

Trends and Treatment Outcomes of Pediatric Tuberculosis at Mbale Regional Referral Hospital, in Eastern Uganda, 2013-2017

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Abstract

Background: Childhood tuberculosis (TB) remains a major public health problem in Uganda. Failure to complete TB treatment is associated with development of multi-drug-resistant TB, continued spread of TB, and death. The World Health Organization (WHO) recommends treatment success rates of $\geq 85\%$ to achieve TB control, but children often have lower success rates due to challenges in case identification and treatment adherence. We assessed trends in childhood TB case notification rates, spatial case distribution, treatment outcomes, and predictors of treatment completion at Mbale Regional Referral Hospital (MRRH) in Eastern Uganda.

Methods: We reviewed TB registers and extracted data for patients aged 0-14 years with presumptive TB at MRRH for 2013-2017. We determined the childhood TB case notification rate in the MRRH catchment area, performed a TB case notification rate trend analysis and described spatial TB case distribution. We used logistic regression to identify patient-related and hospital-related factors associated with completion of TB treatment at MRRH among HIV-positive and HIV-negative patients.

Results: We identified 331 TB case notifications among children <15 years. TB case notification rates declined from 6.6/100,000 in 2013 to 2.2/100,000 in 2017 [odds ratio (OR)=0.81; 95% confidence intervals (CI)=0.58-1.1]. Mbale District recorded the highest TB case notification rate (79/100,000), and Kapchorwa District recorded the lowest TB case notification rate (3.8/100,000). Completion rates varied from 35% to 80%. Of the 331 patients, 167 (50%) completed TB treatment. In logistic regression, 142 (75%) of 189 HIV-negative TB patients completed TB treatment compared to 25 (54%) of 46 HIV-positive TB patients (OR=2.5; 95%CI=1.3-4.9). Seventy-four (63%) of 117 patients in the facility-based model and 93 (79%) of patients in the community-based model completed TB treatment (OR=0.47; 95% CI=0.26-0.83).

Conclusions: Only half of childhood TB patients completed treatment, well below the WHO target of $\geq 85\%$ completion. Although TB completion was associated with treatment model and HIV-negative status, neither HIV-positive nor HIV-negative patients had acceptable completion rates. MRRH should strengthen HIV treatment services among childhood TB patients by engaging peer groups and trusted community leaders to provide education on the importance of completing TB treatment.

Background

Tuberculosis (TB) is an airborne bacterial infection that affects persons of all ages [1]. Tuberculosis bacteria can survive in the body as a latent infection or active disease; active disease can be transmitted to others when an infected person coughs, sneezes, or speaks near an uninfected person [2, 3]. At least one-third of the global population is estimated to harbor latent TB infection, and up to one-quarter of these will develop active TB at some point during their lifetime [4, 5]. However, persons with compromised immune systems, such as persons living with HIV, renal insufficiency, silicosis, diabetes, and other co-morbidities have a much greater risk of developing active TB [6].

Because of their immature immune systems, children (especially children < 2 years of age) are also considered a high-risk group for developing active TB [7]. Globally, there was an estimated one million two hundred thousand (1,200,000) cases of childhood TB and two hundred and thirty thousand related deaths (230,000) deaths in 2019, mostly in South-East Asia and Africa [8]. From a public health perspective, childhood TB is of particular concern for two reasons. First, not only do they carry latent TB infection, which may progress to active TB disease in adults, but but cases in children are also reflective of poor recent TB control [9]. However, the disease is notoriously difficult to diagnose in children, partly because the symptoms of childhood TB can be non-specific, especially in the early stages, and partly due to the paucity of TB bacilli in sputum samples and the difficulties of obtaining a good sputum sample from a child [10]. Due to these difficulties, TB in children is often neglected by health care professionals, scientists, and policymakers. Even drug makers have historically excluded children from TB drug trials [11, 12].

Like adult TB treatment, childhood TB treatment can be complex and difficult. All children diagnosed with TB are treated with four medicines (Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and Ethambutol (E)). The duration of treatment ranges from six to nine months, depending on the site of disease, and requires regular follow-up at clinic visits, for weight checks to ensure proper dosing and to ensure that the patient is adherent [10, 13]. According to the World Health Organization (WHO), the minimum targeted TB treatment completion rate is 85% [14]. Failure to complete treatment leads to persistence of infection, drug resistance, continued TB transmission, and increased mortality [15–17].

In 2013, the National Tuberculosis and Leprosy Programme (NTLP) strengthened efforts to improve diagnosis and treatment outcomes of TB in children in Uganda, including through appointment of a national pediatric TB focal person and mentorships in pediatric TB care, recording, and reporting [18]. However, understanding the impact of these interventions has been difficult, as data on pediatric TB treatment completion rates in Uganda are sparse. The first major TB prevalence evaluation, conducted in 2015/2016, excluded children < 15 years of age. Although data are available on treatment completion rates in adults in Uganda, there are no programmatic data on completion rates for TB pediatric cases [19]. To provide information about the status of childhood TB in Uganda and evaluate the impact of interventions, we analyzed reported childhood TB case notifications in Eastern Uganda from 2013–2017, established the spatial distribution of cases, evaluated treatment outcomes, and identified predictors of treatment completion. These data will provide a baseline for monitoring the effect of interventions for prevention and control of childhood TB and help guide decision-making for public health.

Methods

Study setting

This study was conducted at Mbale Regional Referral Hospital (MRRH) in Mbale District, Eastern Uganda. MRRH is a referral facility for 14 districts in Eastern Uganda [20, 21] and is also the major provider of TB diagnosis and treatment services for the catchment area.

Study design and population

We reviewed secondary TB data that are routinely collected within the catchment area of MRRH. We extracted data from TB registers for children under 15 years of age treated for TB at MRRH during 2013–2017. We excluded patients whose residence was outside the catchment area of MRRH.

Data source

The TB register is a TB patient data collection tool that is regularly provided by the National Tuberculosis and Leprosy Programme (NTLP) of the Uganda Ministry of Health to all health facilities in the country. The register is filled by attending physicians at the health facility. Data from the tool are summarized monthly in MS Excel by the TB unit in Health Management Information System (HMIS) Form 105 and quarterly in HMIS Form 106a in Microsoft Excel and shared with the Ministry of Health.

Data abstraction

We captured the following variables, using a pretested data abstraction form: patient location/residence (≤ 20 km or ≥ 21 km away from MRRH), age ($0 \leq 4$, $5 \leq 9$, and $10 \leq 14$ years old), sex (female or male), type of TB patient ['existing' (already on treatment at time of first presentation at MRRH), or 'new' (treated for the first time at MRRH)], TB classification (pulmonary clinically-diagnosed tuberculosis, extra-pulmonary tuberculosis [TB in other body organs such as gastrointestinal tract, kidneys, spleen], and pulmonary bacteriologically-confirmed tuberculosis), HIV status (positive or negative), treatment model (facility-based or community-based treatment model), and treatment outcome (completed TB treatment or not). For children < 18 months, a virological test for HIV was used instead of serology. Facility-based model was defined as daily drug administration at a health facility, supervised by a healthcare worker, while community-based model was defined as supervision of daily drug administration at home by a personal contact. Failure to complete treatment comprised persons who defaulted/were lost to follow-up or who died before completing treatment. Persons who were documented as having transferred to another site before completing treatment at MRRH were not included in the bivariate and multivariate analyses.

Data management and analysis

We entered data into Epi Info version 7.2.2.6. Missing data and outliers were identified and corrected, where possible, using the TB registers or talking to the lead of the TB unit and his or her colleagues. We computed the TB case notification rate per 100,000 population among persons aged 0–14 years (Note: Denominator was the annual total number of children presented with symptoms and signs suggestive of TB or screened for TB at MRRH) and performed a trend analysis of childhood TB over time using logistic regression. We used QGIS to draw an area map to show the spatial distribution of childhood TB cases based on the patients' home addresses. We also analyzed by age groups ($0 \leq 4$, $5 \leq 9$, and $10 \leq 14$) and then separated out categories due to the following reasons: 1) Younger children less than 2 years have a greater risk of active TB disease compared to those above 2 years, 2) HIV positive children aged less than

12 months receive Isoniazid Preventive Therapy (IPT) only if there is a history of contact with an active Pulmonary TB case. Factors associated with treatment completion were evaluated by chi-square test. Logistic regression (Epi Info version 7.2.2.6) was used to test for predictors of treatment completion, and odds ratios (OR), adjusted odds ratios (aOR) and 95% confidence intervals (CI) were calculated. Only factors significant at bivariate analyses were included in the multivariate analysis model.

We conducted a trends analysis. Statistical significance of the trend was determined using logistic regression. A $p < 0.05$ was used to indicate statistical significance.

Results

During 2013–2017, we identified 331 TB childhood TB patients at MRRH, including 111 (34%) TB cases in 2013, 38 (11%) in 2014, 81 (24%) in 2015, 59 (17%) in 2016 and 42 (13%) in 2017. Fifty-eight children were excluded. Of the 331 patients, 175 (53%) were males, and the mean age was 6.1 years (range: 2 months – 14 years). The largest subgroup among the TB patients was children < 5 years, comprising 148 (45%) TB patients. In total, 222 (67%) had clinically-diagnosed pulmonary TB, 44 (13%) had bacteriologically-confirmed pulmonary TB, and 65 (20%) had extrapulmonary TB (Table 1).

Table 1
Clinical Characteristics of Tuberculosis Patients Aged 0–14 Years at Mbale Regional Referral Hospital in Eastern Uganda, 2013–2017

Characteristics	Patients n = 331	Percent
Age (years)	33	10
< 1	62	19
1–2	53	16
3–4	97	29
5–9	86	26
10–14		
Sex	175	53
Male	156	47
Female		
Type of Patient	327	99
Newly initiated on TB treatment	4	1
Already on TB treatment		
TB Classification	222	67
PCD	65	20
EP	44	13
PBC		
HIV status	72	22
Positive	259	78
Negative		
Facility Based Treatment Model	173	52
Yes	158	48
No		
TB: Tuberculosis; HIV: Human immunodeficiency virus; PCD: Pulmonary Tuberculosis Clinically Diagnosed; EP: Extra pulmonary Tuberculosis; PBC: Pulmonary Tuberculosis Bacteriologically Confirmed		

TB trend analysis of case notification among children aged 0–14 years in the catchment area of MRRH showed a nonsignificant decline from 6.6/100,000 in 2013 to 2.2/100,000 in 2017 (OR = 0.81; 95% CI

0.58–1.1) (Fig. 1). TB patients originated from 12 districts, with case notification rates generally declining with increasing distance from MRRH. Mbale District (which includes MRRH) had the highest TB case notification rate (79/100,000), and Kapchorwa District had the lowest case notification rate (3.8/100,000) (Fig. 2).

Of 331 childhood TB patients, 167 (50%) completed TB treatment. Among districts reporting at least 10 cases, completion rates ranged from 29–80% (Table 2); however, several districts had too few cases notified to reliably calculate their completion rates. Of 164 childhood TB patients that did not complete TB treatment, 96 (59%) were documented as having transferred out before completion (data not shown). Among 30 TB patients who died, 28 (93%) did not complete TB treatment (data not shown). Because their time and cause of death were not documented, it is not known whether their death was a cause or effect of their failure to complete treatment. Of the five patients with multidrug-resistant (MDR)-TB, four (80%) did not complete TB treatment at MRRH and subsequently died (data not shown).

Table 2
Differences in Completion of Tuberculosis Treatment among Districts in the Catchment Area of Mbale Regional Referral Hospital in Eastern Uganda, 2013–2017

District	TB treatment Completion (N = 167)	TB treatment Non-completion (N = 164)	% Completion of TB treatment
Mbale	92	100	48
Budaka	14	16	47
Sironko	8	15	35
Manafwa	15	6	71
Butaleja	5	9	29
Tororo	7	6	54
Bulambuli	8	2	80
Busia	8	1	-
Pallisa	6	2	-
Bududa	1	4	-
Kibuku	2	2	-
Kapchorwa	1	1	-

*** Dashed line (-) indicates too few tuberculosis cases notified to reliably calculate completion rate. TB: tuberculosis**

Among 189 HIV-negative and 46 HIV-positive TB patients who did not transfer from MRRH during their treatment, 142 (75%) HIV-negative patients and 25 (54%) HIV-positive patients completed TB treatment

(OR = 2.5; 95% CI = 1.3–4.9) (Table 3). Among 117 patients who were treated with the facility-based model and 118 patients who were treated with the community-based model, 74 (63%) patients using the facility-based model and 93 (79%) using the community-based model completed TB treatment (OR = 0.47; 95% CI = 0.26–0.83). Persons with clinically-diagnosed TB had lower odds of completing TB treatment, compared with persons diagnosed in other ways (OR = 0.46; 95% CI = 0.21-1.0) (Table 3).

Table 3

Variables Associated with Treatment Completion of Tuberculosis at Mbale Regional Referral Hospital in Eastern Uganda, 2013–2017

Independent variable	Percent of Treatment Outcomes		Crude OR (95% CI)	aOR (95% CI)
	Completed (n = 167)	Not completed (n = 68)		
Age (years)	44	49	1	
0–4	32	22	1.6 (0.79–3.2)	
5–9	26	29	0.93 (0.47–1.8)	
10–14				
Sex	50	40	1	
Female	50	60	0.67 (0.38–1.2)	
Male				
Patient type	99	98.5	1	
New ^a	1	1.5	0.40 (0.025–6.5)	
Already on treatment ^b				
TB classification	23	13	1	
EP	18	12	0.89 (0.31–2.6)	
PBC	59	75	0.46 (0.21–1.0)	
PCD				
HIV status	15	29	1	1
Positive	85	71	2.3 (1.3–3.9)*	2.5 (1.3–4.9)*
Negative				
Treatment model	56	37	1	1
Community-based	44	63	0.46 (0.26–0.83)*	0.47 (0.26–0.84)*
Facility-based				
* indicates significant values; aOR: adjusted odds ratio; CI confidence interval; PCD: Pulmonary Tuberculosis Clinically Diagnosed; EP: Extrapulmonary Tuberculosis; OR: odds ratio; PBC: Pulmonary Tuberculosis Bacteriologically Confirmed; TB: tuberculosis; a: Newly initiated on TB Treatment; b: Already on TB Treatment; HIV: Human immunodeficiency virus; HIV status and Treatment model were included in the aOR model.				

Discussion

Our investigation demonstrated that the childhood TB treatment completion rate at MRRH in Eastern Uganda was well below the minimum completion rate recommended by the WHO [14]. Children living with HIV were less likely to complete TB treatment compared to children without HIV and children in the community treatment model were more likely to complete TB treatment than children in the facility based model. TB notification rates varied widely across districts in Eastern Uganda and were highest in the district with the regional hospital. Although TB case notifications declined over the evaluation period (2013–2017), the trend was not statistically significant.

The completion rate of childhood TB treatment for our study population was only 50%. Failure to complete treatment leads to increased transmission, increased risk of multi-drug-resistant TB, and increased mortality [15–17]. Indeed, in our study, of the TB patients who died, nearly all failed to complete treatment. Other studies that evaluated poor completeness of TB treatment in Kenya and South Africa found associations between poor completion rates and a knowledge gap about TB, TB stigma, poverty, and lack of follow-up of the TB patients during treatment [22, 23]. It is possible that some TB patients did not complete TB treatment because the patient failed to return, and no one at the facility followed them up, or they died and were thus unable to complete treatment, as identified in a TB pediatric study in the rural communities of Uganda and Kenya [23]. Unfortunately, we were unable to determine the reasons for patient death from our data because the cause of death was not recorded. Additional studies about the causes of incomplete TB treatment in Eastern Uganda could facilitate the development of targeted interventions.

TB notification rates varied across districts in Eastern Uganda during the study period. Increasing distance (beyond 10km) from the hospital was associated with declines in notification rates. This may be reflective of differences in reporting and completion rates between districts. However, it also may be related to the ease of access to MRRH and/or TB treatment for persons living in Mbale, or to the relative urbanity of Mbale District, compared with other districts. Increased population density and urban settings, such as those that exist in Mbale town, are well-known to increase the risk for TB [24–27]. A small study using active surveillance approaches across this region would inform the existing data and could yield important insights into the differences in reporting rates.

Childhood TB is a sentinel for infectious adult TB cases [28], as children are most often infected by adults in their homes or close social networks [28]. It is reasonable to assume that the childhood TB cases reflect adult infections in the area. In Uganda, TB infection control include recommendations to reduce TB exposure in households, including adequate ventilation, appropriate cough etiquette and hygiene, separation of smear-positive persons from uninfected persons, and screening and treatment of household members of infected persons [29]. Other studies in Uganda have found that TB infection control practices were not being implemented in some health facilities, primarily due to lack of resources. In addition, poor ventilation was frequently a problem in households with TB patients [30–32]. To fully address the problem of childhood TB, these issues will need to be tackled in full.

Although there was a decrease in the TB notification rates at MRRH from 2013 to 2017, the trend was not significant. This is largely due to annual fluctuations in the notification rates. The reasons for the fluctuations aren't clear. A larger study might identify a more obvious pattern. If a true decline exists, it might be associated with the recent scale-up of Anti-Retroviral Therapy (ART) at MRRH as pointed out in a study in African countries [33]. In 2013, in order to increase access to ART and improve clinical outcomes, the Uganda Ministry of Health began recommending that all HIV-infected children under the age of 15 years must be initiated on Highly Active Antiretroviral Therapy (HAART) at the time of diagnosis (15); this would have been expected to lead to a decline in TB cases [34–36]. Examination of national routine TB data might be useful in informing the true patterns of childhood TB in this region.

Poor completion of TB treatment among children aged 0–14 years at MRRH in Uganda was associated with HIV infection; three-quarters of patients with TB completed treatment, compared with only half of TB/HIV coinfecting patients. Other studies in Democratic Republic of Congo, Ethiopia, Nigeria, Ghana and Vietnam have identified similar results [37–42]. There may be multiple factors that influence this finding: HIV-infected patients may be more prone to depression, lowered family support, and reduced income, which could impact their treatment adherence [43]. Other factors, such as the high pill burden associated with multiple treatments, the dependency on a caregiver to administer the medication, the bad taste or challenges of administering medications to a child, or the side effects, may make adherence and completion challenging [44]. TB patients with HIV infection may need special attention as they proceed through their TB treatment to ensure adherence and completion.

In our investigation, community-based treatment was a better model, in terms of completion, than facility-based treatment. Community-based treatment models allow a patient to complete treatment in their own homes, under the supervision of a close contact. This incurs fewer transportation costs to the patients, and in some cases provides better home care and improved social wellbeing as well as an improved ability to continue with daily activities [45–48]. Specifically, rural community-based models have been shown to be more effective than urban community-based models, in part due to the organized referral system in rural settings and perhaps due to the increased advantages of not traveling to a distant clinic for care [29]. Facility-based models have the advantage of higher-quality monitoring; however, for improvements in treatment completion, they may be best suited for patients who either live near to a clinic or require daily clinical care for other reasons.

A key strength to this project is that it will provide a baseline for monitoring the effect of interventions for prevention and control of childhood TB and help guide decision-making for public health.

Our investigation had some limitations. We only reviewed secondary TB data that were routinely collected within the catchment area of MRRH in Eastern Uganda. These data did not include variables that could have further informed our analyses, such as date or causes of patient death, or facility to which the patient transferred. This might have led to an underestimation of the completion rate of TB treatment and missed opportunities to further explore the association between treatment completion and death. In

addition, the completeness of reporting was not known, preventing our evaluation of the validity of the declining trends in notification rates.

Conclusions

The childhood TB treatment completion rate in Eastern Uganda was well below the WHO target rate of at least 85%. Poor TB completion was negatively associated with HIV-positive status and positively associated with community treatment models. TB notification rates varied across districts in Eastern Uganda. To improve completion of TB treatment, MRRH should strengthen HIV treatment services among childhood TB patients through engaging peer groups and trusted community leaders. Data systems should be strengthened and combined with routine analysis for pediatric TB cases, to demonstrate the importance of data quality. MRRH should further strengthen community-based TB treatment models through continued sensitization of the communities with its catchment area. The Ministry of Health should enhance education of TB patients on the importance of completing TB treatment and conduct retrospective, longitudinal studies to identify the root causes of low TB completion rates as a first step. A small study using active surveillance approaches across this region would inform the existing data and could yield important insights into the differences in reporting rates.

Abbreviations

aOR

adjusted odds ratio, CI:confidence interval, DHO:District Health Officer, EP:Extra Pulmonary Tuberculosis, HIV:Human Immunodeficiency Virus, HMIS:Health Management Information System, ICF:Intensified Case Finding, IRB:Institutional Review Board, MDR TB:Multi-Drug Resistant Tuberculosis, MRRH:Mbale Regional Referral Hospital, NTLP:National Tuberculosis and Leprosy control Program, OR:odds ratio, PBC:Pulmonary Tuberculosis Bacteriologically Confirmed, PHFP:Uganda Public Health Fellowship Program, PCD:Pulmonary Tuberculosis Clinically Diagnosed, QGIS:Quantum Geographical Information System, TB:Tuberculosis, US CDC:United States Centers for Disease Control and Prevention.

Declarations

Ethical approval

We sought permission and approval to conduct this analysis from Ministry of Health and administration of MRRH. Further clearance was sought from the Uganda Public Health Fellowship Program (PHFP) and US CDC, which determined that this activity was not human subjects research.

Consent for publication

Not applicable

Availability of data and materials

The datasets upon which our findings are based belong to the MRRH and the Uganda Public Health Fellowship Program. The datasets generated and /or analyzed during the current study are not publicly available due to confidentiality reasons. However, the datasets can be availed upon reasonable request from the corresponding author and with permission from the MRRH and the Uganda Public Health Fellowship Program.

Competing interests

The authors declare that they had no competing interests.

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Authors' contributions

FM designed the study, and took lead in data collection, analysis, interpretation and drafting of the manuscript. YO and DK supervised and provided technical assistance for protocol development, project design, data collection, analysis, and abstract and manuscript development. LB participated in the project design, analysis, and data interpretation. ARA participated in protocol development, project design, data collection, analysis, and TB data interpretation. JRH reviewed the manuscript for intellectual content and approved it for publication. All the authors reviewed the manuscript to ensure scientific integrity and intellectual content.

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Figures

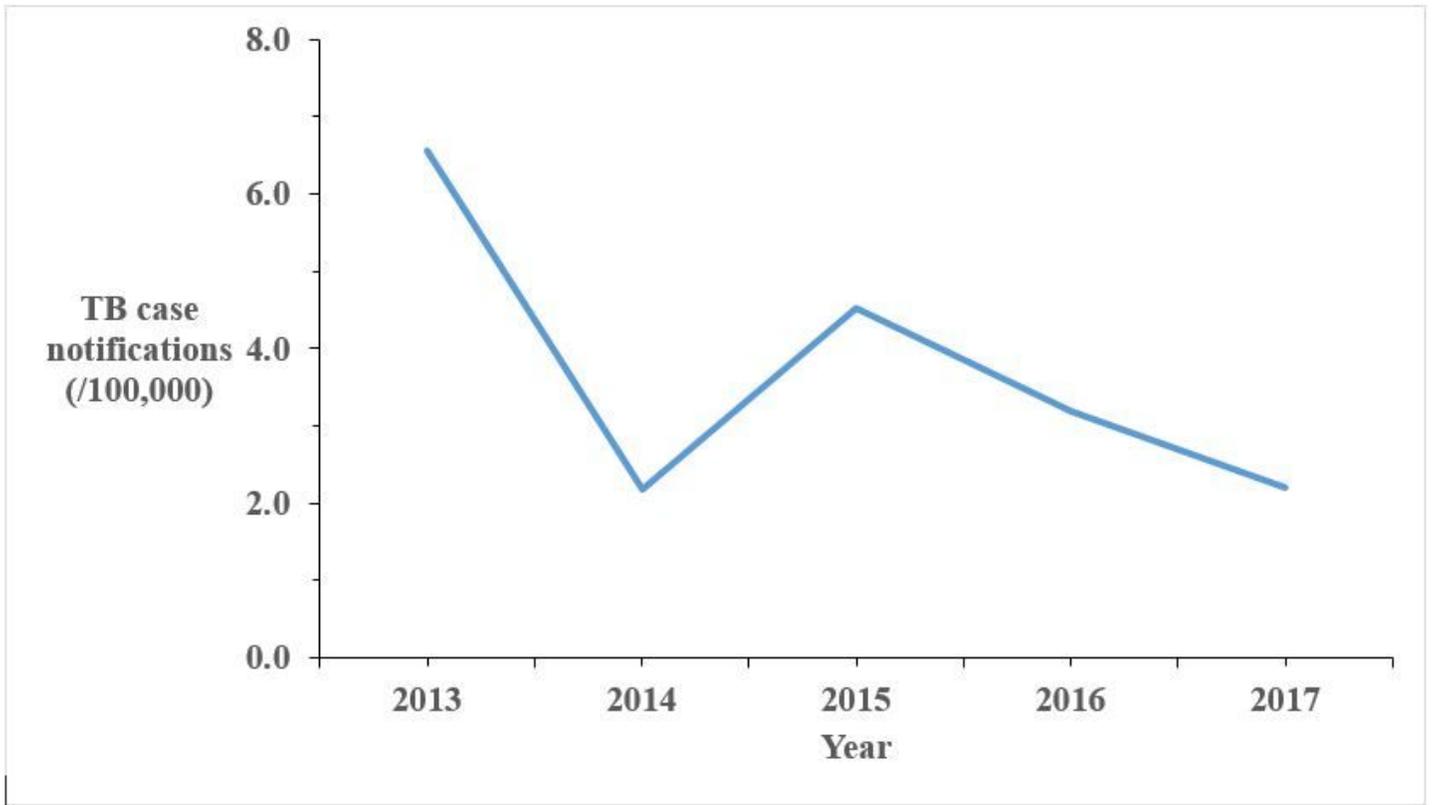


Figure 1

Trends of Tuberculosis Case Notification Rates among Children under 15 years at Mbale Regional Referral Hospital in Eastern Uganda, 2013-2017

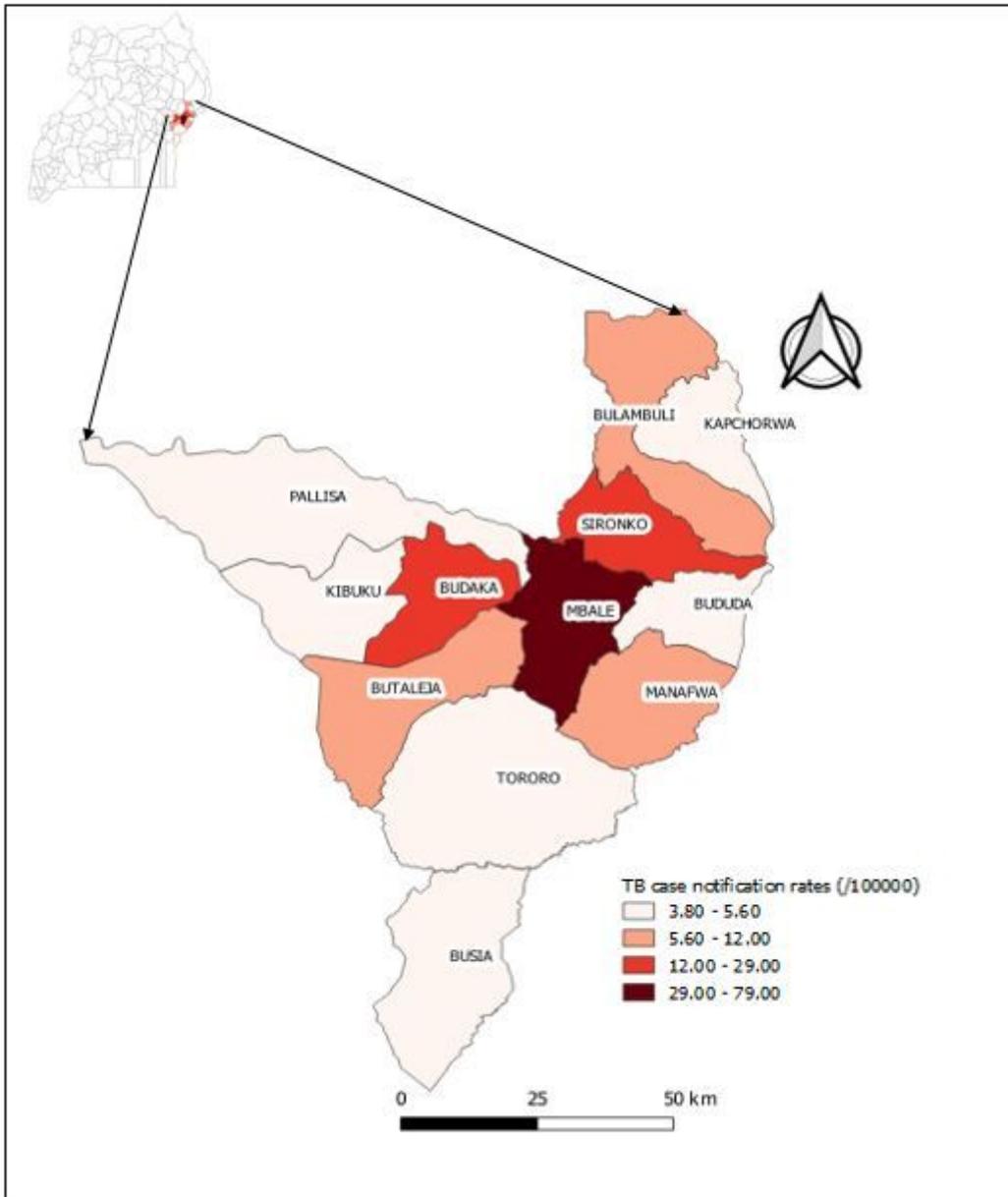


Figure 2

Tuberculosis Case Notifications among Children under 15 years at Mbale Regional Referral Hospital by District of Residence in Eastern Uganda, 2013-2017 Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.