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Outcome of Children with Presumptive Tuberculosis in Mbarara, Rural Uganda

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ABSTRACT

Background

Mortality among children with presumptive tuberculosis (TB) empiric TB treatment can be high. We describe the predictors of death among children with presumptive TB, and the relation between treatment and mortality.

Methods

A prospective cohort of children with presumptive TB who underwent clinical assessment, chest radiograph, tuberculin skin test and sputum bacterial tests for TB was followed up for 3 months. TB diagnosis was based on mycobacterial, clinical and radiologic findings. Predictors of deaths were determined using cox regression model.

Results

Of 360 children included in the analysis, 31.4% were younger than 2 years; 31.6% were HIV infected and 11.3% were severely malnourished. One hundred forty (38.9%) were diagnosed with TB, 18 (13%) of whom were bacteriologically confirmed. At 3 months of follow up, 25/360 (6.9%) children had died: 15/140 (10.7%) were receiving TB treatment vs 10/220 (4.5%) were not receiving treatment (p=0.025). Severely malnourished children (aHR 9.86, 95%CI 3.11-31.23) and those with chest radiographs suggestive of TB (aHR 4.20, 95%CI 0.93-19.01) were more likely to die. Children receiving empiric TB treatment had an increased risk of death (aHR 2.37, 95%CI 1.01-5.55) compared with children without treatment after adjustment for age, sex, HIV status and BCG vaccination.

Conclusions

The high mortality in children receiving empirically TB treatment highlights the difficulty in diagnosing childhood TB, the increased likelihood of starting treatment in critically ill children

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and in children with chronic disease, and the possibility of misdiagnosis. It strengthens the need to invest further in early TB detection and diagnosing non- severe illness.

Key words: tuberculosis, treatment, children, mortality

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INTRODUCTION

In 2015 the WHO estimated that there were one million new cases of tuberculosis (TB) and 210,000 deaths due to TB among children[1]. However, only one third of estimated cases (359,000) were notified to the WHO due to the lack of effective tools to diagnose TB in children, especially in resource limited settings. The pauci-bacillary nature of TB disease and challenges to obtain quality specimens in children reduces the yield of TB diagnostic tests, such as XpertMTB/RIF and culture, especially in young children[2–4]. This situation leads to the prescription of empiric TB treatment in most of the presumptive TB cases, without confirmation of disease.

Previous studies show that mortality of childhood TB in limited resource countries can vary between 6 and 11% with a trend of higher mortality among younger children[5–8]. In some sub-Saharan African countries, especially during the pre-antiretroviral therapy era, higher mortality was documented among smear-negative cases and HIV infected children, highlighting the issue of potential misdiagnosis and co-infections[6,9]. In the absence of a reference standard for diagnosis of childhood TB, the accuracy of treatment decisions cannot be adequately assessed[10]. This study aimed to describe mortality and predictors of death in children with presumptive TB, and to assess the relation between TB treatment and mortality.

METHODS

Study population

The study was a prospective observational cohort of children aged one month to 14 years presenting to the pediatric outpatient and inpatient units of Mbarara regional referral hospital, Uganda with presumptive TB. Presumptive TB was defined by the presence of at least one of the following symptoms or signs: reported fever for 7 days after exclusion of malaria; non -

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remittent cough or wheeze, night sweats, chest pain or unexplained apathy or reduced playfulness for the last 2 weeks; unexplained weight loss or documented failure to thrive over the past 3 months despite adequate nutrition and deworming; painless superficial lymph node mass(es); recent gibbus; or abdominal distention with ascites. Children with meningitis with lymphocytic predominance in cerebro-spinal fluid (CSF) or meningitis not responding to antibiotic treatment and those with a chest x-ray suggestive of TB were also eligible to be included in the study[11]. Children who completed a full course of TB treatment in the past 6 months, who were on treatment $\geq$ 3 days or on isoniazid prophylaxis and children living outside a 20km radius around Mbarara city, were excluded.

Procedures

At initial assessment, the parent/guardian was interviewed about the child's medical history, household TB contact history with a smear- or culture positive TB index case and child's symptoms followed by a physical exam. BCG vaccination was documented by the observation of a BCG scar or verbal information by the guardian. Tuberculin skin test (TST) was done using an intradermal injection of 2 tuberculin units (1 mL) of purified protein derivative 23 (Statens Serum Institute, Copenhagen, Denmark). Five and ten mm cut-off were used to define positive results for HIV infected and non-infected children, respectively regardless on nutritional status[12]. Postero-anterior and lateral chest x-ray digital images were obtained for all children, read and recorded by the doctor on-site using pre-determined tick-sheets and classified according to a structured approach as follows: "normal", "abnormal suggestive of TB" or "abnormal non-suggestive of TB" (Supplemental Digital Content, http://links.lww.com/INF/C812). A suggestive x-ray was defined by presence of hilar/paratracheal adenopathy with/without airway compression, airspace opacification not responding to antibiotics or with documented TB

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contact, lung cavities or miliary infiltrates. Children were offered HIV testing using the nationally approved testing algorithm with PCR confirmation for positive children younger than 18 months[13]. Two sputum specimens were collected over 2 consecutive days using induced sputum for children unable to produce specimen, pooled and tested with XpertMTB/RIF assay (Cepheid, Sunnyvale, US), two Lowenstein Jensen (LJ) cultures and one MGIT culture from each sputum sample at the Mbarara Epicentre Research Laboratory. Similar tests were performed on extra-pulmonary specimens collected according to the clinical presentation. Bacterial culture, cryptococcal antigen test, microscopy examination for cryptosporidium and cytology from lymph node aspiration or biopsy were irregularly available at the hospital laboratory. After initial assessment, children with any positive TB bacteriological test, chest x-ray or clinical presentation that were suggestive of TB disease according to an experienced pediatrician were started on TB treatment using rifampicin (R), isoniazid (H), pyrazinamide (Z) FDC for 2 months followed by 4 months of HR under drug observation by a family member[14]. Ethambutol (E) was added to the regimen during intensive phase in the presence of extensive disease (excluding TB meningitis), smear-positive results, HIV infection and/or suspicion of isoniazid drug resistance[15]. HIV infected children were referred to the hospital HIV clinic for appropriate treatment. Children started on TB treatment were followed monthly for 6 months with a last visit at month 12, and children who were not started on treatment had an additional study visit after 3 months.

Retrospective tuberculosis case classification:

Digital images of chest x-ray were all read by an external radiologist who was blinded to the child's clinical presentation. The onsite reading and all patients' files were retrospectively reviewed by two independent senior pediatricians using the 2012 published consensus case definitions for childhood TB classifying children as confirmed, probable, possible, unlikely and

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not TB[16]. Possible cause of death was proposed after the review of serious adverse event reports and patients' file by two study clinicians including one senior pediatrician.

Sample size and data analysis

Consecutive children with presumptive TB were recruited over 2 years. Data were entered using Voozanoo (Epiconcept, Paris, France) and were analyzed using Stata® 13 software (College Station, Texas, USA). Baseline children's characteristics (demographic, medical history, TB exposure, clinical, radiologic and bacteriologic) were summarized using frequencies and percentages for categorical variables, and medians and interquartile ranges (IQR) for continuous variables; and were compared across groups of children started on TB treatment confirmed with TB (at treatment start using Xpert or later with culture results); started on treatment without bacteriological confirmation (empirical treatment) and not treated for TB. Survival analysis using Kaplan-Meier estimates was performed separately for the three groups. After initial assessment, all patients were censored at the date of death or at 3 months. Predictors of death among baseline characteristics were explored using univariate and multivariate Cox regression model. Covariates associated with a p-value <0.4 in univariate analysis were included in the initial multivariate model; a manual backward stepwise approach was used to obtain the final multivariate model. Statistical significance ($p< 0.05$) was assessed with the likelihood-ratio test. In addition, the association between the decision to initiate treatment and mortality was assessed after adjusting on baseline characteristics that were not directly associated with the treatment decision (age, sex, HIV status and BCG vaccination).

The study was approved by the Mbarara University Research Ethics Committee, the Uganda National Council for Science and Technology and The Comité de Protection des Personnes of Ile

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de France XI, Saint-Germain, Laye, France. Written informed consent was given by the parent or legal guardian and assent by children of 7 years or older.

RESULTS

Out of 392 patients enrolled between April 2012 and January 2014, 144 (36.7%) were started on treatment. Majority (126/144, 87.5%) of them were not bacteriologically confirmed (Figure 1). A total of 32 (8.2%) children were lost to follow-up and excluded from the analysis. This resulted in a total of 360 children: 18 treated with TB confirmation, 122 treated empirically and 220 not treated. Children treated empirically were more likely to be younger and malnourished as compared to the two other groups of children. Of the 18 children treated with TB confirmation, 13 (72.2%) had MTB detected using Xpert (Table 1). A 2 years old HIV infected child with severe malnutrition and confirmed TB by Xpert died 7 days later at home without been started on TB treatment because parents left the ward before the child's discharge and the family could only be traced after few days. This child was analyzed in the group of non-treated cases. Of the 122 children on empirical treatment, 38 (31.1%) were classified as probable TB using the consensus case definitions for childhood TB. Of the 220 children not treated, 205 (93.2%) were classified as unlikely or not TB (Table 2).

A total of 25/360 (6.9%) children died during the first 3 months of follow-up, 15/140 (10.7%) among children treated for TB vs 10/220 (4.5%) among children not treated, p=0.025. None of the 18 treated TB confirmed children died versus 15/122 (12.3%) for the group of children treated empirically (Figure 2). The estimated cumulative mortality at 1 month of treatment in children started on empirical treatment was 9.8%, (95%CI 5.7 – 16.7) whereas in the group of children not treated it was 3.2%, (95%CI 1.5 – 5.6) (Figure 2). The median time to death was 11 days [IQR 7 – 22] vs 20 days [IQR 11 – 34] in the groups of children treated empirically and

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children not treated, respectively. Most children who died were younger than 2 years (60.0%). Severe malnutrition (47.8%) and HIV infection (44.0%) were common among children with a fatal outcome (Table 3). Although non-significant, there was 2-fold increased risk of death related to not having a BCG scar. Of 121 children started on empirical treatment, 30 (24.5%) were HIV-positive, and of them 18 were on ART at the time of TB diagnosis. There was a trend on higher mortality in the group of HIV-positive children not on ART (6/22, 26.3%) as compared to those already on ART (2/18, 11.1%) or who were HIV-negative (7/81, 8.6%), p=0.06.

Using the consensus case definitions for childhood TB, out of the 15 deaths from the group of children treated empirically for TB, two were classified as probable TB. However, in one of the two cases, death occurred three months after starting treatment and was due to chicken pox. For the second child, death occurred two days after starting TB treatment in a context of jaundice, hematemesis and fever. The other causes of death for children on empirical treatment classified as unlikely TB, not TB or unclassified were severe pneumonia with comorbidities for 12 children (HIV infection without ART and severe malnutrition in 8 cases and only severe malnutrition in 4 cases) and suspicion of lymphoma in one HIV-positive child. Of the children non started on TB treatment, the causes of death were tuberculosis (n=1), acute cardiac failure with valvular heart disease (n=2); severe malnutrition with nephrotic syndrome (n=1); empyema due to staphylococcal pneumonia (n=1); pyogenic pneumothorax without bacterial identification (n=1); hypovolemic shock due to severe diarrhea and malnutrition (n=1); suspicion of central neurological opportunistic infection in HIV infected children failing ART (n=2) and bacteriologically unconfirmed severe pneumonia in a HIV infected child (n=1). Among children started on empirical TB treatment, the case fatality of children classified as probable or possible

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TB was 3.9% (3/76) vs 24.3% (9/37) for children classified as unlikely TB or not TB, p=0.001 (Table 2).

Patients' baseline characteristics independently associated with mortality were severe malnutrition (aHR 9.86, 95%CI 3.11-31.23) and chest X-ray suggestive of TB (aHR 4.20, 95%CI 0.93-19.01) (Table 3). In univariate analysis, patients who were admitted after receiving a non-specific antibiotic course within the past two weeks were more likely to die than children who did not receive antibiotics (HR 3.5 95%CI 1.12-12.53). Although not significant, there was a trend on higher mortality among HIV-positive children not on ART as compared to HIV-negative children. After excluding baseline patients' characteristics that could be included in the decision to start or not a TB treatment at initial assessment (chest x-ray findings, TB contact history, and weight for height score), being started on empirical TB treatment was independently associated with death (aHR 2.37, 95%CI 1.01-5.55) compared to no treatment after adjustment for sex (female aHR 0.49 [0.20-1.18] and age (2-5years aHR 0.34 [0.11-1.04], 5-10 years aHR 0.42 [0.13-1.33] and >10 years aHR 0.39 [0.88-1.78]).

DISCUSSION

In this cohort, we report more than 2-fold increase of deaths among children started on TB treatment compared to those not treated (10.7% vs 4.5%), and among treated children all death occurred among those started on empiric treatment. The mortality of children treated for TB is similar to what has been reported in previous studies[5–9]. Retrospective cohort studies have shown a trend of increased mortality in smear-negative children as compared to smear-positive ones[5,6,9]. Using more sensitive tests than microscopy (Xpert and culture), our study confirms this trend with no death among children treated with TB confirmation vs 12.3% among children treated empirically. While previous studies have shown an increased mortality among HIV-TB co-

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infected children, our study was not powered to evaluate the effect of HIV[6]. However, we noticed a trend of higher mortality in the group of HIV-positive children who were not on ART at the time of TB diagnosis. This highlights the needs of systematic HIV screening during pregnancy and access to early ART for infected children. The trend of lower mortality among children without BCG scar is consistent with previous studies reporting non-specific effects of BCG vaccination beyond the protecting effect against tuberculosis, that could be explained by the epigenetic modulations in monocytes and increased responsiveness against unrelated stimuli[17,18]. Comparative mortality data for the group of non-treated children admitted for presumptive TB are very scarce. However, the mortality (4.5%) was close to what has been recently reported for admitted children including post discharge mortality from high HIV burden countries[19,20]. The low proportion of non-TB treated cases retrospectively classified as confirmed or probable TB (1%) seems to indicate that the risk of missed diagnosis of TB was low in this cohort.

The increased mortality in the group of children receiving empirical treatment most likely reflects the increased likelihood of initiating an empiric TB treatment in children with either critical conditions, comorbidities or younger age and TB exposure[14,21]. Indeed, there were significantly more malnourished and younger children in this group compared to the two other groups. Both factors are known to be associated with an increased risk of death[14,20,22]. In our cohort, majority of deaths (12/15) from the group of TB treated children, occurred in severely malnourished children presenting with severe pneumonia. However, although malnutrition is known to increase the pneumonia-related mortality and children with severe malnutrition treated for pneumonia might have TB, the role of TB remains still unclear mainly due to the difficulty of TB diagnosis in this population[23–26].

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The other issue raised from the high mortality among children treated empirically is the risk of misdiagnosis of other infection or disease, especially in children with comorbidities. The proportion of potential misdiagnosis and its impact on mortality is very difficult to estimate in settings with limited diagnostic capacity and without autopsy report. Only 2/3 of children started on empirical TB treatment were retrospectively classified as probable or possible TB (67.3%). This might indicate a non-negligible proportion of children who did not require TB treatment.

The study had several limitations: i) The main limitation was the absence of autopsy reports that prevent knowing how much TB contributed to death; ii) The lack of diagnostic tests for other infections such as blood culture and PCR for respiratory virus did not allow to further investigate the differential diagnosis of TB; iii) With only one follow-up visit for non-treated children, we could not keep lost-to follow-up cases in the time dependent analysis and we had to exclude them resulting in the loss of power and potential bias if some of the lost-to follow-up were dead; iv) We applied the standard case definitions of intrathoracic childhood TB for the review of the diagnostic accuracy for unconfirmed TB in a prognosis study, which was not the purpose of the development of these standard definitions. They were proposed for diagnostic studies in order to reduce intra-study variability and their limitation for the diagnostic accuracy of unconfirmed TB is well recognised[27].

The goal to reach zero death from TB in children spearheaded by the WHO includes taking every opportunity for intervention to improve diagnosis and treatment, especially among those presenting with severe clinical conditions or chronic disease[28,29]. This includes the use of empirical TB treatment for such group of children to prevent death from undiagnosed TB. However, the high mortality of children receiving empirical TB treatment strengthens the need to invest further in robust TB diagnosis, particularly in more sensitive, non-sputum based, point of

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care tests to identify true TB cases that can be cured[10]. TB detection approach may need to be adapted in the light of recent studies showing high proportion of undiagnosed TB in young children admitted with acute severe pneumonia and in children with severe malnutrition aiming for more rapid and systematic detection of TB in these groups[24,25]. However, although better diagnostics are essential, it is important to consider and reduce non-TB cause of chronic diseases. In the context of lethal viruses and bacteria causing respiratory tract infections, there is also an urgent need to further invest in diagnosing non-TB severe illnesses that mimic TB to avert this high mortality in children empirically started on TB treatment[30].

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Figure1. Study profile

Figure 2: Three months survival curves for children treated tuberculosis confirmed; treated empirically and not treated children

Supplemental Digital Content: Chest x-ray tick sheet

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Table 1. Baseline characteristics of included children according to treatment decision

Characteristics,	All cases N=360	Treated confirmed, N=18	Empirical treatment, N=122	Not treated N=220	p
Sex, female	162 (45.0)	8 (44.4)	53 (43.4)	101 (45.9)	0.907
Age (years) category, n (%)					<0.001*
< 2	113 (31.4)	4 (22.2)	59 (48.4)	50 (22.7)	
2-5	94 (26.1)	4 (22.2)	37 (30.3)	53 (24.1)	
5-10	102 (28.3)	4 (22.2)	17 (13.9)	81 (79.4)	
>10	51 (14.2)	6 (33.3)	9 (7.4)	36 (70.6)	
HIV positive, n (%)	113/357 (31.6)	7/17 (41.2)	40/121 (33.0)	66/219 (30.1)	0.185
On ART, n (%)	68 (60.2)	3 (42.9)	18 (45.0)	47 (71.2)	0.018
Weight for height Z score, N	353	18	120	215	<0.001*
Normal	211 (59.8)	7 (38.9)	50 (41.7)	154 (71.6)	
≤ -1 to -1.9SD	72 (20.4)	7 (38.9)	27 (22.5)	38 (17.7)	
<-2 to -2.9SD	30 (8.5)	1 (5.6)	17 (14.2)	12 (5.6)	
≤-3SD	40 (11.3)	3 (16.7)	26 (21.7)	11 (5.1)	
BGC immunized, n (%)	312 (86.9)	14 (77.8)	102 (83.6)	196 (89.1)	0.091
TB contact history, n (%)	75 (20.8)	7 (38.9)	44 (36.4)	24 (10.9)	<0.001
< 2 years old	23/113(20.5)	3/4 (75.0)	17/58 (29.3)	3/50 (6.0)	<0.001
TST positive, n (%)	95/351(27.1)	8/17 (47.1)	59/117 (50.4)	28/217 (12.9)	
Antibiotics in last 2 weeks, n(%)	241(66.9)	11 (61.1)	76 (62.3)	154 (70.0)	0.302

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Clinical presentation, n (%)					
> 2weeks cough	330 (91.7)	17 (94.4)	103 (84.4)	210 (63.6)	0.002
≥ 7 days reported fever	136 (37.8)	8 (44.4)	57 (46.7)	71 (32.3)	0.026
> 2 weeks night sweats	180 (50.0)	11 (61.1)	60 (49.2)	109 (49.8)	0.630
> 2 weeks unexplained fatigue	125 (43.1)	9 (50.0)	60 (49.2)	56 (25.4)	<0.001
Peripheral adenopathy	19 (5.3)	6 (33.3)	7 (5.7)	6 (2.7)	<0.001
Chest x-ray, n (%)					
Consolidation	49 (13.6)	7 (43.7)	28 (23.5)	14 (6.5)	<0.001
Cavity	4 (1.1)	1 (6.2)	2 (1.7)	1 (0.5)	0.086
Mediastinal adenopathy	68 (18.9)	7 (43.7)	54 (45.4)	7 (3.2)	<0.001
Broncho-pneumonic patterns	147 (40.8)	12 (75.0)	70 (58.2)	65 (30.1)	<0.001
Suggestive of TB	130 (36.1)	12 (75.0)	97 (81.5)	21 (9.7)	<0.001
TB laboratory					
Sputum positive culture	15 (4.2)	13/17(76.5)	1/108 (0.9)**	1/205 (0.5)	
Xpert MTB detected	14 (3.9)	13/15 (86.7)	0/104	1/202 (0.5)	

* Pearson chi square

**Non tuberculosis mycobacteria

SD: standard deviation; TB tuberculosis; TST: tuberculin skin test.

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Table 2. Retrospective case review using consensus case definition for children started on empirical TB treatment and children not started on TB treatment

Review	Empirical treatment	No treatment
All cases, n (%)	N=122	N=220
Classified	113 (92.6)	213 (96.8)
Confirmed TB	0	1 (0.5) *
Probable TB	38 (33.6)	1 (0.5)
Possible TB	38 (33.6)	6 (2.8)
Unlikely TB	17 (15.0)	37 (17.4)
Not TB	20 (17.7)	168 (78.9)
Deaths, n (%)	N=15	N=10
Classified	12	9
Confirmed TB	0	1*
Probable TB	2	0
Possible TB	1	0
Unlikely TB	2	1
Not TB	7	7

TB: tuberculosis

* Child with XpertMTB positive result who died without been started on treatment

Confirmed tuberculosis: 1 sign or symptom of tuberculosis + microbiological confirmation

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Probable tuberculosis: 1 sign or symptom of tuberculosis + chest x-ray suggestive of tuberculosis + positive clinical response to tuberculosis treatment, or tuberculosis contact history or positive tuberculin skin test.

Possible tuberculosis: 1 sign or symptom of tuberculosis + positive clinical response to tuberculosis treatment or tuberculosis contact history or positive tuberculin skin test or chest x-ray suggestive of tuberculosis

Unlikely tuberculosis: 1 sign or symptom of tuberculosis but not fitting the above definitions and no alternative diagnosis established

Not tuberculosis: fitting the definition of unlikely tuberculosis but with an established alternative diagnosis.

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Table 3. Predictors of deaths

Risk factors	N	Death, n(%)	HR	95% CI	aHR	95% CI
Age category, years						
< 2	113	15 (13.3)	1		1	
2-5	94	4 (4.3)	0.30	0.10-0.91	0.49	0.15-1.54
5-10	102	4 (3.9)	0.27	0.09-0.82	0.86	0.26-2.85
>10	51	2 (3.9)	0.28	0.06-1.21	0.62	0.13-2.92
Child sex						
Male	198	18 (9.1)	1		1	
Female	162	7 (4.3)	0.47	0.20-1.12	0.42	0.16-1.10
Child HIV status						
Negative	243	14 (5.8)	1			
Positive on ART	68	5 (7.3)	1.26	0.45-3.49		
Positive not on ART	45	6 (13.3)	2.46	0.94-6.39		
Contact history*						
No	284	24 (8.4)	1			
Yes	75	1 (1.33)	0.15	0.02-1.13		
BCG*						
No BCG scar	11	2 (18.2)	1			
BCG scar	312	22 (7.0)	0.35	0.08-1.49		
Antibiotic trial						
No	119	3 (2.5)	1			

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Yes	241	22 (9.1)	3.5	1.12-12.53		
Weight for height Z score*						
Normal	211	5 (2.4)	1		1	
≤ -1 to -1.9SD	72	6 (8.3)	3.62	1.10-11.86	2.94	0.86-9.99
<-2 to -2.9SD	30	1 (3.3)	1.44	0.17-12.31	1.07	0.12-9.63
≤-3SD	40	11 (27.5)	13.95	4.84-40.18	9.86	3.11-31.23
Chest X-ray*						
Normal	120	2 (1.7)	1		1	
TB suggestive	130	16 (12.3)	7.79	1.79-33.88	4.20	0.93-19.01
Abnormal non TB suggestive	101	6 (5.9)	3.60	0.73-17.82	3.29	0.66-16.51
Bacteriologically confirmed						
No	341	24 (7.0)	1			
Yes	19*	1 (5.3)	0.75	0.10-5.57		
Treatment decision						
No treatment	220	10 (4.0)	1		NA	NA
Empirical treatment	122	15 (12.3)	2.85	1.28-6.34	NA	NA
TB confirmed treatment	18	0	NA		NA	NA

* Missing values excluding from the multivariate analysis

SD: standard deviation; NA: not applicable; TB: tuberculosis; HR: hazard ratio

*Including the child with Xpert confirmed TB who died without been started on treatment.

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Figure 1

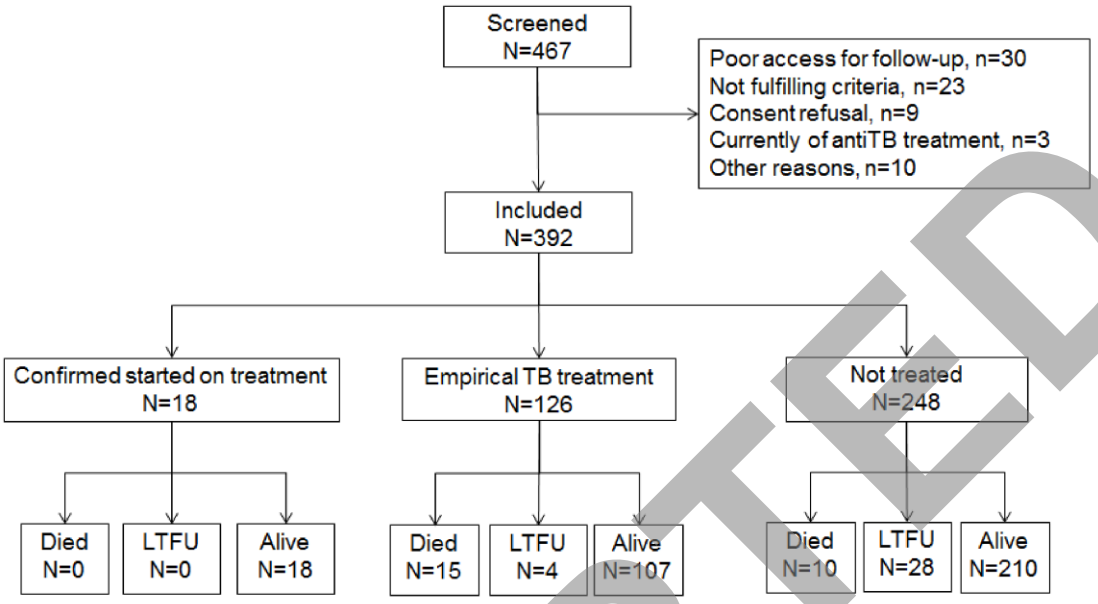

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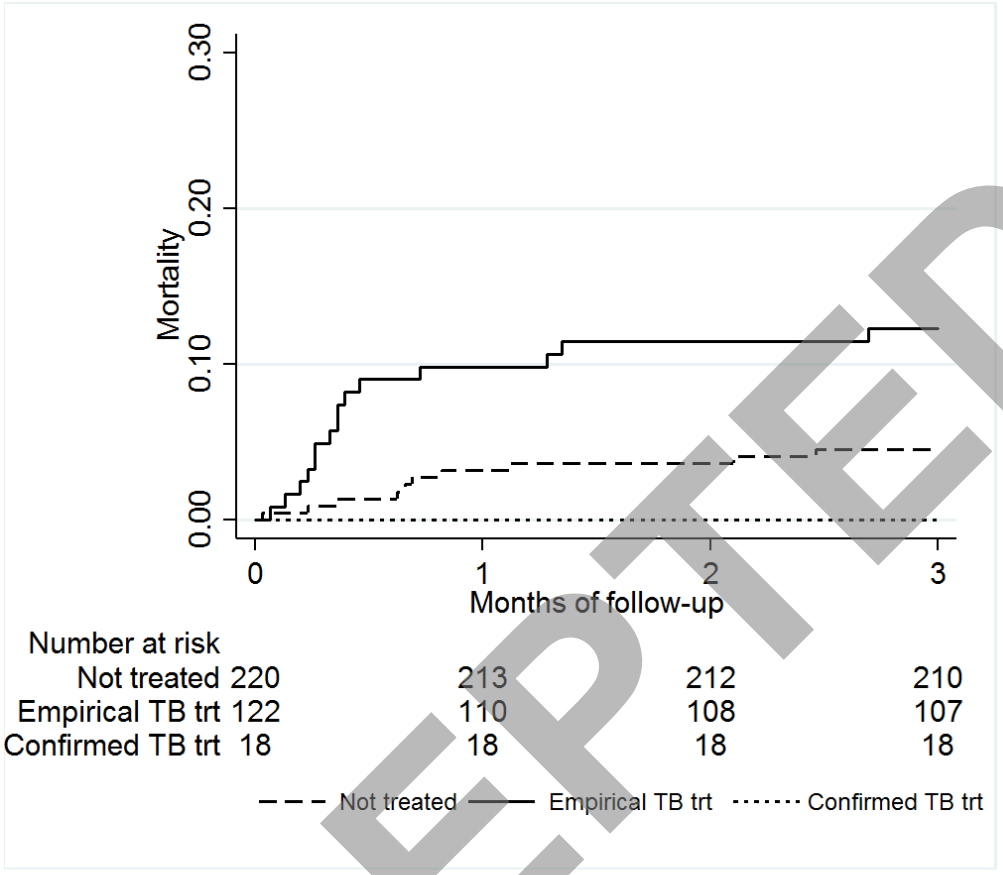
Figure 2



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