# CHALLENGES OF STUDYING CHILDHOOD TUBERCULOSIS MORTALITY IN A LOW-INCOME COUNTRY: A CASE STUDY OF UGANDA.

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ABSTRACT

CHALLENGES OF STUDYING CHILDHOOD TUBERCULOSIS MORTALITY IN A LOW-INCOME COUNTRY: A CASE STUDY OF UGANDA.

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**Objective**: To investigate the case fatality rate and risk factors for childhood tuberculosis mortality during treatment in low-income health facilities. **Methods**: In this retrospective case series study, we used secondary hospital data extracted from tuberculosis treatment medical records at Mulago Hospital Pediatric Tuberculosis clinic, Kampala, Uganda. Children aged 0-14years treated for Tuberculosis at this hospital from 2012 to 2015 were included in this study. **Results**: We enrolled 494 children into the study and 83(16.8%) were lost to follow up. The analytic sample consisted of 411 children followed up. The proportion of missing observations ranged from 0% to 53% among variables. More males 225(54.7%) and children aged 0-4years, 252(61.5%) were enrolled. Children without BCG vaccine and HIV positive children with failure to thrive were more likely to be lost to follow up. The childhood case fatality rate was 9.3% but estimates varied from 7.7% -24.5% depending on assumptions about mortality for those lost to follow up. The multivariable logistic regression model showed that children with a negative tuberculin skin test were less likely to survive TB, p-value = 0.04; [OR = 0.2, 95% CI 0.04, 0.9]. **Conclusion**: In settings with high TB burden, like Uganda, we need complete clinical data on childhood TB to gain more precise estimates case-fatality and its risk factors. This is vital in monitoring progress and informing policy makers.

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KEY TO ABBREVIATIONS

| | |
|---|---|
| ART | Antiretroviral Therapy |
| AIDS | Acquired Immune Deficiency Syndrome |
| Anti-TB | Anti-Tuberculosis |
| BCG | Bacillus Calmette–Guérin |
| CI | Confidence Interval |
| CD4 | Cluster of Differentiation 4 |
| CXR | Chext X-Ray |
| DOT | Directly Observed Therapy |
| EPTB | Extrapulmonary Tuberculosis |
| FTT | Failure To Thrive |
| HR | Hazard Ratio |
| HIV | Human Immune Virus |
| HCW | Health Care Workers |
| HERZ | Isoniazid Ethambutol Rifampicin Pyrazinamide |
| IQR | Interquartile Range |
| IRIS | Immune Reconstitution Inflammatory Syndrome |
| LostTF | Lost to Follow Up |
| Mg | Milligrams |
| MDR | Multidrug Resistance |
| M. bovis | Mycobacterium bovis |
| OR | Odds Ratio |

| | |
|---|---|
| PTB | Pulmonary Tuberculosis |
| RR | Rifampicin Resistance |
| Rx | Treatment |
| RIF | Rifampicin |
| SAS | Statistical Analysis System |
| TB | Tuberculosis |
| WHO | World Health Organization |
| XDR | Extensive Drug Resistance |
| ZN | Ziehl–Neelsen |

# CHAPTER 1

# INTRODUCTION

## Overview of tuberculosis.

From antiquity to renaissance, tuberculosis has been a disease of both clinical and public health significance. Around 160 – 370 BC, Hippocrates, a famous Greek physician, and his apprentices used the terms phthisis or consumption to describe this disease because it always resulted in death of its victims (1,2). Tuberculosis was also the leading cause of mortality in man during that time. Hippocrates believed that tuberculosis was a hereditary disease, then in 384-322 BC Aristotle postulated its infectious origin. Caelius Aurelias, a Roman physician, further described it during the 5th century AD as a latent intermittent evening fever. In 1882, Robert Koch identified tubercle Bacillus as the etiological agent. The first epidemics of tuberculosis were reported in Europe and North America between the 18$^{th}$ and 19$^{th}$ (1–3).

During the 19$^{th}$ century, several tuberculosis-related breakthrough discoveries of both clinical and public health significance were made. The first included improvement in screening when Clemens Von Pinquet discovered the tuberculin skin test in 1907. The second was the development of new treatments for tuberculosis in 1944 and 1952 which included aminoglycoside and isoniazid antibiotics respectively (1,3). Lastly, development of the Bacillus Calmette–Guérin (BCG) vaccine, which helped reduce the transmission and severity of the disease among humans. These discoveries were followed by declines in tuberculosis epidemics in Europe and North America during the latter 20$^{th}$ century(1,3,4). However, in 1993, WHO declared tuberculosis[TB] a global public health emergency (5). The current sustainable development goals together with the end TB strategies set up by the United Nations and WHO

both aim at achieving 90% and 95% reduction in TB incidence and deaths respectively by the year 2035 (6–8).

**Tuberculosis disease.**

Human tuberculosis is caused mainly by three strains of mycobacterium, Mycobacterium Tuberculosis (most common), Mycobacterium Bovis and Mycobacterium Africanum (least implicated in disease) (9). TB is classified into two clinical types based on the body site involvement. Pulmonary tuberculosis, which involves the lungs, is the most common form and diagnosed as either sputum positive or sputum negative. Most children are sputum negative with only 15% positivity on sputum exam(10). The second type is extra-pulmonary TB, which infects other body parts besides the lungs. In Children, 20-30% of all cases are extra-pulmonary; in these cases adenitis and pleural effusion are the most frequent presentations (4).

**Tuberculosis morbidity and mortality.**

Despite tuberculosis being a preventable and curable disease, it has persisted among the top 10 causes of death worldwide. This burden is more significant in low-income countries such as Asia and Africa. In 2016, 10.4 million incident cases of TB [4.1%] were reported by WHO of which, 90% were adult cases, 65% were males, 19% were multi-drug resistant and 10% co-infected with HIV/AIDS. The high burdened countries are in Asia [India is the leading, Indonesia, China, Philippine and Pakistan] and then Africa. By the WHO regions, 45% of all the incident cases are from South-eastern Asia, 25% from Africa, 17% from Western pacific, 7% from East Mediterranean and 3% from America (6–8,11). During this same period, the global TB mortality in all age groups was reported to be 1.7 million death with 400,000 cases due to co-infection

with HIV/AIDS. Low and middle income countries contributed 95% of this mortality (6,8,12,13).

**Classification of TB Cases.**

Confirmation of any true TB case starts with screening of patients who present with signs or symptoms suggestive of TB. These were formerly termed as TB suspects but currently described as presumptive TB cases. Following the confirmation of a TB diagnosis, TB cases are classified broadly into two types:

1) Microbiologically confirmed cases usually have a biological specimen that is positive by smear microscopy, culture or WHO-approved rapid diagnostic tests like Xpert MTB/RIF and,

2) Clinically confirmed case of TB which doesn't fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioners based on evidences from clinical, medical and radiological investigations (14–16).

The two broad categories of TB described above are sub-classified further based on several factors including anatomical sites affected by the TB, history of previous TB treatments, drug resistance of the TB, and co-infection with HIV. The pulmonary TB [PTB] involves lesions in the lung parenchyma or the tracheobronchial tree while extra-pulmonary TB [EPTB] TB involves lesions in organs other than the lungs, for example the pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, or meninges. Any patient found to have both PTB and EPTB is classified as PTB. The treatment history groupings include the following TB categorizations: i). new patients who have never been treated for TB or have taken anti-TB drugs for no more than 1 month; ii). previously treated patients who have received anti-TB therapy for at least 1one month. This latter group is further subdivided into: 1). relapse patients who have

previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with another episode of TB which can be a true relapse or a new episode; 2). patients who previously have been treated for TB but treatment failed at the end of their most recent therapy; iii). patients previously treated for TB and declared lost to follow-up or default at the end of their most recent treatment; and iv). patients with previous history of TB treatment but the treatment outcome is unknown. TB cases also are classified based on drug susceptibility testing of confirmed mycobacterium. Cases can be: 1). monoresistant if the resistance is to one first-line anti-TB drug only; 2). polydrug resistant if the resistance is to more than one first-line anti-TB drug other than both isoniazid and rifampicin; 3). multidrug resistant if at least both isoniazid and rifampicin are involved; 4). extensive drug resistant if in addition to multidrug resistance, any fluoroquinolone and to at least one of three second-line injectable drugs like capreomycin, kanamycin and amikacin are involved; and 5). Rifampicin resistant cases if it is rifampicin resistance involved. Regarding HIV co-infections, TB cases are noted as HIV-positive TB patient, HIV-negative TB patient or HIV status unknown TB patient (14).

**Transmission.**

Tuberculosis is transmitted through either inhalation of contaminated aerosol when an adult infected with pulmonary TB coughs/sneezes or ingestion of dairy products contaminated with Mycobacterium bovis (17). Children commonly have paucibacilliary tuberculosis hence hardly produce infectious aerosols. Those most at risk of contracting TB include children (especially ages 0 to 4 years), immunocompromised individuals like HIV/AIDS patients, malnourished, patients on cancer chemotherapy or corticosteroid treatment, post organ transplant patients or previous cases of TB (9,10). Among the immunocompetent individuals, only 5-10% of the

people being exposed to the disease progress to active illness while the rest remain with a latent infection due to the work of their competent cell-mediated immunity (18). However, these latent cases risk future reactivation into active disease when the body immunity is compromised as stated above.

**Clinical presentation of tuberculosis.**

Signs and symptoms of tuberculosis might vary based on the body site involvement. However, most cardinal signs and symptoms are consistent in most of the TB cases regardless of site involved and these include: 1). Loss of or failure to gain weight for at least three months. This is common because most times the patients have poor appetite for food hence they always risk being malnourished; 2). Intermittent evening fevers persisting for at least 2 weeks; 3). Cough for at least 2 weeks is also very common among cases of pulmonary TB. This triad of symptoms is used in the clinical tools to screen for presumptive TB cases in all age groups. Other signs and symptoms are drenching night sweats, hemoptysis, difficulty in breathing especially in cases where it is complicated by pleural or pericardial effusion, ascites, meningism in TB meningitis, and enlargement of lymph nodes which is most common with cervical and abdominal TB (4).

**Diagnosis of tuberculosis.**

Diagnosis of PTB is still a big challenge, especially in children as majority are sputum negative and exhibit non-specific symptoms due to the paucibacilliary nature of the disease(19) The diagnosis in children relies mainly on careful history taking plus physical examination and hence starts with screening for probable TB cases through history taking. Then confirmation is based on microbiological/culture evidence of the mycobacteria in respective specimens or a clinical

decision by a physician based on the clinical evidence in the patient as per the World Health Organization guidelines (4,16,18).

During screening, the most important history to look out for includes contact with a person with or suspected of TB and cardinal signs and symptoms, e.g. progressive and non-remitting cough for more than 2 weeks, fever for more than 2 weeks, lethargy or reduced playfulness or less active for more than 2 weeks, weight loss, no weight gain or poor weight gain (failure to thrive). Other useful information comes from the respiratory physical exam by a clinician which may detect signs of increased respiratory rate, respiratory distress, abnormal percussion, abnormal sounds on auscultation like wheezing, crackles, or bronchial breathing. Some children can present with severe acute pneumonia. A more detailed clinical assessment involving routine medical history taking and physical examination by a physician to establish any risks/exposures, other danger signs/co-morbidities in the patients will help bolster the diagnosis. Any patient meeting these screening criteria becomes a presumptive case of TB (20).

Further evaluation for tuberculosis diagnosis follows a number of therapeutic, laboratory and radiological tests. Laboratory tests that are usually done include tuberculin skin test [TST], and where applicable, examination of sputum, ascites, cerebral spinal fluid, pleural fluid using microscopy auramine or ZN staining, Xpert MTB/RIF and culture, and lastly biopsy and histology (16,18,21–23). Tuberculin skin test is used to assess previous TB exposure or presence of latent TB infection, Xpert MTB/RIF identifies the mycobacterium and its drug resistance and susceptibility profile. Biopsy and histology are done in suspected cases of spinal, cervical or abdominal tuberculosis lymph node enlargement. Histological evidence of caseous inflammation suggests TB in these cases.

Radiological investigations are done to look for any evidence of tuberculosis. These include chest/spinal x-ray and abdominal ultrasound scan. The chest/spinal x-ray and ultrasonography provide evidences of pulmonary/spinal and abdominal tuberculosis involvement respectively (24). Decision on diagnosis is made by at least having one positive laboratory finding of mycobacterium. In cases where all the laboratory tests are negative for the mycobacterium, a clinical diagnosis is made by a physician using radiological, therapeutic and clinical evidences available as per the WHO's recommendation.

**Management of tuberculosis.**

In management of TB, the focus is on strategies aimed at treating individual TB cases and also controlling or preventing transmission from person to person in the community.

Treatment regimen and duration for childhood tuberculosis is determined using factors like whether the patient has drug susceptible or resistant TB, history of previous treatment and sometimes the anatomical site of TB involved. The medication used is classified as first line drugs which typically includes isoniazid[H], rifampicin[R], pyrazinamide[Z], and ethambutol[E] commonly prescribed for new TB cases and then, the second line treatment consists of drugs like capreomycin, kanamycin and amikacin. Usually for drug-sensitive TB, the first line treatment consists of a two-month intensive phase with a four-drug regimen [HERZ] in settings with high prevalence of HIV/AIDS/isoniazid resistance or in case of extensive TB disease. Otherwise a three-drug regimen [HRZ] is sufficient followed by a continuation phase with two drugs [RH] for at least four more months. Recently, WHO guidelines were revised to introduce the fixed-dose combination treatment for children. The aim was to reduce the pill burden and improve adherence to treatment without compromising efficacy. A tablet combination given in the intensive phase of TB treatment consists of Rifampicin 75 mg + Isoniazid 50 mg + Pyrazinamide

150mg and then Rifampicin 75mg + Isoniazid 50 mg for the continuation phase of TB treatment. It is vital to always add ethambutol in the intensive phase of treating children with extensive disease or children living in settings with high HIV or isoniazid resistance TB. The number of pills prescribed is calculated using the child's current body weight. Adult dosages are used if a child weighs more than 25 kilograms. HIV co-infected children require antiretroviral therapy (ART) and prophylaxis with co-trimoxazole in addition to TB treatment (23,25–27). Latent TB infection in children under five is treated using similar dosing of isoniazid to prevent future development of active TB disease.

TB Control and Prevention strategies are usually public health approaches aimed at interrupting person to person transmission. Control of TB is categorized into three levels and each is operative at a specific point in the transmission pathway. These include administrative/managerial, environmental and personal respiratory protection measures.

Administrative control is the most effective hence should be given priority implementation. Its target is to reduce the generation of TB infectious droplet nuclei into the environment which ultimately reduces the exposure of health care workers [HCW] and patients. Hypothetically, complete blockage of the production of TB infectious droplet nuclei would be sufficient in eradicating the TB transmission process without the need for additional control strategies but this is usually not the case. Administrative measures are never effective one hundred percent. Solid administrative measures commonly recommended include early diagnosis of infectious TB cases, urgent isolation of confirmed infectious TB cases, and urgent initiation of the right anti-tuberculosis treatment (2,4,28,29).

Environmental control of TB tries to reduce the concentration of infectious TB droplet nuclei in air, especially at high risk places like health care settings. Such measures include optimization of the natural ventilation and controlling the direction of airflow. This is commonly limited by availability of resources in low income settings. Personal respiratory protection is used to protect health care workers from being exposed to infectious droplets nuclei in the air. Health workers use specialized respiratory protective devices designed to fit over the mouth and nose and filter out infectious aerosols during inhalation (28).

Other approaches to TB prevention include identification and effective treatment of people with active disease, and administration of prophylactic anti-TB chemotherapy to cases of latent TB. This is done routinely using isoniazid to prevent the latent TB from becoming active and infectious. Lastly, pasteurization of milk helps prevent M. bovis TB in humans, and in some settings, the recommendation is to use the Bacillus Calmette-Guerin [BCG] vaccine. This vaccine is widely administered in early childhood across the world and its uptake is estimated to be at least 80% of all new-borns in countries where it's part of the national immunization program. However, the vaccine is only believed to provide children with protection against the disseminated forms of TB. It's protection of adults against pulmonary TB is non-significant. Since adulthood PTB is the major source of TB transmission, the role of the vaccine in reducing transmission is of less value (23,28,30).

**Outcomes of TB treatment.**

The WHO has come up with standard definitions for TB treatment outcomes to ensure consistency in reporting by the different national TB programs. These definitions are similar for both adults and children but they create a clear distinction between patients treated for drug

susceptible and drug resistant TB. Outcome assessment among smear positive PTB is done through repeated sputum smear exam at 2 and then 5 months' post-treatment initiation. For the sputum smear, negative PTB or cases for whom no sputum exam was done prior to starting treatment, ascertainment of treatment response and outcome is done by monthly evaluation of weight gain and symptom improvement. Any patient treated for TB must be assigned one of the outcome definitions in the table 1 & table 2 (14,15,31).

Table 1: Treatment outcomes for TB patients excluding those treated for RR-TB/MDR-TB

| OUTCOMES | DEFINITIONS |
|---|---|
| Cure | A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion. |
| Treatment completed | A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable. |
| Treatment failed | A TB patient whose sputum smear or culture is positive at month 5 or later during treatment. |
| Died | A TB patient who dies for any reason before starting or during the course of treatment. |
| Lost to follow up | A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more. |
| Not evaluated | A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit. |
| Treatment success | The sum of cured and treatment completed |

***Source:*** *https://www.ncbi.nlm.nih.gov/books/NBK214446/table/annex2.t1/?report=objectonly.*

Table 2: Treatment outcomes for RR-TB/MDR-TB/XDR TB patients with second line treatment.

| OUTCOMES | DEFINITIONS |
|---|---|
| Cured | Treatment completed as recommended by the national policy without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase |
| Treatment completed | Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase |
| Treatment failed | Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:<br>• lack of conversion by the end of the intensive phase or<br>• bacteriological reversion in the continuation phase after conversion to negative, or<br>• evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or<br>• adverse drug reactions (ADRs) |
| Died | A patient who dies for any reason during the course of treatment. |
| Lost to follow up | A patient whose treatment was interrupted for 2 consecutive months or more. |
| Not evaluated | A patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown. |
| Treatment success | The sum of cured and treatment completed. |

***Source:*** *https://www.ncbi.nlm.nih.gov/books/NBK214446/table/annex2.t2/?report=objectonly*

**Tuberculosis in Uganda.**

A study of TB was conducted in western Uganda by Ashley Wynne et al and published in 2014. This was a secondary qualitative analysis from a bigger study and it investigated the challenges in TB care in this region. They reported two broad categories of factors affecting TB care and these were individual-related and health care system weaknesses. Individual factors were delay in diagnosis which ultimately delays initiation of treatment, self-medication, and financial burden on patients associated with TB care especially transport costs for follow-up visits and refilling medication. This is unfortunate since the people most likely to be afflicted by TB come from poor communities. Health system weaknesses included fewer trained staff in TB care, lack of enough funds to ensure patient follow-up through phone calls, Directly Observed Therapy [DOT] and home visits where necessary(32). These weaknesses usually culminate in higher

frequencies of patient loss to follow-up, defaulting on treatment and poor treatment adherence leading to treatment failures or deadly drug resistance TB. Uganda is currently one of countries with a significant prevalence of drug resistant TB globally (11).

## Childhood tuberculosis.

### *Global Burden of Childhood TB.*

While tuberculosis is implicated in all age groups, less attention has been paid to childhood cases, yet they represent a significant public health challenge. The most probable reason for the lack of emphasis on childhood TB is that these cases are less implicated in transmission of the disease. Childhood TB contributes about 10-11% of the total global TB burden. Some sources report these estimates to be as high as 11% - 40%. The absolute number for incidence has been reported to be at least 1 million new childhood TB cases every year (6,7,11).

In 2016 Childhood tuberculosis caused 253,000 deaths including the 52,000 cases co-infected with HIV/AIDS (8,12). A recent systemic review of studies about global childhood TB mortality estimated the case-fatality rate at 0.9% during this treatment era (33). However, higher estimates have been recorded in high burdened areas. A review article published in 2017 reported a TB case-fatality rate of 34% among HIV negative childhood TB in sub Saharan Africa (34).

### *Natural History of Childhood TB.*

Childhood TB is usually curable and in many cases, preventable through established public health measures like early childhood BCG vaccination and prophylactic chemotherapy. BCG vaccination has been documented as being protective against severe forms of tuberculosis especially in endemic populations. However, WHO estimates only a third of the true childhood TB burden is notifiable to national TB programs and this is partly due to challenges in

confirming childhood TB diagnosis using the available methods in hospitals. As an example of challenges in childhood tuberculosis diagnosis, many TB have been diagnosed and treated for pneumonia and the TB diagnosis was confirmed only following autopsy. Such diagnostic challenges are mainly due to the fact that childhood TB is known to be paucibacilliary in nature. With such challenges, reports of TB incidence and related mortality are likely to be underestimates. Therefore, understanding the natural history of untreated TB in children is fundamental in informing public health and clinical interventional decisions (23,28,35).

B.J Marais et al (2014) published a systemic review article in the International Journal of TB and Lung Disease. The aim was to understand the natural course of TB in children below 15 years and define the most at-risk age groups. They reviewed articles of original studies done about childhood PTB in the pre- treatment era [1920-1950]. They included only prospective studies published in the English literature with a sample size of at least 1000 subjects and conducted for 10 years with an exception of two studies that were done for 8 years because of interruption from the world war. The review found that primary infection of children below 2 years of age commonly resulted in severe active TB disease within a period of 12 months without showing any significant prior signs or symptoms that could inform clinical diagnosis. Children diagnosed between 2 -10 years of age rarely progressed to severe disease. In any case, it was always associated with significant clinical symptoms that could be helpful in screening and making an early clinical diagnosis before the disease becomes severe. Children older than 10 years developed adult type of disease with cavitation, hence this age group can be implicated in disease transmission in the community. Early detection and effective treatment turns out to be very critical in controlling the burden (36–38).

At the time of the aforementioned studies above, HIV/AIDS was not as prevalent as it is now in the contemporary world. Therefore, the prognosis in co-infected cases with HIV/AIDS-TB may not be well represented by these study findings. However, this may not be consistently true in all age groups as recent studies in HIV/AIDS-TB co-infected children have reported an identical TB pattern between the HIV positive immunocompromised and children below 2 years. This is because children below 2 years have an immature immune system that is unable to mount a strong cell-mediated defence against the mycobacterium.

*Case-Fatality Rate of Childhood TB.*

After the discovery of effective treatments for TB, noticeable decline in the early TB epidemics in Europe and North America during the 19$^{th}$ century was reported and the treatment effectiveness was credited for this decline. It is therefore expected that the case-fatality rate in the pre-chemotherapy era would be higher than the current rates with effective treatment. To understand these dynamics, Helen E Jenkins et al in 2017 conducted a systemic review of published articles worldwide on childhood tuberculosis mortality. They wanted to compare the global case-fatality rates during the pre-chemotherapy era [before 1946] with that in the modern times/chemotherapy era [after 1980] where treatment was available and more accessible. They found a higher pooled case-fatality rate of 21.9% [95% CI, 18.1-26.4] for the pre-chemotherapy period and this was higher in children aged 0-4 years, 43.6% [95% CI, 36.8-50.6] than in those 5-14 years, 14.9% [95% CI, 11.5-19.1]. For studies in the chemotherapy era (current), they found a lower pooled case-fatality rate of 0.9% [95% CI, 0.5-1.6]; children aged 0-4 years had a case-fatality rate of 2.0% [95% CI, 0.5-7.4] (39). While we can easily attribute the difference in the two case-fatality rates of the different treatment era to the role of effective TB treatment in the current era, we should be careful not to underestimate the additional roles of increased public

sensitization about TB and early TB case detection in bringing about this decline (5–7,28). Unlike the current period, the general public and clinical staff of the pre-treatment era hardly knew much about TB. Also, the few diagnostic methods were limited to a few health facilities amidst the TB diagnosis challenges that still exist to date. These led to patients presenting late and in severe forms which predictively resulted in death more often (16,21,23).

The last finding reported by Jenkins et al was on the Childhood TB case-fatality in cases co-infected with HIV/AIDS before and after widespread access to antiretroviral drugs. Their analysis reported a higher case-fatality rate of 14.3% [95% CI 7.4-24.1] before widespread access to antiretroviral drugs versus 3.4% [95% 0.7-9.6] with wider use of antiretroviral therapy (ART). ART is reported to reduce viral load and improve body immunity among the HIV/AIDs patients hence improving the prognosis of TB disease (39). However, we should also note that due to the specialized nature of HIV/AIDs care centres, all their clients receiving treatment tend to be screened for TB more regularly than those not attending such care. So partly, the reduced case- fatality rate among those accessing ART could be attributed to early detection and treatment of TB during the routine HIV/AIDS care visits. The decline in TB case-fatality can further be explained by decline in the risk posed by co-morbidities like malnutrition and HIV/AIDS. Malnutrition and HIV/AIDS are known contributors to increased mortalities risk in TB patients but with improved access to care and HAART, this risk has been reduced to lower levels. Most national health programs require evaluations for TB in all children diagnosed with either malnutrition or HIV/AIDS.

Interestingly, when looking at the estimates from a report by J R Starke et al in 2016, the pooled case- fatality-ratio reported for childhood TB in the modern times/chemotherapy era was 22%,

higher than the case-fatality ratio estimate in the pre-treatment era [before 1946] reported by Jenkins et al systemic review (6,39). In this report, there were significant differences in case-fatality rates between geographical regions with a range from 2% for Europe to 34% in Africa (34). These rates reflect the challenges faced in low income settings. Explanations for the higher case-fatality rates include less access to accurate diagnostic kits and trained healthcare personnel which can lead to problems of misdiagnosis/under-diagnosis of TB. Clinical autopsy studies done in regions with high burdens of TB have reported TB being misdiagnosed as acute severe pneumonia (40). Most studies of childhood TB case-fatality use data aggregated at a global or continental population-level, but rates and circumstances may vary across low income countries. Therefore, more localized, in-depth studies are warranted to identify successes and challenges and to customize effective interventions.

*Risk Factors for Childhood TB Mortality.*

There have been some studies focused on risk factors for childhood TB mortality in low income settings. The most recent was done in Lagos, Nigeria and published in 2016. It investigated the treatment outcomes of childhood TB in Lagos through a retrospective review of program data of Lagos state TB and Leprosy control program from Jan 2012 to December 2012. They evaluated 535 childhood TB cases which they estimate represented 6.3% of the total TB cases in the state that year. The prevalence of HIV co-infection in the 535 cases was 29%. The most significant risk factor for mortality in this study was age less than 1year (p-value < 0.0001) (31).

S. Ade et al (2013) reported on the burden and outcome of childhood TB in Cotonou, Benin. This retrospective review of medical records from 2009 to 2011 covering childhood TB cases below 15 years of age. Within the study duration, the authors estimated that paediatric TB cases

contributed from 3.1% to 4.9% of the total TB burden the region and the prevalence of HIV co-infection was 29%. They reported variations in TB case-fatality rates among different TB types, with the highest being 13% for sputum smear negative PTB, 6% for sputum smear positive PTB and 5% among EPTB cases. Because the process of making a diagnosis for sputum smear negative TB requires supporting clinical evidences from several timing consuming investigations, this is routinely associated with delays in starting TB treatment which can increase mortality risk in the patient. This might explain the higher case-fatality rate among sputum smear negative TB cases versus sputum smear positive cases. The case-fatality rate also varied with HIV status. Children with unknown HIV status had the highest case-fatality rate of 71%, followed by HIV positive cases with 13%, and the lowest rate of 8% in HIV negative cases. As expected, due to the immunosuppression caused by HIV, HIV/AIDS patients co-infected with TB tend to have faster TB disease progression to severe forms than their HIV negative counterparts, hence higher mortality risks. However, establishing the HIV status helps clinician to plan the best TB treatment options in addition to timely initiation of ART or co-trimoxazole prophylaxis against opportunistic infections. This might help explain why cases with unknown HIV status experience the highest mortality rate; they may not have received optimal interventions for co-infections. These authors also reported increased case-fatality rates in younger age groups, especially 0–4 years, i.e. 12% compared to 7% among those aged 5-14 years (41).

A 2012 retrospective cohort study from Malawi investigated the burden of TB disease, treatment outcomes and risk factors for TB-related death among 295 children treated for TB. They reviewed routinely collected programme data from the Malawi Ministry of Health TB Treatment Registries at 10 health facilities. Paediatric TB represented 8% of all TB cases and 32.8% of

these paediatric cases had HIV co-infection. The case-fatality rate was 9.5%, 13.2% were lost to follow up and 77.3% survived. One factors found to increase risk of death, after controlling for age, TB type and sex, was being on ART at the time of initiating anti-tuberculosis treatment [OR=2.75, 95% CI 1.25-5.96] compared to if ART was initiated during or after TB treatment initiation. Death occurred, on average, after 2 months post starting anti-TB treatment in these cases (42). This increased mortality risk can be attributed to TB immune reconstitution recovery syndrome [IRIS](43,44). Normally, HIV infection suppresses the CD4+ cells leading to a weakened cell-mediated immunity which decreases a body's normal immune response to certain infections. This makes it hard for the body to fight against certain infections and symptoms of infection related to a normal immune response are often lacking. The lack of immune response and symptoms may interfere with timely disease detection. Initiation of ART in these patients can lead to rapid recovery of CD4+ cells and cell-mediated immunity which in turn leads to an overwhelming inflammatory immune response and a worsening of TB symptoms, thereby causing more organ damage and increased risk of death (45). The risk of IRIS could be avoided if the anti-TB drugs are started before ART; the goal is to clear the TB infection then follow with HIV treatment at least two weeks later. In cases where patients are already on ART, adjunct therapy with steroids can reduce the risk of IRIS. The other reported risk for mortality in the Malawi study was having EPTB, especially TB pericarditis [OR=15.21, 95% CI 136-169.5] and pleural effusion [OR=13.55, 95% CI 1.63-112] (OR adjusted for age, sex and HIV status). More favourable outcomes were noted for sputum smear positive PTB [OR=0.12, 95% CI 0.02, 0.75] relative to the sputum smear negative cases; most likely because the latter are more likely to be misdiagnosed initially (42).

A 25-year retrospective cohort study was conducted with 2,392 hospitalized children below 15 years of age in Peru, another low-income country with high TB burden, but in Latin America. The aims of this study were to investigate risk factors of in-hospital TB mortality, case-fatality rate and median time of death during hospitalization. The HIV co-infection was 0.1% and the case-fatality rate was reported to be 11.1% in general but a higher estimate of 46.9% was reported in those less than 1year of age. The Median time to death post admission was 16 days [IQR=4-44 days]. Factors associated with mortality were a negative tuberculin skin test, Tuberculin skin test < 5 mm [HR=3.01 95% CI 2.15-4.1], young age, i.e. 0-4years [HR=3.53, 95% CI 2.4-5.18], duration of hospitalization, altered mental status [HR 3.25, 95% CI 2.4-8.4], and severe EPTB [HR=4.06 95% 3.17-5.2]. Reduced risk of death was associated with; hemoptysis, rifampicin containing treatment regimen, history of BCG vaccination, female gender, weight loss and bacteriological confirmation of TB diagnosis h (46).

*Childhood Tuberculosis in Uganda.*

Data are scarce concerning childhood tuberculosis in Uganda. The first database capturing information on childhood TB in the country was started recently in 2009 at Mulago National referral hospital. Few studies have been done in Uganda to investigate issues surrounding childhood tuberculosis. Reports of 2009 revealed that 7.5% of all the registered tuberculosis in Kampala district were due to childhood cases, with an incidence rate of 44 cases in every 100,000 population, all in Kampala district(10). Among these, the HIV/AIDS co-infection rate was found to be 47% (10). No data concerning case-fatality rate and risk factors of inpatient or outpatient case-fatality has been documented in childhood TB in Uganda. While studies conducted in other settings have analysed children hospitalized with TB, their results may not apply to the Ugandan setting. Therefore, our goal was to estimate childhood TB case-fatality

rates and risk factors associated with case-fatality in Uganda at a locality that had high quality care and available data.

# CHAPTER 2

# COMPLETENESS OF CLINICAL DATA MATTERS: THE EXAMPLE OF CHILDHOOD TUBERCULOSIS.

## Introduction.

In 1993, WHO declared tuberculosis (TB) a global public health emergency. Tuberculosis morbidity & mortality rates have declined comparing the pre-treatment era to the treatment[current] era indicating some success in the available intervention being used. Despite the decline, tuberculosis is still among the top 10 infectious causes of death globally (5–7). In 2015 WHO estimated the global childhood TB burden to be 10-11% of the total TB burden. At least 1 million new cases are diagnosed annually and 210,000 children die every year from TB. These estimates are likely underestimates because 5 countries still don't report to WHO their TB-related cases or mortality (6,8). Also, because it can be difficult to confirm TB microbiologically, especially in children, many cases may go undiagnosed. Most childhood TB cases are sputum smear negative because of the paucity of TB bacilli in this age group. This means many TB cases are missed, not treated adequately and hence die unconfirmed. These diagnostic challenges, along with other comorbidities and undernutrition, can lead to higher rates of TB-related mortality in children despite availability of effective treatment.

Historically, data on childhood tuberculosis in Uganda had been scarce. The first concerted effort to assemble childhood TB data started in 2009. Few studies have focused on Uganda to examine progress in preventing and treating childhood TB. One study reported that of all registered TB cases, 7.5% were in children with an incidence rate of 44 cases in every 100,000 population of children at risk, all in Kampala district. Among these childhood TB cases, the HIV/AIDS co-infection rate was found to be 47% (10). No data concerning case-fatality rate or risk factors of

inpatient case-fatality have been independently documented for childhood TB in Ugandan setting.

Our initial goal was to investigate the case-fatality rate of childhood TB among Ugandan children receiving treatment at a major paediatric hospital-based clinic in Kampala. We hypothesized that their TB case-fatality rate would be higher than the global rate of 0.9% reported in a recent systemic review of childhood TB around the world (39). Quantifying the childhood TB case-fatality rate in low-income countries can inform policy makers when they consider equitable resource allocation.

We were also interested in evaluating risk factors associated with mortality among children with TB who were receiving treatment. Advent of effective treatments for TB has led to high hopes of preventing mortality among accurately identified TB cases; most high income countries have managed to reduce TB-related mortality to very low levels by using these treatment options. Understanding risk factors for childhood TB mortality can help identify children at high risk and motivate systems-based interventions to address these risk factors. These goals are in sync with the WHO and United Nation's strategies to end tuberculosis by 2035 (6).

In this study, we use clinical data to estimate the childhood TB case-fatality rate and TB mortality risk factors. We recognize that clinical data are not recorded for these purposes, but are often the source for these estimates. Anticipating some incompleteness in clinical data, we further examine the impact of this incompleteness on our estimates and conclusions we might form.

**Methods.**

*Study design.*

We conducted a retrospective case series study on children with TB. We did secondary data analysis using medical records of children aged 0-14years who were diagnosed and treated for TB at Mulago Hospital paediatric tuberculosis unit between 2012 – 2015.

*Ethical considerations.*

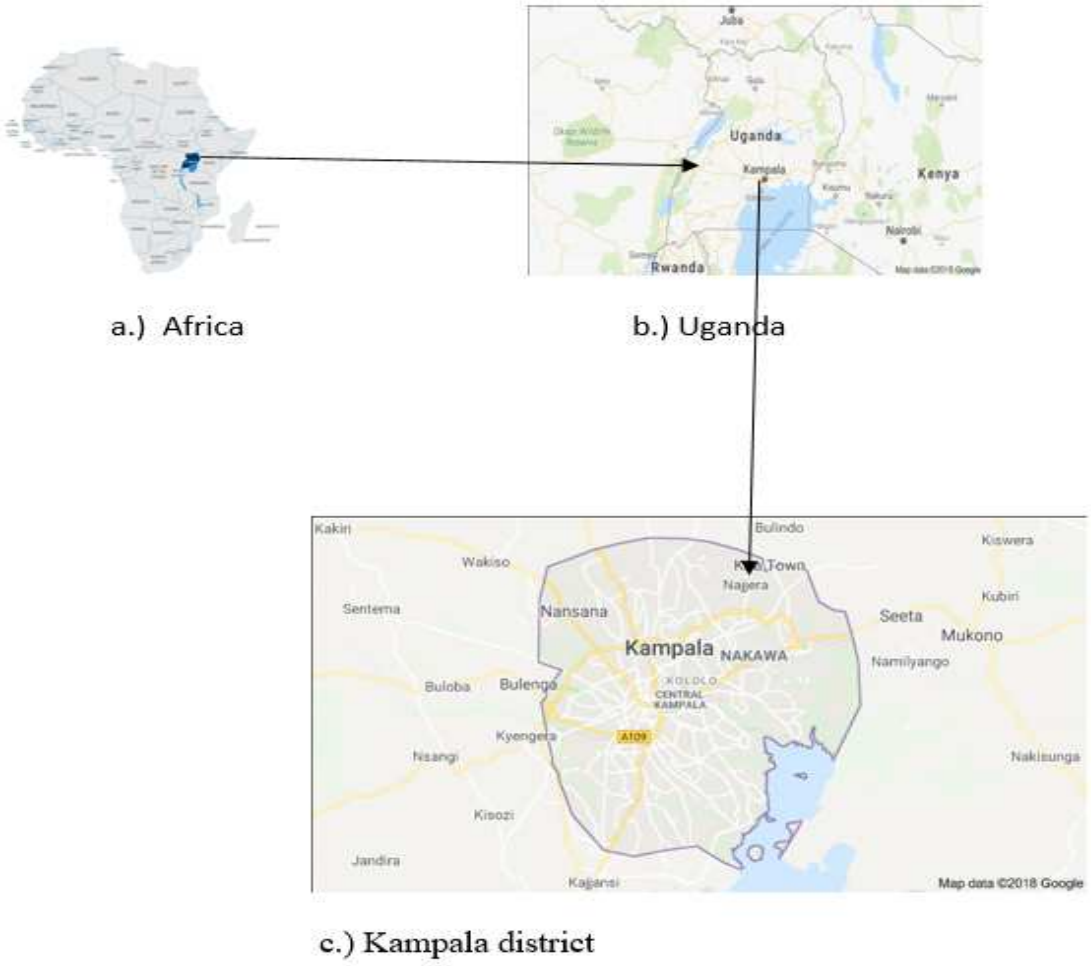
We sought ethical approval from Mulago National Referral & Teaching Hospital Institutional review board and consent from the Uganda Ministry of Health. We de-identified all patients' data by removing all possible identifiers and using proxy identification numbers. As part of the data use approval process, investigators agreed to share all study findings with Mulago Hospital staff and the Uganda Ministry of Health.

*Study population and area.*

This study was conducted at Mulago National referral hospital, Kampala Uganda. It's a public hospital and the largest national referral hospital in the country with paediatric, internal medicine, surgery and obstetrics/gynaecology departments. It receives both walk-in and referred patients from all around the country and provides free medical care. All new paediatric patients have one entry point into the hospital services, the Mulago assessment centre, where they are screened before being allocated to the respective clinical units. Among other paediatric clinical units are the pulmonary ward and the paediatric outpatient TB unit for managing admitted and follow-up childhood TB cases respectively. Mulago hospital is located at Mulago Hill in Kampala district, the home of Makerere University Medical School.

Kampala district is the capital city of Uganda consisting of five administrative divisions. Each administrative district has a regional health unit that also treats tuberculosis patients. In addition, there are private health facilities and HIV/AIDs centres with TB patients in Kampala. Thus, not all childhood TB cases from Kampala are cared for through the Mulago Hospital and our sample is not population-based.

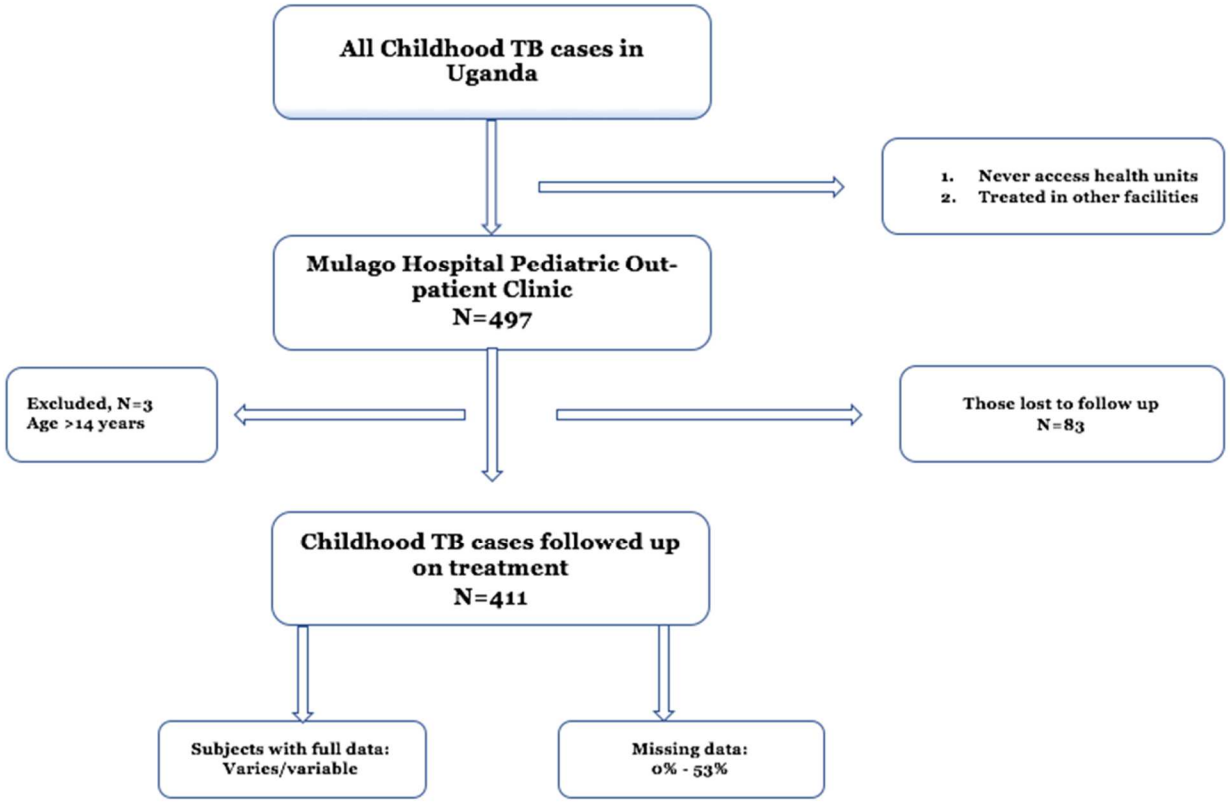
Figure 1: The geographic location of Kampala district in Uganda, Africa



*Study eligibility.*

Only children aged 0-14years with a diagnosis of TB, either pulmonary TB (PTB) or extra-pulmonary TB (EPTB) were included in this study. Below is a diagram showing the 494 children who met these criteria. Of them, 83 were lost to follow-up and not all had complete registry data for the variables of interest.

*Figure 2: Patients Flow to Mulago Hospital*



*Data collection.*

We reviewed the treatment registry for tuberculosis at Mulago Hospital paediatric TB unit between the years 2012 to 2015. The registry routinely captures all cases of tuberculosis notified by the paediatric wards at this hospital. Other information captured by the registry includes the patients' residence, age, sex, HIV status, tuberculosis diagnosis, start and end dates of treatment, treatment regimen, treatment outcome, and post treatment smear results. The registry ascertains patient deaths by using death certificates, hospital clinical files, or oral reports from a child's parents or guardians for deaths occurring outside the hospital.

*Patient follow-up.*

We used the date for starting treatment as the enrolment date. Data collected on this day included initial medical history, physical exam findings, weight, age, and treatment regimen prescribed. The first hospital follow-up visit was after 2 weeks during which there was a re-assessment of weight, clinical symptoms and treatment adherence. After this, monthly follow-up visits were scheduled with repeated assessment of parameters similar to those at the 2-week visit. In case of previously confirmed sputum smear positive PTB, the sputum smear exam was repeated at the $2^{nd}$ and $5^{th}$ months of treatment to evaluate microbiological clearance with treatment. Our study focuses on covariates collected at the baseline enrolment date. Follow-up periods varied across cases from 6 to 18 months' post-diagnosis, not including those lost to follow-up.

*Outcome variables.*

Our study period for each patient began at the initiation of treatment and lasted for at least 6 months of treatment/follow-up visits depending on the form and body site of TB. Our primary outcome of interest for this period was categorized into a three-level variable; *died*, *survived*, or

loss to follow-up. *Survival* or *death* during TB treatment was ascertained from registry data and no further verification was done. The '*survived'* group included all patients who were coded as *cured*, *completed treatment* or *failed* on treatment but still alive after at least 5 months under observation. The loss to follow-up group included cases defaulting on treatment, transferred out to other facilities before completing treatment, those who disappeared from care without communicating to the clinic, and anyone missing the outcome in the registry.

*Hypothesized factors affecting childhood TB mortality.*

Based on previous studies, we investigated the following variables for possible associations with TB mortality: patient's age at start of treatment date (calculated from their birth certificate or as reported by the primary guardian), sex of the child, patients residence, HIV/AIDS status (positive or negative), diagnostic criteria (bacteriological confirmation of TB versus clinical diagnosis), history of BCG vaccination in early life, malnutrition, failure to thrive, TB regimen prescribed, tuberculin skin test results, clinical signs and symptoms (e.g. cough, fever), TB type (PTB, versus EPTB), patients tuberculin skin test results and anti-TB regimen prescribed.

*Statistical analysis.*

Continuous variables were described using means while proportions and frequency tables were used for categorical data. Chi-square and TTEST tests were used for bivariate analyses of categorical and continuous data. Multivariate logistic regression models were used to assess associations between mortality and the independent variables. To assess bias in our analytic sample, we compared the characteristics of those not lost to follow-up with those lost to follow-up (chi-square tests and TTESTs). These tests were conducted at alpha level 0.05 and those with

a p-value less than 0.05 suggested that the two groups were different. We used SAS software 9.4v for all data analyses.

Case-fatality rate: To quantify this estimate, we initially included only those cases not lost to follow-up and divided the total number of childhood TB deaths by the total number of childhood TB cases, then multiplied by 100. We next examined the potential impact on our estimate of those lost to follow-up. We repeated the above analyses and included the loss to follow-up cases under two extreme assumptions, i.e. all loss to follow-up cases survived or all loss to follow-up cases died. A Z-test was used to compare our estimated case-fatality rate to a global rate and to rates reported in other studies of childhood TB in low income settings.

Associations between risk factors and TB mortality were evaluated through bivariate analyses of each factor and the outcome (survived/died) using a chi-square test and TTEST for categorical and continuous variables respectively, at alpha=0.25 (47). A more generous p-value was used to increase the sensitivity of selecting factors for the later multivariable analysis since we had a small number of deaths. All factors with a p-value $\leq 0.25$ and those known to influence TB mortality based on the literature were further incorporated into a multi-covariate analysis with only those cases not lost to follow-up (48). Factors with p-values less than 0.05 coupled with established scientific knowledge from the literature were retained in the final multi-covariate model. These models left out cases with missing data for the various risk factors. We used Firth's penalized multivariate logistic regression to estimate the maximum likelihood (49–51). This was because we anticipated small sample sizes in subgroups, bias and separation of data. To evaluate the impact of missing data in our risk factor analyses, we repeated the above modelling strategy under two different assumptions: first, that signs and symptoms or other

parameters not documented were absent/negative; and second, a more unlikely scenario, that the missing signs and symptoms were all present/positive.

**Results.**

*Baseline sample characteristics.*

We reviewed medical records of 497 childhood TB cases; 3 were excluded for being older than 14 years and 83(16.8%) were lost to follow-up leaving 411 cases that were followed for our analysis. Most cases, 368(96.3%) were diagnosed at the Mulago Hospital; 214(52.1%) of the cases resided within the Kampala district. The mean weight and age for this analytic sample (those followed-up) was 14 kg and 4.2 years respectively. About 252(61.5%) of cases were age 0 to 4 years of age, 102(24.8%) were 5 to 9 years of age and the rest were between 10 to 14 years of age; 186(45.3%) of cases were female. Only 40(10%) of cases had their diagnosis confirmed bacteriologically. PTB accounted for 285(69.3%) of cases, tuberculin skin test was reactive in 137(70.3%) and only 172(41.9%) were prescribed ethambutol containing regimen (see Table 3). The HIV co-infection rate was 23(6.1%), 134(49.8%) of the children were categorized as having failure to thrive, 56(20.1%) had previously been treated for malnutrition. Abnormal chest X-ray findings were observed in 271(91.6%) of cases. Symptoms of weight loss were reported in 214(65%), fever in 266(75.1%), coughing in 287(79.5%) and coughing for more than 2 weeks in 243(90.7%) while 274(85.9%) of cases reported having received BCG vaccine early in life. These are shown in Table 4 below.

Table 3: Description of demographic, case classification and treatment covariates with their respective proportions of missing data in the analytic sample.

| Variables | Total Sample (N=411) | | | % of Missing data | |
|---|---|---|---|---|---|
| | N | Mean | (%) | N | ( %) |
| $Weight_1$(Kg) | 342 | 14.0 | | 69 | (17%) |
| $Weight_2$(Kg) | 350 | 13.8 | | 61 | (15%) |
| Age(years) | 410 | 4.2 | | | |
| Age (years) | | | | | |
| 0-4 | 252 | | (61.5) | 01 | (0.2%) |
| 5-9 | 102 | | (24.8) | | |
| 10-14 | 56 | | (13.7) | | |
| Gender | | | | | |
| Female | 186 | | (45.3) | 00 | (0%) |
| Male | 225 | | (54.7) | | |
| Case Criteria | | | | | |
| Confirmed | 40 | | (10) | 09 | (2%) |
| Clinical | 402 | | (83.4) | | |
| TB Type | | | | | |
| PTB | 285 | | (69.3) | 00 | (0%) |
| EPTB | 126 | | (30.7) | | |
| Diagnosis Point | | | | | |
| Mulago | 368 | | (96.3) | 29 | (7%) |
| Outside | 14 | | (3.7) | | |
| Residence | | | | | |
| Kampala | 214 | | (52.1) | 00 | (0%) |
| Outside | 197 | | (47.9) | | |
| Regimen | | | | | |
| Ethambutol | 172 | | (41.9) | 00 | (0%) |
| No Ethambutol | 239 | | (58.2) | | |
| Tuberculin test | | | | | |
| Positive | 137 | | (70.3) | 216 | (53%) |
| Negative | 58 | | (29.7) | | |

Table 4: Description of analytic sample signs, symptoms and medical history covariates with respective proportions of missing data.

| Variables | Total Sample (N=411) | | Missing data | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| Cough | | | | |
| Yes | 287 | (79.5) | 50 | (12%) |
| No | 74 | (20.5) | | |
| Cough duration(Weeks) | | | | |
| <2 | 25 | (9.3) | 143 | (35%) |
| >2 | 243 | (90.7) | | |
| Fever | | | | |
| Yes | 266 | (75.1) | 57 | (14%) |
| No | 88 | (24.9) | | |
| Weight loss | | | | |
| Yes | 214 | (65) | 82 | (20%) |
| No | 115 | (35) | | |
| BCG Vaccination | | | | |
| Yes | 274 | (85.9) | 92 | (22%) |
| No | 45 | (14.1) | | |
| CXR | | | | |
| Abnormal | 271 | (91.6) | 115 | (28%) |
| Normal | 25 | (8.5) | | |
| Rx Malnutrition | | | | |
| Yes | 56 | (20.1) | 132 | (32%) |
| No | 223 | (79.9) | | |
| HIV status | | | | |
| Positive | 23 | (6.1) | 36 | (8%) |
| Negative | 352 | (93.9) | | |
| FTT | | | | |
| Yes | 134 | (49.8) | 142 | (35%) |
| No | 135 | (50.2) | | |

*Differences between cases followed and those lost to follow-up.*

Cases lost to follow-up were more likely to; i). Be positive for HIV, 10(14.5%) versus 23(6.1%) in cases followed, p-value = 0.02, ii). Have failure to thrive (FTT), 33(70.2%) versus 134(49.8%), p-value = 0.01, and less likely to be vaccinated with BCG vaccine, 46(75.4%) versus 274(85.9%), p-value = 0.04 (See Table 6). No association was noted in Table 5.

Table 5: Demographic, case classification and treatment covariates of children, 0-14years who were lost to follow up versus the non-lost to follow up while on treatment for tuberculosis from 2012-2015 at Mulago Paediatric TB Clinic, Kampala Uganda, N=494.

| Variables | Total Sample N=494 | | | LostTF N = 83(16.8%) | | | Not LostTF N = 411(83.2%) | | | p-values |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | (%) | N | Mean | (%) | N | Mean | (%) | |
| $Weight_1$(Kg) | 409 | 14.1 | | 67 | 14.3 | | 342 | 14.0 | | 0.79 |
| $Weight_2$(Kg) | 416 | 13.9 | | 66 | 14.7 | | 350 | 13.8 | | 0.41 |
| Age(years) | 493 | 4.3 | | 83 | 4.9 | | 410 | 4.2 | | 0.13 |
| Age (years) | | | | | | | | | | |
| 0-4 | 299 | | (60.7) | 47 | | (56.6) | 252 | | (61.5) | 0.17 |
| 5-9 | 120 | | (24.3) | 18 | | (21.7) | 102 | | (24.8) | |
| 10-14 | 74 | | (15.0) | 18 | | (21.7) | 56 | | (13.7) | |
| Gender | | | | | | | | | | |
| Female | 230 | | (46.6) | 44 | | (53.0) | 186 | | (45.3) | 0.20 |
| Male | 264 | | (53.4) | 39 | | (47.0) | 225 | | (54.7) | |
| Case Criteria | | | | | | | | | | |
| Confirmed | 45 | | (9.3) | 5 | | (6.2) | 40 | | (10) | 0.30 |
| Clinical | 437 | | (90.7) | 75 | | (93.8) | 402 | | (83.4) | |
| TB Type | | | | | | | | | | |
| PTB | 337 | | (68.2) | 52 | | (62.7) | 285 | | (69.3) | 0.23 |
| EPTB | 157 | | (31.8) | 31 | | (37.3) | 126 | | (30.7) | |
| Diagnosis Point | | | | | | | | | | |
| Mulago | 441 | | (96.3) | 73 | | (96.0) | 368 | | (96.3) | 0.91 |
| Outside | 17 | | (3.7) | 3 | | (4.0) | 14 | | (3.7) | |
| Residence | | | | | | | | | | |
| Kampala | 242 | | (49.0) | 38 | | (45.8) | 214 | | (52.1) | 0.30 |
| Outside | 252 | | (51.0) | 45 | | (54.2) | 197 | | (47.9) | |
| Regimen | | | | | | | | | | |
| Ethambutol | 209 | | (42.3) | 37 | | (44.6) | 172 | | (41.9) | 0.6 |
| No ethambutol | 285 | | (57.7) | 46 | | (55.4) | 239 | | (58.2) | |
| Tuberculin skin test | | | | | | | | | | |
| Positive | 160 | | (30.4) | 23 | | (65.7) | 137 | | (70.3) | 0.6 |
| Negative | 70 | | (69.6) | 12 | | (34.3) | 58 | | (29.7) | |

***Missing Data:*** *Age (N=1), Case Criteria (N=12) Diagnosis Point (N=36),* $Weight_1$ *(N=85),* $Weight_2$ *(N=78) Tuberculin skin test (N=264). LostTF = Loss to follow up.*

Table 6: Signs, symptoms and medical history covariates of children 0-14 years of age who were treated for tuberculosis at Mulago Paediatric TB Clinic, Kampala Uganda from 2012-2015, N=494.

| Variables | Total Sample N=494 | | LostTF N = 83 | | Not LostTF N = 411 | | p-values |
|---|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) | |
| Cough | | | | | | | |
| Yes | 341 | (79.3) | 54 | (78.3) | 287 | (79.5) | 0.82 |
| No | 89 | (20.7) | 15 | (21.7) | 74 | (20.5) | |
| Cough duration(Weeks) | | | | | | | 0.62 |
| <2 | 31 | (9.7) | 6 | (11.5) | 25 | (9.3) | |
| >2 | 289 | (90.3) | 46 | (88.5) | 243 | (90.7) | |
| Fever | | | | | | | |
| Yes | 317 | (75.1) | 51 | (75) | 266 | (75.1) | 0.98 |
| No | 105 | (24.9) | 17 | (25) | 88 | (24.9) | |
| Weight loss | | | | | | | |
| Yes | 253 | (65.0) | 39 | (65) | 214 | (65) | 0.99 |
| No | 136 | (35) | 21 | (35) | 115 | (35) | |
| BCG Vaccination history | | | | | | | 0.04 |
| Yes | 320 | (84.2) | 46 | (75.4) | 274 | (85.9) | |
| No | 60 | (15.8) | 15 | (24.6) | 45 | (14.1) | |
| CXR | | | | | | | |
| Abnormal | 320 | (91.7) | 49 | (92.5) | 271 | (91.6) | 0.83 |
| Normal | 29 | (8.3) | 4 | (7.5) | 25 | (8.5) | |
| Rx Malnutrition | | | | | | | |
| Yes | 69 | (20.4) | 13 | (22) | 56 | (20.1) | 0.73 |
| No | 269 | (79.6) | 46 | (78) | 223 | (79.9) | |
| HIV status | | | | | | | |
| Positive | 33 | (7.4) | 10 | (14.5) | 23 | (6.1) | 0.02 |
| Negative | 411 | (92.6) | 59 | (85.5) | 352 | (93.9) | |
| FTT | | | | | | | |
| Yes | 167 | (52.9) | 33 | (70.2) | 134 | (49.8) | 0.01 |
| No | 149 | (47.1) | 14 | (29.8) | 135 | (50.2) | |

***Missing Data:*** *Cough (N=64), Cough duration (N=174), Fever (N=72), Weight loss (N=105), BCG Vaccination (N=114), CXR (N=145), Rx Malnutrition (N=156), HIV (N=50), FTT (N=178)*

*Case-fatality rate.*

The TB case-fatality rate was 9.3% [95% CI, 6-12] among children who were not lost to follow-up (Table 7). Upon including those lost to follow-up in the analyses, the case-fatality rate was 24.5% if we assumed that all those lost to follow-up had died and 7.7% if we assumed that all those lost to follow-up survived. Our childhood TB case-fatality rate [9.3%] among those not lost to follow-up from the Ugandan Hospital is significantly greater than the estimated global childhood TB case-fatality rate of 0.9%, p-value = 0.04 (39). However, the Ugandan TB case-fatality rate is similar to those reported by retrospective cohort studies in other low income settings, i.e. Malawi,9.5% (42) and Peru,11.1% for which the p-values are 0.51 and 0.56 respectively when each compared 9.3% (46).

*Risk Factors for TB mortality among cases followed up.*

In bivariate analyses that ignored missing values for covariates, TB cases who died were more likely to have received Ethambutol, 25(65.8%) versus 147(39.4%); p-value=0.001. Other comparisons between those who died and the survivors showed that death was less likely to be among Kampala residents, 13(34.2%) versus 201(53.9%); p-value = 0.02 and those with a positive tuberculin skin test, 01(14.3%) versus 136(72.3%); p-value = 0.003 (see Table 7). Regarding signs and symptoms, cases who died were more likely to have a history of weight loss 14(100%) versus 200(63.5%); p-value = 0.03 and then previous treatment for malnutrition, 5(50%) versus 51(19%); p-value = 0.03 (see Table 8). In a multivariate analysis, the only covariates that remained statistically significant was tuberculin skin test results. Cases with a negative tuberculin skin test had lower odds of surviving as compared to those with a positive test, p-value = 0.04; OR = 0.2, 95% CI 0.04, 0.9 (see Table 9).

Table 7: Demographic, case classification and treatment covariates of children, 0-14years who died versus the survivors while on treatment for tuberculosis from 2012-2015 at Mulago Paediatric TB Clinic, Kampala Uganda, N=411.

| Variables | Total Sample N=411 | | | Died N = 38 (9.3%) | | | Survived N = 373 (90.7%) | | | p-values |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | (%) | N | Mean | (%) | N | Mean | (%) | |
| $Weight_1$(Kg) | 342 | 14.0 | | 14 | 14.7 | | 373 | 14.0 | | 0.76 |
| $Weight_2$(Kg) | 350 | 13.8 | | 19 | 14.0 | | 328 | 13.8 | | 0.92 |
| Age(years) | 410 | 4.2 | | 37 | 4.5 | | 331 | 4.2 | | 0.63 |
| Age (years) | | | | | | | | | | |
| 0-4 | 252 | | (61.5) | 22 | | (59.5) | 230 | | (61.7) | 0.60 |
| 5-9 | 102 | | (24.8) | 8 | | (21.6) | 94 | | (25.2) | |
| 10-14 | 56 | | (13.7) | 7 | | (18.9) | 49 | | (13.1) | |
| Gender | | | | | | | | | | |
| Female | 186 | | (45.3) | 18 | | (47.4) | 168 | | (45) | 0.78 |
| Male | 225 | | (54.7) | 20 | | (53.6) | 205 | | (55) | |
| Case Criteria | | | | | | | | | | |
| Confirmed | 40 | | (10) | 1 | | (2.7) | 39 | | (10.7) | 0.12 |
| Clinical | 402 | | (83.4) | 36 | | (87.3) | 326 | | (89.3) | |
| TB Type | | | | | | | | | | |
| PTB | 285 | | (69.3) | 22 | | (57.9) | 263 | | (70.5) | 0.11 |
| EPTB | 126 | | (30.7) | 16 | | (42.1) | 110 | | (29.5) | |
| Diagnosis Point | | | | | | | | | | |
| Mulago | 368 | | (96.3) | 30 | | (100) | 338 | | (96) | 0.27 |
| Outside | 14 | | (3.7) | 0 | | (00) | 14 | | (4) | |
| Residence | | | | | | | | | | |
| Kampala | 214 | | (52.1) | 13 | | (34.2) | 201 | | (53.9) | 0.02 |
| Outside | 197 | | (47.9) | 25 | | (65.8) | 172 | | (46.1) | |
| Regimen | | | | | | | | | | |
| Ethambutol | 172 | | (41.9) | 25 | | (65.8) | 147 | | (39.4) | 0.001 |
| No Ethambutol | 239 | | (58.2) | 13 | | (34.2) | 226 | | (60.6) | |
| Tuberculin test | | | | | | | | | | |
| Positive | 137 | | (70.3) | 1 | | (14.3) | 136 | | (72.3) | 0.003 |
| Negative | 58 | | (29.7) | 6 | | (85.7) | 52 | | (27.7) | |

***Missing Data:*** *Age (N=1), Case Criteria (N=9 Diagnosis Point (N=29) $Weight_1$ (N=85), $Weight_2$ (N=78) Lost to follow up=83 Tuberculin skin test (216).*

Table 8: Signs, symptoms and medical history covariates of children, 0-14years who died versus the survivors while on treatment for tuberculosis from 2012-2015 at Mulago Paediatric TB Clinic, Kampala Uganda, N=411.

| Variables | Total Sample N=411 | | Died N = 38(9.3%) | | Survived N = 373(90.7%) | | p-values |
|---|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) | |
| Cough | | | | | | | |
| Yes | 287 | (79.5) | 15 | (79) | 272 | (79.5) | 0.95 |
| No | 74 | (20.5) | 4 | (21) | 70 | (20.5) | |
| Cough duration(Weeks) | | | | | | | |
| <2 | 25 | (9.3) | 0 | (0) | 25 | (9.8) | 0.22 |
| >2 | 243 | (90.7) | 14 | (100) | 229 | (90.2) | |
| Fever | | | | | | | |
| Yes | 266 | (75.1) | 12 | (66.7) | 254 | (75.6) | 0.39 |
| No | 88 | (24.9) | 6 | (33.3) | 82 | (24.4) | |
| Weight loss | | | | | | | |
| Yes | 214 | (65) | 14 | (100) | 200 | (63.5) | 0.003 |
| No | 115 | (35) | 0 | (0) | 115 | (36.5) | |
| BCG Vaccination | | | | | | | |
| Yes | 274 | (85.9) | 13 | (81.3) | 261 | (86.1) | 0.58 |
| No | 45 | (14.1) | 3 | (18.7) | 42 | (13.9) | |
| CXR | | | | | | | |
| Abnormal | 271 | (91.6) | 16 | (100) | 255 | (91.1) | 0.21 |
| Normal | 25 | (8.5) | 0 | (0) | 25 | (8.9) | |
| Rx Malnutrition | | | | | | | |
| Yes | 56 | (20.1) | 5 | (50) | 51 | (19) | 0.03 |
| No | 223 | (79.9) | 5 | (50) | 218 | (81) | |
| HIV status | | | | | | | |
| Positive | 23 | (6.1) | 4 | (11.8) | 19 | (5.6) | 0.14 |
| Negative | 352 | (93.9) | 30 | (88.2) | 322 | (94.4) | |
| FTT | | | | | | | |
| Yes | 134 | (49.8) | 8 | (72.7) | 126 | (48.8) | 0.12 |
| No | 135 | (50.2) | 3 | (27.3) | 132 | (51.2) | |

***Missing Data:*** *Cough (N=50), Cough duration (N=143), Fever (N=57), Weight loss (N=82, BCG Vaccination (N=92), CXR (N=115), Rx Malnutrition (N=132), HIV (N=36), FTT (N=142), Lost to follow up=83.*

Table 9: Results of multivariate analysis from subjects not lost to follow up, N=411.

| Variables | Reference category | OR | 95% CI | P-value |
|---|---|---|---|---|
| Age | 5-14 years | 1.4 | 0.2, 9.0 | 0.7 |
| Tuberculin test | Positive | 0.2 | 0.04, 0.9 | 0.04* |
| TB type | PTB | 0.5 | 0.1, 3.7 | 0.5 |
| Residence | Kampala | 0.4 | 0.1, 2.0 | 0.2 |
| Regimen | No Ethambutol | 0.8 | 0.1, 4.6 | 0.8 |
| Cough duration | Less Than 2 weeks | 0.6 | 0.02,12.9 | 0.7 |
| Case Criteria | Clinical | 1.7 | 0.1, 30.0 | 0.7 |
| History of weight loss | Yes | 2.7 | 0.2, 32.9 | 0.4 |
| Malnutrition treatment History | Yes | 2.2 | 0.4, 14.2 | 0.4 |

** p-value $\leq$ 0.05, CI= Confidence Intervals, OR=Odds Ratio.*

The proportions of missing data varied between 0 - 53 % among the demographics, case classification and treatment covariates, and 8 – 35% among the signs, symptoms and medical history covariates. Under the assumption that all the missing observations on patients' symptoms take on the value 'NO' or not present, bivariate analysis showed the same factors discussed above being associated with case-fatality plus a few additional symptoms; i.e. residence (p-value = 0.02), regimen (p-value = 0.001) tuberculin skin test (p-value = 0.03), having a history of cough (p-value < 0.0001), fever (p-value = <0.0001), weight loss (p-value = 0.05) and BCG vaccination (p-value < 0.0001) Table 10. However, in Firth's penalized logistic multivariable analysis, we observed a significant inverse association only with tuberculin skin test results, p-value =0.02, OR = 0.2, 95% CI 0.04, 0.8 and borderline associations for regimen, p-value = 0.08, OR = 0.4, 95% CI 0.2, 1.0, and fever with P-value= 0.05, OR=0.3, 95% CI 0.1, 1.0.

Under the assumption that all the missing observations on symptoms take on value 'YES' or present, bivariate analysis showed that residence (p-value = 0.02), regimen (p-value = 0.001), tuberculin skin test (p-value = 0.03), history of weight loss (p-value < 0.01), previous treatment for malnutrition (p-value < 0.01) and failure to thrive (p-value < 0.01) were statistically associated with case-fatality (see Table 11).

In the multivariable analysis using Firth's penalized logistic regression model, children residing outside Kampala and those presenting with weight loss were less likely to survive, p-value = 0.05, OR = 0.5, 95% CI 0.2,0.99;, p-value = 0.03, OR = 0.06, 95% CI 0.01, 0.8.

Table 10: Bivariate analysis results under the assumption that all missing categorical observations were not present.

| Variables | Sample N=411 | | Died N = 38 (9.3%) | | Survived N 373 (90.7%) | | p-value |
|---|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) | |
| Cough | | | | | | | |
| Yes | 287 | (69.8) | 15 | (39.5) | 272 | (73.1) | <0.0001 |
| No | 124 | (30.2) | 23 | (60.5) | 100 | (26.9) | |
| Fever | | | | | | | |
| Yes | 266 | (64.7) | 12 | (31.6) | 254 | (68.5) | <0.0001 |
| No | 145 | (35.3) | 26 | (68.4) | 117 | (31.5) | |
| Weight loss | | | | | | | |
| Yes | 214 | (52.1) | 14 | (36.8) | 200 | (54.4) | 0.05 |
| No | 197 | (47.9) | 24 | (63.2) | 168 | (45.6) | |
| BCG Vaccination | | | | | | | |
| Yes | 274 | (66.7) | 13 | (36.1) | 261 | (74.6) | <0.0001 |
| No | 137 | (33.3) | 23 | (63.9) | 89 | (25.4) | |
| Rx Malnutrition | | | | | | | |
| Yes | 56 | (13.6) | 5 | (13.2) | 51 | (13.7) | 0.93 |
| No | 355 | (86.4) | 33 | (86.8) | 322 | (89.3) | |
| FTT | | | | | | | |
| Yes | 134 | (32.6) | 8 | (21) | 126 | (35.7) | 0.11 |
| No | 277 | (67.4) | 30 | (79) | 227 | (64.3) | |
| Tuberculin test | | | | | | | |
| Positive | 137 | (33.3) | 1 | (2.6) | 136 | (36.5) | <0.0001 |
| Negative | 274 | (66.7) | 37 | (97.4) | 237 | (63.5) | |

Table 11: Bivariate analysis results under the assumption that all missing categorical observations were present.

| Variables | Sample N=411 | | Died N = 38 (9.3%) | | Survived N 373 (90.7%) | | p-values |
|---|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) | |
| Cough | | | | | | | |
| Yes | 337 | (82) | 34 | (89.5) | 302 | (81.2) | 0.27 |
| No | 74 | (18) | 4 | (10.5) | 70 | (18.8) | |
| Fever | | | | | | | |
| Yes | 323 | (78.6) | 32 | (84.2) | 289 | (77.9) | 0.37 |
| No | 88 | (21.4) | 6 | (15.8) | 82 | (22.1) | |
| Weight loss | | | | | | | |
| Yes | 296 | (72) | 38 | (100) | 253 | (68.8) | <0.01 |
| No | 115 | (28) | 0 | (0) | 115 | (31.2) | |
| BCG Vaccination | | | | | | | |
| Yes | 391 | (95.1) | 35 | (97.2) | 331 | (94.6) | 0.71 |
| No | 20 | (4.9) | 1 | (2.8) | 19 | (5.4) | |
| Treatment history for malnutrition | | | | | | | <0.01 |
| Yes | 188 | (45.7) | 33 | (86.8) | 155 | (41.6) | |
| No | 223 | (54.3) | 5 | (13.2) | 218 | (58.5) | |
| FTT | | | | | | | |
| Yes | 276 | (67.2) | 35 | (92.1) | 221 | (62.6) | <0.01 |
| No | 135 | (32.8) | 3 | (7.9) | 132 | (37.4) | |
| Tuberculin test | | | | | | | |
| Positive | 353 | (85.9) | 32 | (84.2) | 321 | (86.1) | 0.8 |
| Negative | 58 | (14.1) | 6 | (15.8) | 52 | (13.9) | |

**Discussion.**

We observed a gender difference in childhood TB cases treated at Mulago hospital. More male children 225 (54.7%) were diagnosed with and treated for TB from 2012 to 2015 at this health facility. This could have been a result of detection and treatment biases. Previous literature has reported gender based inequity with female children having less access to health care compared to their male counterparts in developing countries. Societies with high regards for sons tend to be quicker to seek modern health care when their sons report being unwell as compared to their daughters (52–54). The Childhood TB case-fatality rate was 9.3% among followed up children, which is significantly higher than a recently reported global rate of 0.9%. But this is comparable to fatality rates in studies from Malawi, 9.5% and Peru 11.1% (42,46). The high childhood TB case-fatality rate mirrors the high adulthood TB burden these countries. Uganda, Malawi and Peru are all part of the WHO 30 TB high burden countries. In addition, the global case-fatality rate of 0.9% for childhood TB incorporates both high and low burden countries across the world to calculate an average rate. The accuracy of our case-fatality estimate is in question due to the 16.8% of cases lost to follow-up. We show that under different assumptions about the outcome of those lost to follow-up, the 'true' case-fatality rate during our observation period could vary anywhere from 7.7 % to 24.5%. Comparisons of childhood TB case-fatality rates across studies need to consider both rates of loss to follow-up and the period of follow-up.

In the multivariable analysis that ignored missing data, we showed that a negative tuberculin skin test, N=102 (24.8%), was associated with increased risk of death among childhood TB cases. This finding is consistent with previous studies' findings (46). Because of the paucibacilliary nature of childhood TB, fewer cases are sputum positive. In these cases, a positive tuberculin skin test becomes an important contributor to the signs and symptoms algorithm used for

establishing a clinical diagnosis of TB (16,22,23). A negative tuberculin skin test may delay the accurate diagnosis and treatment initiation. In addition, false negative tuberculin skin tests are often associated with co-morbidities such as malnutrition, HIV/AIDS, or other causes immunosuppression, and these may be the underlying causes of death (55–58). Among cases with complete follow-up, 6.1% had HIV/TB co-infection, 49.8% had failure to thrive, and 20.1% presented with previous history of treatment for malnutrition. Only one mortality case was co-infected with TB and HIV. These figures suggest that in this study sample with full follow-up, malnutrition and failure to thrive could have contributed to the negative tuberculin skin test more than HIV/TB co-infection. Our conclusions are limited, however, by the 9% missing HIV status, 32% missing malnutrition status, and 35% missing failure to thrive status in the clinical database. Children's age, HIV/AIDS and nutritional status have been reported by other studies as independent risk factors for childhood TB mortality (39,55,58). Children with HIV/TB co-infection tend to have faster progression to severe forms of TB (34,56). In our current analysis, case-fatality was not associated with HIV status or age in bivariate and multivariable analysis, and history of malnutrition stood out as a prognostic indicator of death in bivariate analysis only. These unexpected findings might be due to the small number of cases who died in our followed sample (n=38) leading to limitations in statistical power, but also due to biases introduced by missing covariate data and cases lost to follow-up.

To assess the impact of missing covariate data on our results, we reanalysed our cases with complete follow-up, once assuming all missing symptom observations were a 'NO' (the more likely scenario) and once assuming all missing symptom observations were a 'YES' (the less likely scenario). With the assignment of missing to 'No,' the association between a negative tuberculin skin test and death was attenuated. Conversely, the variables 'prescribed regimen' and

patient ‘TB category’ became significantly associated with death, whereas they were not significant covariates in models that ignored missing data. When a value of ‘YES’ was given to missing observation, tuberculin skin test, regimen and patient TB treatment category became significantly associated with case-fatality. Such inconsistency in results is a challenge that crops up whenever we have incomplete data/observations in hospital records. We can never be sure of answers to questions that have clinical implications for prognosis, intervention strategies, and monitoring of progress over time.

This study had several limitations. As mentioned above, the uncertainty of estimates and associations is compounded by missing data and the potential bias it introduces. Also, studying childhood TB cases treated at one hospital in Uganda could limit the extent to which our findings can be generalized; This study sample may or may not have similar demographic and disease characteristics in comparison to all childhood TB cases in Uganda during the same time period. The other limitations are related to the retrospective nature of the study design and methodologies used in ascertainment of some fundamental variables. Ascertainment of true TB diagnosis is prone to measurement errors using either microbiological or the clinical approach. However, it is important to note that this study is unique in focusing on Ugandan childhood TB, and for a low income setting our loss to follow-up of 16.8% is modest. Bias introduced by loss to follow-up is hard to quantify; our analyses found those lost to follow-up likely to be non-BCG vaccinated, HIV positive children with a history of failure to thrive. It is likely that most TB/HIV co-infected children were referred and transferred to specialized HIV/AIDs treatment clinics for comprehensive management of both illnesses. Those not vaccinated may be under the care of parents who have negative bias/attitude against vaccines and other modern healthcare services, or are overall lacking in resources to access healthcare. The failure to thrive children may be a

group with TB co-morbidities like HIV/AIDS. However, failure to detect statistical differences between these two groups with respect to other variables might have been due to limited statistical power of the study and a 'type II error'.

**Conclusion.**

Results from this study suggest that childhood TB cases with negative tuberculin skin test results should be considered a higher risk group for mortality and hence monitored more closely. More studies are needed to investigate other risk factors of childhood TB mortality. In settings with high TB burden, like Uganda, we need complete clinical data on childhood TB to improve our outcomes and monitor our progress. Complete documentation of all patient information by healthcare workers is fundamental in developing comprehensive medical records/data bases that can be used to obtain accurate prognostic factors for childhood TB. If healthcare workers become more aware of potential biases introduced by incomplete medical record data, and if they are regularly encouraged to make the effort to obtain and record necessary data, then these data become a valuable source for improving health outcomes.

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