of suspicion and appropriate diagnostic tools are needed in evaluation particularly in EPTB which will assist in early management of the patients.

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