**College of Medicine**

# Factors Associated with Mortality among Paediatric Tuberculosis Patients in Blantyre and Knowledge, Attitudes and Practice on Tuberculosis Transmission among Parents and Guardians of Children with Tuberculosis at Ndirande Health Centre in Blantyre, Malawi

**By**

**Mable Cynthia Kisyombe**

***(BSc Biomedical Sciences)***

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# DECLARATION

I, Mable Cynthia Kisyombe, hereby declare that this thesis is my original work and has not been submitted at this University or elsewhere for examination, award of a degree or publication.

Signature:

Date: 12th March 2022

# CERTIFICATE OF APPROVAL

The Dissertation of Mable Cynthia Kisyombe is approved by the Dissertation Examination Committee:

_____

Associate Professor Genesis Chowe

(Chairman, Post Graduate Committee)

_____

Dr Marriot Nliwasa

(Supervisor)

_____

Dr Fatsani Ngwalangwa

(Internal Examiner)

_____

Professor Adamson Muula

(Head of Department)

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# ABSTRACT

Although there is highly effective treatment, tuberculosis (TB) remains a leading cause of death in children. In 2018, 1.2 million deaths from TB among HIV-negative individuals and 251,000 deaths among HIV-positive people were estimated. Identifying patients at risk of death during TB treatment should be a priority for proper management. It helps in assessing the needs and identifying potential interventions that contributes to the End TB Strategy of reducing TB mortality by 95%. The study assesses factors associated with mortality amongst paediatric TB patients in Blantyre and knowledge, attitude and beliefs of TB disease transmission among parents/guardians of children. This was a cross-sectional study using retrospective records review of data extracted from Helse Nord Tuberculosis Initiative (HNTI) for different health facilities in Blantyre district and a primary data collection in assessing the knowledge, attitude and practice of the parents/guardians of children with TB and those with cough for more than a week at Ndirande Health Centre in Blantyre. The proportion of deaths was similar among males and females (5.1% compared to 5.6% respectively, with a P-value of 0.73). The death was higher among children of age group of 1 to 5 years with a death proportion of 6.9% compared to older children of 5-14 years (5.0%) although the results were not statistically significant P-value 0.374. Deaths numbers was higher among HIV positive children as 6.6% HIV positive children died comparing to 4.1 HIV negative patients who died with a P-value of 0.194. For the KAP study, parents/guardians had poor knowledge, attitudes and practices towards TB disease as of 150 participants interviewed in the primary data, 54.7% scored poor in knowledge, 68.7% had poor attitude and 22.0% displayed poor practices towards TB disease. There is a need to develop some effective techniques to educate the public on TB and improve the detection and management of tuberculosis in children.

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| | |
|---|---|
| AIDS | Acquired Immunodeficiency Syndrome |
| ART | Antiretroviral Therapy |
| ATT | Anti-Tuberculosis Treatment |
| BCG | Bacillus Calmette-Guerin |
| Cap | Catalyzing Paediatric |
| COM | College of Medicine |
| COMREC | College of Medicine Research Ethics Committee |
| DOT | Direct Observed Treatment |
| EPTB | Extra-Pulmonary Tuberculosis |
| FNA | Fine Needle Aspiration Biopsy |
| GDF | Global Drug Facility |
| HIV | Human Immunodeficiency Virus |
| HNTI | Helse Nord Tuberculosis Initiative |
| HTS | HIV Testing Services |
| IPT | Isoniazid Preventive Therapy |
| KAP | Knowledge Attitude and Practice |
| LTBI | Latent Tuberculosis Infection |
| MDR TB | Multidrug Resistant Tuberculosis |
| MLW | Malawi- Liverpool-Wellcome Trust Clinical Research Programme |
| NTP | National Tuberculosis Program |
| PITC | Provider-Initiated Testing and Counselling |
| QECH | Queen Elizabeth Central Hospital |
| RHF | Right Heart Failure |
| RIF | Rifampicin |
| RNTCP | Revised National Tuberculosis Control Program |

| | |
|---|---|
| TB | Tuberculosis |
| UN | United Nation |
| WHO | World Health Organization |

# CHAPTER 1: INTRODUCTION

## 1.1 Background

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* [1]. In most cases it affects the lungs (pulmonary TB), but can also affect other parts of the body (extra-pulmonary TB). The disease transmits when patients with TB disease expel droplets with bacteria into the air by coughing. Tuberculosis (TB) is one of the leading cause of death from infectious disease globally [1]. Children accounted for 12.5% of all TB infections in 2019 [2]. Among the total number children contracting the TB infection, only 39% are diagnosed and reported to national programs [3]. 10 million new TB cases were reported in 2020 of which 1.1 million were in children under 15 years of age representing about 11 percent of all TB case s [1]. In the year 2017 a number of children 194,000 died of the disease. The estimated mortality of children who do not receive specific treatment is 22% compared with 0.9% in treated children[4].

Children with TB disease presents with fever, tiredness, night sweats, and weight loss, while if the children have TB of the lungs they usually have coughing and chest pains [1]. Children have their immune system under developed so with TB disease their body cannot fight the TB bacteria under control. Children with TB have their immune system not as developed as that of adults therefore they have a higher chance of developing active TB 70-80% of children with TB, have the disease in their lungs (pulmonary TB) while the rest are affected by Extra-Pulmonary TB [5].

In Ethiopia 13% of all the TB cases occur in children and South Africa had a magnitude of 7% of notified TB cases [6,7]. The 98% of all the TB cases in children are acquired via the respiratory route[8]. Transmission of TB to children is mostly from adults with smear positive TB disease

[1,9]. The most major determinants of occurrence of childhood TB in the endemic areas include adult TB prevalence value which is estimated at 1% in some other endemic areas [10]. Another determinant is the smear positive rate which is reported to be about 56% in Nigeria [9].

The 2018 edition of the global TB report in the lead of UN high level meeting provides a comprehensive and current assessment data of TB epidemic and provides the way forward in the response to the epidemic at global, regional and country level [1]. It also states that a small proportion of about (5–10%) of the estimated 1.7 billion people infected with TB bacteria will develop TB disease during their lifetime [1]. Although the possibility of developing TB disease is much higher among people infected with HIV, it is also believed to be higher among people affected by risk factors such as undernutrition, diabetes, smoking and alcohol consumption.

### 1.2 Statement of the Problem

Malawi is implementing some activities to control TB and these includes; active case finding in communities by using the mobile Van to identify and treat TB cases, the health care facilities which are the primary case identifier [11]. The new identified cases are immediately prompt the initiation of TB treatment using Direct Observed Treatment (DOT) and home self-administration of the treatment. Many countries have challenges with TB diagnosis in children due to the limited ability of children to produce sputum and paucity of TB bacilli in samples produced. In Malawi there is lack of information for what has been done to establish factors associated with mortality in children who are on TB treatment. This study was responding to the recommendation by a survey done in central region of Malawi on “burden of disease and risk factors for death among children treated for TB in Malawi [12].” A study referred was conducted in Ntcheu district in

Malawi, in which gaps were discovered on the same topic and their findings were for a district with low population size, therefore, the results of their study could not be generalized hence recommended further investigations on the factors associated with mortality in children with tuberculosis in the country on a large scale.

## 1.3 Literature Review

### 1.3.1 Globally

Tuberculosis (TB) is a major and often recognized cause of morbidity and mortality globally (global tuberculosis 2021). In 2020, 1.5 million people died from TB disease among which 214,000 had HIV [1]. 10 million people were found to be infected with TB and 1.4 million deaths were reported in all age groups in 2019. In 2017, 233,000 children aged 0-14 years died of TB among which 17% died with HIV globally [13]. However, Up to 74,000 HIV-uninfected children die of TB every year[14]. Among the 233,000 childhood TB deaths occurred, 80% were in children <5 years, 96% of deaths were in children who did not access TB treatment and 17% of the deaths were among children with HIV [13]. TB affects all groups of people and age. The most exciting thing with TB is that it is curable and preventable. While a number 1.1 million of children are in need of treatment for TB, only 39% are diagnosed and reported to national programs [3]. This is so because of lack of innovative diagnostic tools to help in expand access to case identification which delay child friendly treatment that are now available.

### 1.3.2 Africa

In Africa, 20%-40% of TB cases is borne by children. According to WHO, over 95% of TB cases and deaths are in the developing countries which are the resource constraints countries [1]. There

is not enough data for the childhood TB burden in Africa due to the difficulties in diagnosis since many developing countries do not have the capacity for the TB diagnosis in children. The per-capita TB mortality was highest in sub-Saharan Africa, where roughly 36% of tuberculosis deaths were in children infected with HIV [15]. Infected infants have excessively high TB morbidity and mortality [16]. Most disseminated TB and central nervous system TB occur in at the age of 1-4 years while the age of 5-10 has least morbidity but increase mortality [16]. Africa is one of the WHO regions with the highest prevalence needing an immediate intervention and a regional strategy [15,17].

### 1.3.3 Malawi

In Malawi, TB is the second leading infectious cause of death after HIV/AIDS [3,18]. In 2016, Malawi registered 16,959 TB cases (NTP, 2016 report) of which childhood TB made up to 8.6% of these cases [3]. Catalysing Paediatric (CaP) TB is a four-year project, funded and supported by Unitaid, which aims to reduce paediatric TB morbidity and mortality in nine sub-Saharan Africa countries including Malawi [3]. As CaP TB hopes to double the paediatric TB case detection globally, Malawi will not be left out. The cap TB targets to identify approximately 2000 paediatric cases, treat at least 1,700 paediatric TB cases and initiate at least 2,400 children on preventive treatment [3] but this will not benefit all Malawian children with TB infection because projects have their targeted locations leaving others unreached. Much that TB cases are declining in Malawi, the country needs to continue scaling up ART to 100% of its HIV-infected population as a means of controlling both HIV and TB epidemics[19]. In Malawi HIV is contributing to TB deaths in children[12].

## 1.4 Risk Factors

There is high risk of having TB infection in men than women because of some of the behavior men do practice like taking alcohol and smoking which increases the possibilities of having TB [20]. Also people who are HIV positive are up to 20 times more likely to develop active TB disease [21]. HIV-infected children are at a high risk of severe disease and death due to MDR TB taking advantage of their body immunes system which is under developed [18]. Children with vulnerable immune systems, such as the very young, HIV infected or severe malnourished are most at risk for falling ill or dying from TB disease [1]. Malnutrition and not being treated for HIV (if the child was HIV positive) during TB treatment significantly increase the risk of poor outcomes. Disseminated TB and TB meningitis are also associated with high mortality and are more common in young children [22]. Weight loss is also found to be a contributing factor to TB death in children. HIV-coinfection poses special challenges to clinical management in patients with active TB and it is also a predict of deaths [22]. The article also revealed that age group of 5-14 years is also found to have highly contributing to early childhood TB death, this implies that attention is required for this age group.

## 1.5 Prevention

In 2017, over 75% (of 1.3 million eligible household contacts under 5 years of age) did not access preventive therapy [13]. A reason to having more TB infections in children. Behavior change communication addressing avoidance of overcrowding, ensure adequate ventilation, better personal habits with regards to spitting and coughing, and good nutrition are among the controlling measure to undertake in preventing TB in children [23]. Prevention of new infections of *Mycobacterium tuberculosis* and their progression to tuberculosis is critical to reduce the

burden of ill health and death caused by TB, and to achieve the End TB Strategy targets for 2030 and 2035 [18]. The current health interventions for TB prevention are treatment of people with TB infection (TB preventive treatment), prevention of M. tuberculosis through infection prevention and control and vaccination of children with the Bacillus Calmette-Guerin (BCG) vaccine [18]. The United Nations is committed to providing TB preventive treatment to at least 30 million people in the 5-year period 2018-2022 in which 4 million are children aged under 5 years who are household contacts of people with bacteriologically confirmed TB [18]. It is reported that although BCG vaccine has a documented protective effect against meningitis and disseminated TB in children it does not prevent primary infection and more importantly does not prevent reactivation of latent pulmonary infection [24]. Prevention of TB disease is cross cutting, we cannot prevent it in children while leaving adults TB unattended to.

Children with HIV are at an increased risk of both developing tuberculosis and dying from it, prevention of mother-to-child transmission of HIV and ART initiation for children who are HIV-positive should reduce child tuberculosis deaths [15]. Isoniazid Preventive Therapy (IPT) is intended to prevent recent TB infection from progressing to active TB disease and to prevent Latent TB infection (LTBI) from reactivation [25]. IPT is given for 6 months after a TB contact. If a patient is diagnosed with active TB they need a full TB treatment and not Isoniazid monotherapy [25]. Contact screening and management has enormous potential to prevent children exposed to and infected with TB from developing TB disease [1] intensifying TB screening can help identify and give treatment to the cases.

## 1.6 Multidrug Resistant - TB

The burden of MDR TB in children is likely to reflect that which occurs in adults [26]. Globally between 25,000 and 32,000 children develop MDR-TB disease each year, accounting for around 3% of all pediatric TB cases [4]. Only 3-4 of these children are likely to receive MDR-TB treatment. Hellen E. Jenkins et al estimated that 21% of the children who develop MDR-TB die, we can reverse this by identifying and isolating all MDR-TB cases [4]. UN general assembly high level meeting on TB committed to providing care to at least 3.5 million children with TB and 115,000 children with MDR-TB [18]. There were 3,400 and 5,500 children with MDR TB started on second-line treatment in 2018 and 2019 respectively meaning we have only reached 8% of the global target of 115,000 in two years [18]. Julie Huynh observed that although child-friendly drug formulation for susceptible and drug resistant TB are now available through the Global Drug Facility (GDF) major barriers still include inadequate diagnostic and treatment access in resource-limited setting [26].

This is because diagnosing children with MDR-TB is very challenging though they are some ways to detect this type of TB in children [27].

## 1.7 HIV in Tuberculosis

HIV-infected children are at high risk of severe disease and death due to MDR TB. Low success rate in children infected with HIV who did not receive ART during their MDR-TB treatment highlights the need to ART in these children [30,31]. About 17% of deaths were in children with HIV [15]. Children do well when treated with second-line MDR-TB medications (78% overall

had successful treatment outcomes) [18]. Malnutrition and not being treated for HIV (if the child was HIV positive) during TB treatment significantly increase the risk of poor outcomes.

### 1.8 Diagnosis and Treatment

Most childhood TB cases are sputum smear-negative, diagnosis relies largely upon clinical presentation, tuberculin skin testing, and chest radiography [30]. Diagnostic limitations contribute to treatment delays and high mortality [30]. In 2015, >96% of childhood TB deaths occurred in children who were not receiving treatment for the TB [15]. Globally, the political declaration at United Nations high-level meeting on tuberculosis (TB) in 2018 included targets to diagnose and treat 40 million people among which 3.5 million are children and 1.5 million people with drug-resistant TB among which 115,000 are children in the 5-year period 2018-202 [13,18]. These targets can only be achieved if there is awareness and communities' commitment to change. Out of the global total of the notified TB cases in 2019, 8% were children aged <5 years [18]. About half a million children were diagnosed and notified in both 2018 and 2019; the combined total of 1.04 million was 30% of the 5-year global target (for 2018–2022) of 3.5 million [18].

In sub-Saharan Africa, TB diagnoses have been based on certain validated traditional criteria for decades. These could be grouped into clinical, bacteriological, immunological and radiological criteria [31]. Principles of treatment of TB in children are same as for adults – with similar regimens. Children respond favorably to MDR-TB treatment [32]. Isoniazid preventive therapy (IPT) is one of the most effective but under-utilized tool against TB in children [33]. WHO guidelines recommend that all children should receive all oral regimen, many of the second line medicines now have child friendly formulations, and available through the STOP TB

Partnership's Global Drug Facility (Overcoming the drug resistant TB crisis in children and adolescents). In general, children do well when treated with second-line MDR-TB medications (78% overall had successful treatment outcomes) [18].

In Malawi, the recommended approach to diagnosing TB in children are: gathering a detailed patient history, including history of TB contacts, BCG status and symptoms consistent with TB; clinical examination including growth assessment; HIV testing which is called provider-initiated testing and counselling (PITC); sputum microscopy, Gene Xpert and culture testing when possible [11]. In children with palpable lymph nodes, collecting of an FNA offers a convenient way of collecting samples for GeneXpert, microscopy and culture [11].

### 1.9 Treatment Outcomes

There are different treatment outcomes to children who are on TB therapy. These outcomes are grouped into two categories; *treatment success* and *unsuccessful treatment* outcomes [36,37] Treatment success are those patients that had completed treatment and cured, while unsuccessful treatment are all those patients who had defaulted, died, or experienced treatment failure. There is no significant difference in the treatment success among male and female patients [35]. Identified risk factors for unsuccessful treatment outcomes in children are; being HIV positive, having low body weight, smear positive and being <5 years [35–37]. The study done in Nigeria found that childhood TB treatment was characterized by relatively poor outcomes. Children 0-4 years males and those with bacteriologic confirmation disease have higher chances of experiencing an unsuccessful treatment outcomes [38]. In 2010, Malawi in general had high rates of TB/HIV co infection resulted in worse treatment outcome and higher mortality [39].

## 1.10 Knowledge Attitude and Practice

Knowledge regarding any disease is very crucial in order to cure and ensure the good quality of life of patients [40]. Knowledge is also considered as a key factor in determining the attitude and practices of an individual [41]. The study in Gambia found that 25.2% defaulted from treatment and the defaulting rate was higher among those who said they were uncertain that their treatment would work [42]. This uncertainty came in because of lack of knowledge towards TB disease. There is gap in knowledge, attitude and practice towards TB in many African countries as Malaysia study found that the respondent had moderate knowledge and practice but poor attitude towards TB and TB patients [41]. New TB patients had better TB knowledge than non-TB patients but they had similar attitude and practice towards TB [43]. Lack of knowledge in TB disease would encourage people to seek other alternatives for their health care and this result into patient delay and default among newly diagnosed pulmonary TB patients [46,47]. However, patients that have ever suffered from TB before or have active disease have better knowledge than those that have never suffered from TB [43]. Negative attitude of individuals towards health care seeking was identified as an important attribute for delay for diagnosis and treatment [46]. In some studies, participants demonstrated to have received information on TB but their practical knowledge, attitude and practices does not reflect the information they received [47]. Medical personnel and mass media are acting as the successful means of disseminating information about TB [43]. Raising communities' awareness contributes to early diagnosis of TB, one of the pillars of the End TB Strategy [18]. There is a positive association between TB knowledge, care seeking and treatment adherence [48].

Perceived risk of transmitting TB to the healthy community members is a leading cause of stigmatization in other setting [51,52]. The fear of infection is often exaggerated and usually commences after the diagnosis and may persist even after treatment completion [51]. However, this kind of stigma is due to incorrect knowledge about transmission of TB. TB is known to have a great risk of transmission when one has prolonged close contact with untreated acid-fast smear positive TB patients, after two weeks of effective treatment, most patients the chances of transmitting the bacteria is minimized [54,55].

## 1.11 Conceptual Framework

As the way of interrelating factors associated with TB pediatric mortality, we thought of using a hybrid conceptual framework for risk factors for child death and disease ecology. This approach integrates ecological, social and biological variables in the analysis. We have direct and indirect effects of the deaths risk factors to TB pediatric patients. Variables are either endogenous (outcome) or exogenous (explanatory). We used the depended variable (deaths) as outcome, we determined the effects between categories to establish factors that lead to child TB mortality. Refer to figure 1 below.

**Figure 1: Conceptual framework diagram**

## 1.12 Rationale/Justification for the Research Project

In Malawi, there has been limited data to establish factors associated with death in children who have tuberculosis and paediatric TB outcomes are not reported. Some studies had been done in

remote setting where the population is low due the geographical location, hindering the ability to identify the child TB mortality determinants that can help in provision of proper childhood TB management. Malawi as a low-income country has limited diagnostic capacity, usually relying on sputum microscopy and GeneXpert tests with low sensitivity in the few children who can produce specimen. The study was conducted to assess risk factors associated to mortality in TB children as recommended by a survey done on "burden of disease and risk factors for death among children treated for tuberculosis in Malawi [12]". The study referred was conducted in Ntcheu district in Malawi, in which gaps were discovered on the same topic and their findings were for a district with low population size, therefore, the results of their study could not be generalized hence recommended further investigations on the factors associated with mortality in children with tuberculosis in the country on a large scale.

## 1.14 Broad Objective

The main aim of this study is to determine factors that are associated with deaths among paediatric TB patients in Blantyre.

### 1.14.1 Specific Objectives

The study would like to address the following:

1. To describe pediatric TB treatment outcomes
2. To describe the association between HIV/AIDS and TB
3. To investigate risk factors for death among pediatric TB patients
4. To assess knowledge, attitude and practice on TB transmission and prevention in parents/guardians of children attending TB care services in Ndirande Health Centre

# CHAPTER 2: METHODOLOGY

## 2.1 Study Design

This study was a cross-sectional study design that used two approaches; a retrospective records review of secondary data obtained from the previous studies conducted by Helse Nord Tuberculosis Initiative (HNTI) at different health facilities in Blantyre district. The HNTI is a collaborative programme between the Kamuzu University of Health Sciences (KUHeS) - formerly University of Malawi College of Medicine (UNIMA - COM), - the Malawi- Liverpool-Wellcome Trust Clinical Research Programme (MLW) and the Herse Nord RHF of the University of Tromso in Norway. And primary data collection using knowledge attitude and practice (KAP) methodology to assess the knowledge, attitudes and practices of parents/guardians of children with TB and those with a cough of at least a week presenting to Ndirande Health Centre in Blantyre.

## 2.2 Study Setting

HNTI collected data from different health facilities in Blantyre district to give a representation of both rural and urban settings and this is the data that was later reviewed for this study as secondary. Blantyre is a big district covering an area of 2,012 Sq.km and a commercial city situated in the Southern Region of Malawi where most businesses and offices are with the population size of 800, 264 in 2018 [54]. It has all levels of health care facilities, primary health facilities, which are health centres and clinics; secondary health facilities which include a district and some private hospitals, and tertiary health facilities which is the biggest referral hospital in Malawi the Queen Elizabeth Central Hospital (QECH). Health facilities that were included in the study were: 6 health centres, 4 private hospitals and 1 biggest referral hospital. QECH is the

Malawi's largest referral and teaching hospital which saves patients from neighboring districts, health centres and clinics, and private health care facilities. The health facilities where data was collected are; Health Centres: Bangwe Health Centre, Ndirande Health Centre, Chilomoni Health Centre, Zingwangwa Health Centre, Limbe Health Centre, South Lunzu Health Centre. Private Hospitals: Blantyre Adventist Hospital, Chitawira Hospital, Mlambe Hospital, Mwaiwathu Hospital and the biggest referral Hospital: Queen Elizabeth Central Hospital. For the location of these health facilities where data was collected refer to the map on *appendix 10.*

The KAP study was collected from Ndirande Health Centre. Ndirande Health centre is the busiest health Centre in Blantyre District. It has a big catchment area, patients come from Ndirande Township and other areas surrounding Ndirande like Machinjiri and Nyambadwe refer to *Appendix 10.*

### 2.3 Study Population

For the retrospective record review, the study reviewed the targeted electronic data for the TB patients who were less than 15 years of age that were enrolled in the HNTI study from 2014-2018. In data analysis, children were categorized depending on their age. Subjects that had all their data available were included and children with missing data were excluded from the study.

For the questionnaire survey, children and guardians that were capable of answering questions were included. Children and guardians capable of answering questions but did not show up during the time of the study were excluded.

## 2.4 Study Sample Size

Sample size was calculated using the risk of death as main outcome. The key risk factor being investigated was HIV status. The proportion of death among TB patients were 14.0% among those HIV positive and 7.4% among those HIV negative (HNTI data set). We needed 373 HIV positive patients and 373 HIV negative patients to demonstrate this difference at 80% power and alpha 0.05. STATA software was used for the calculation of the sample size. The available dataset had 512 HIV positive patients and 512 HIV negative patients, which is adequate for the comparison. For primary data, assessing the knowledge, attitude and practice, we purposively interviewed 150 patients and guardians to children attending TB care services at Ndirande Health Centre and those attending HIV during the time of study.

## 2.5 Data Collection Process

For the secondary data, the researcher used the checklist to extract data from HNTI on the following variables: Sex, Age, Education status, Employment, Health facility type, Type of diagnosis, type of TB, HIV status and Observed outcomes, Data was extracted according to the variables targeted, refer to *Appendix 5*. Secondary data was collected from Blantyre district TB surveillance system. In this surveillance system all patients registering for TB treatment were requested for their demographic information and followed up for treatment outcomes. This is standard procedure as TB is a notifiable disease. This information is also recorded in electronic format in addition to paper records (TB registers) in a system maintained by the Malawi-Liverpool-Wellcome Trust. This electronic dataset was made available for purpose of this analysis.

A researcher-administered survey to guardians presenting at the health centre was done using survey questionnaires. Questionnaires collected data on demographic details of the guardian, knowledge on the TB transmission, attitude on the TB patients and infection was assessed and practice pertaining to TB infections and as well how to prevent the tuberculosis disease from spreading refer to *Appendix 3*. Questionnaire used had undergone a pre-test to assess its validity and then revised to correct the gaps captured during pre-test.

### 2.6 Data Management and Analysis

Coded data was entered using statistical programmes; Microsoft Excel spreadsheet and analysed using STATA version 14.0. Data cleaning and cross-checking for missing variables was performed before conducting the analysis.

A multivariate logistic regression analysis with socio-demographic characteristics as covariates were used to determine factors associated with Tuberculosis in children. A Chi square test were used to test for associations between mortality and some covariates. A logistic regression was used to model the relationship between categorical variables. Graphs and tables have been used to present the summarized data. Descriptive statistics has been used to summarize categorical variables.

The independent variables used were child's sex, age, health facility type, HIV status, TB type, bacteriology. The independent variable in primary data analysis were parent/guardian gender, age, marital status, education, occupation, household social-economic status, number in the household,

knowledge, attitude and practice. The dependent variable of the study was mortality due to TB disease.

## 2.7 Ethical Consideration

Before commencement of the study an ethical approval was obtained from University of Malawi, College of Medicine Research Ethical Committee (COMREC) reference Number P.02/20/2968 refer to *Appendix 6*. Permission was sought from Helse Nord Tuberculosis Initiative where secondary data was reviewed, refer to *Appendix 8.* Blantyre District Hospital management where the primary data was collected from their Health Centre (Ndirande), refer to *Appendix 9.* Written informed consent was obtained from parents/guardians. Participants were informed that participation to the study was voluntary, they can choose to participate or not and that they can stop at any point they wish.

No participant identifier was used on the questionnaire or anywhere else. Data collected were considered private and confidential, and were accessible to the researcher only. Participant's information was de-linked from names and information was kept in a password protected computer.

# CHAPTER 3: RESULTS

## 3.1 Social Demographic and Clinical Characteristics of Children with TB

This section presents the results of the quantitative data reviewed to assess factors associated with mortality in pediatric TB patients. The researcher reviewed data of 1,077 children from 2014 to 2018 from children who had suffered from TB in Blantyre district.

### 3.1.1 Baseline Characteristic of the Study Participants

Of 1,077 children that had their data reviewed for the target period of 5 years -Table 1. There were 525 females and 552 males representing 48.8% and 51.2% respectively. The study had a representation from age groups of 0-1 years 191 (17.7%), 1-5 years 289 (26.8%) and 5-14 years 597 (55.4%). Data was also reviewed based on HIV status, it was observed that there was no difference in number between children with HIV negative and HIV positive both with 512 (47.5%), the rest had HIV status not known. Among the health facilities that had data reviewed, it was noted that a minimum number 73 (6.9%) of TB children were from private hospitals. Data was reviewed depending on the TB type a child suffered from and it was observed that among the reviewed data 642 (59.7%) children had Pulmonary TB and the rest had Extra Pulmonary TB. Biological samples were analyzed for the TB diagnosis by smear microscopy, culture and GeneXpert MTB/RIF, the collective results showed that of 1,077 children who had their data reviewed 98 (9.1%) were found to be positive for TB disease.

**Table 1: Baseline characteristics of the study participants**

| Variable | Category | Total Number (1,077) N (%) |
|---|---|---|
| Gender | | |
| | Male | 552 (51.2) |
| | Female | 525 (48.8) |
| Age in years | | |
| | 0 – 1 years | 191 (17.7) |
| | 1 -5 years | 289 (26.8) |
| | 5-14 years | 597 (55.4) |
| HIV Status | | |
| | Negative | 512 (47.5) |
| | Positive | 512 (47.5) |
| | Unknown | 53 (5.0) |
| Health Facility Type | | |
| | Hospital | 832 (77. 1) |
| | Health Centre | 172 (16.0) |
| | Private | 73 (6.9) |
| TB Type | | |
| | Pulmonary | 642 (59.7) |
| | Extra-Pulmonary | 434 (40.3) |
| Bacteriology | | |
| | Negative | 979 (90.9) |
| | Positive | 98 (9.1) |
| Treatment Outcomes | | |
| | Cured | 78 (7.2) |
| | Completed | 833 (77.3) |
| | Died | 58 (5.4) |
| | Lost to follow up | 108 (10.0) |

The figure below shows the trend of TB in children from 2014 to 2018. There were more TB cases in children in 2017, refer to figure 2.

**Figure 2: Trend of child TB cases**

Data was further reviewed depending on the treatment outcomes, the study found that of 1,077 children enrolled in the study, only 58 (5.4%) died of the disease, 78 (7.2%) cured, 833 (77.3%) were cured and 108 (10.0%) were lost to follow up.

**Table 2: Risk factors for mortality in children with TB**

| **Variable** | **Category** | **Dead Percentage N (%)** | **Risk Ratio** | **P-value** |
|---|---|---|---|---|
| Sex | Female | 27 (5.1) | 1 | 0.731 |
| | Male | 31 (5.6) | 1.09 (0.66-1.80) | |
| Age | 0-1 | 8 (4.2) | 1 | 0.374 |
| | 1-5 | 20 (6.9) | 1.65 (0.74-3.67) | |
| | 5-14 | 30 (5.0) | 1.26 (0.56-2-57) | |
| HIV Status | Negative | 21 (4.1) | 1 | 0.194 |
| | Positive | 34 (6.6) | 1.62 (0.95-2.75) | |
| | Unknown | 3 (5.9) | 1.38 (0.45-4.35 | |
| Facility Type | Health Centre | 8 (4.7) | 1 | 0.789 |
| | Hospital | 45 (5.4) | 1.60 (0.56-2.42) | |
| | Private Hospitals | 3 (6.9) | 1.47 (0.50-4.35) | |
| TB Type | Extra-Pulmonary | 35 (5.4) | 1 | 0.918 |
| | Pulmonary | 23 (5.3) | 0.97 (0.58-1.62) | |

Table 2 shows risk factors for mortality. The study found that the odds of mortality is the same among all age groups of children. For HIV status the risk ratio (RR) of death was 1.62 (95% CI: 0.95 to 2.75, p=0.194) for HIV positive children compared to HIV negative. HIV is not considered a risk for death. The RR for facility type was 1.60 (95% CI 0.56 – 2.42) for hospital and 1.47 (95% CI 0.50 – 4.35) for private hospital compared to health centre. The type of TB also did not pose an increased risk to dying RR 0.97 (95% CI: 0.58 -1.62, P-value=0.918), that means there is no difference in death risks for children dying from Extra-Pulmonary and Pulmonary.

### 3.2 Socio-Demographic Characteristics of Respondents of the KAP Study

The socio-demographic characteristics of the participants in the KAP survey were as follows; Out of 150 participants, the majority (136/150, 90.3%) were females, Table 3. Of the participants that were interviewed (42.0%) were among the ages of 26 to 35 years old. The mean age for the participants was 37.5. Most of the participants were married, 81.3%. A higher proportion of the participants (44.7%) attended a secondary and higher education. Most respondents 80.7% were from the households that earn less than k 45000 per month. Most respondents were from the households with 2 children and 2 adults (36.0% and 48.0% respectively).

**Table 3: Background characteristics of the parents/guardians**

| **Variable** | **Category** | **Proportion of respondents 150 (100%)** |
|---|---|---|
| **Sex** | Male | 14 (9.3) |
| | Female | 136 (90.7) |
| **Age** | <15 years | 11 (7.3) |
| | 15-25 years | 45 (30.0) |
| | 26-35 | 63 (42.0) |

| | | |
|---|---|---|
| | >35 | 31 (20.7) |
| | Mean Age | 37.5 |
| | Standard Deviation | 19.0 |
| **Marital status** | Single | 15 (10.0) |
| | Married | 122 (81.3) |
| | Divorced | 13 (8.7) |
| **Education** | None | 30 (20.0) |
| | Primary | 53 (35.3) |
| | Beyond Primary | 67 (44.7) |
| **Employment** | None | 88 (58.7) |
| | Business | 53 (35.3) |
| | Student/other | 9 (6.0) |
| **Household earning/ month** | <45,000 | 121 (80.7) |
| | 45,000-100,000 | 24 (16.0) |
| | >100,000 | 5 (3.3) |
| Number of people in a house | Children 1 | 32 (21.3) |
| | 2 | 54 (36.0) |
| | 3 | 39 (26.0) |
| | > 3 | 25 (16.7) |
| | Adult 1 | 5 (3.3) |
| | 2 | 72 (48.0) |
| | 3 | 44 (29.3) |
| | >3 | 29 (7.3) |

### 3.3 Tuberculosis Knowledge, Attitudes and Practices

*Table 4* describes the knowledge of the respondents about TB transmission and risk factors. Out of 150, the majority 120/150 (80.0%) respondents answered wrongly on whether TB can be transmitted by exchanging clothes with the infected person. Three quarters (113/150, 75.3%) of the respondents were of the opinion that TB can spread through coughing droplets. The majority of the respondents (120/150, 80.0%) expressed that TB patients on treatment should not mix with others though on treatment. Among the participants, (93/150, 62.0%) of respondents accepted that only poor people can spread TB.

**Table 4: Knowledge, Attitude and Practice of TB disease**

| KNOWLEDGE, ATTITUDE AND PARACTICE OF TB DISEASE | | |
|---|---|---|
| **Prompt question** | **Answered correctly n (%)** | **Answered wrongly n (%)** |
| **Knowledge** | | |
| TB is spread through clothes | 30 (20.0) | 120 (80.0) |
| TB is spread through coughing droplets | 113 (75.3) | 37 (24.6) |
| TB patients not to mix with others though on treatment | 30 (20.0) | 120 (80.0) |
| Only poor people can be infected with TB | 57 (38.0) | 93 (62.0) |
| **Attitude** | | |
| Not comfortable to mix with TB patients | 32 (21.3) | 118 (78.7) |
| Not try to touch TB patients | 47 (31.3) | 103 (68.7) |
| Will Stay away from a spouse with TB | 39 (26.0) | 111 (74.0) |
| Will take care of patients despite them having TB | 83 (55.3) | 67 (44.7) |
| **Practice** | | |
| I will go to hospital if have chronic cough | 107 (71.3) | 43 (28.7) |
| Will go to hospital if have other TB related symptoms | 112 (74.7) | 28 (25.3) |
| I will encourage other household members to go for medical check up | 121 (80.7) | 29 (19.33%) |
| I will buy medication from grocery | 53 (35.3) | 97 (64.7) |

Out of 150 respondents, 118 (78.7%) expressed that they cannot be comfortable mixing with TB patients while out of those that were asked if they can try to touch TB patients only 47 (31.3%) expressed that they can. Among the 150 responded, 39 (26.0%) showed interest of staying with their spouse with who infected with TB *(Table 4).*

Out of 150 respondents that were interviewed 107 (71.3%) expressed that they will go to the hospital if discovered to have chronic cough. More than half 112 (74.7%) admitted to go to the hospital if having other TB related symptoms. Among the respondents, the majority 121 (80.7%) showed willingness to encourage other household members to go for medical checkup. To buy medication from grocery for the relations, household members and close friends following diagnosis of TB, the majority of participants 97 (64.67%) declined.

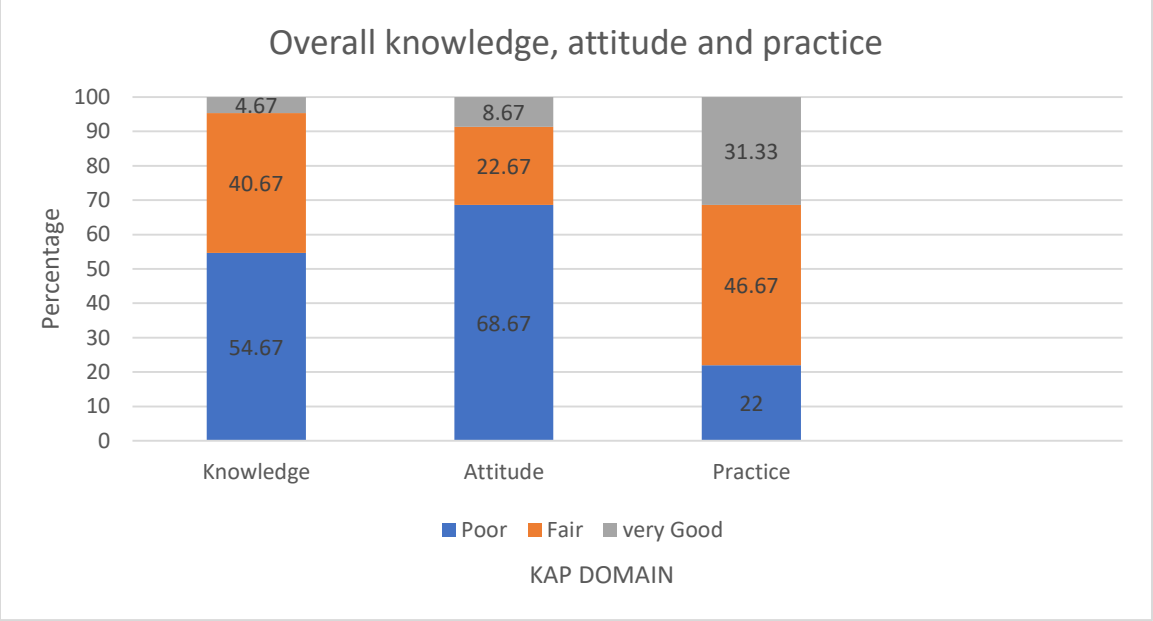


**Figure 3. Overall Scores on Knowledge, Attitude and Practice of TB disease**

Figure 3 shows the overall proportions of guardians on knowledge, attitude and practice for TB disease. Out of 150 participants interviewed 54.7% scored poor in knowledge. Among all the respondents, 68.7% had poor attitude on the TB disease. Of all the respondents that were interviewed 46.7% showed that they go to hospital when having chronic cough, seek medical attention when having TB related symptoms and encourage others to seek medical attention when showing signs and symptoms of TB.

# CHAPTER 4: DISCUSSION

## 4.1 Introduction

The study determined factors that are associated with mortality among paediatric TB patients and described knowledge, attitudes and practices of TB spread and prevention among guardians.

### 4.1.1 Baseline Characteristics of the Study Participants

The study found that there were more children with TB cases in 2017 as the number of cases were 268/1,077 representing 24.90% and the least was in 2015 with 178/1,077 (16.50%) children TB cases. From the TB cases trend, it was observed that Malawi is far away from the STOP TB target of having 100% TB free country. The trend is not consistent and not decreasing as expected with WHO and stop TB partnership[5]. This is in line with WHO findings That states that the TB incidence rate is falling, but not fast enough to reach the 2020 milestone of a 20% reduction between 2015 and 2020 [18]. This could be due to the lack of effort put towards TB in children that could result in having fewer cases as we go with years. The increasing trend of TB cases need to be reversed by adopting the zero combating of tuberculosis strategies that were put in place.

Much that strategies are developed that can be implemented to identify, diagnose and treat infants, under-five and children with TB, Malawi seem to be way behind in implementing these strategies. Children are at higher risk of contracting TB infection and with their underdeveloped immune system they can develop a disease that can result into deaths if not treated immediately hence need to be fast targeted group. Of the 1,077 children with TB, the study observed the majority being male 552 (51.2%) and this is consistent with other studies [35,37,58]. When Malawi is implementing the STOP TB strategies, much consideration should to be put to children.

More TB cases were observed among older children of age 5-14 years. The study found that among the total number of TB children the proportion between HIV Positive and HIV Negative were the same 47.5%. This means that the probability of contracting TB infection is the same whether a child is HIV positive or not, hence proper measures must be followed to prevent children of either age from getting exposed to TB infection. Despite provision of HIV Testing Services (HTS) to almost every TB case 53 (5%) had their HIV status not known. This could be due to; unwillingness of the parents to consent for their children to get tested, quality of counselling being offered to parents. However, studies can be done to determine the reasons in future. The majority of the TB children were from the biggest referral hospital QECH with 832 (77.1%). This was so may be because many cases are left unattended to while at home thinking they will get better at some point, when the condition worsen is when many decide to seek medical care and due to the stage at which the condition is many health centres refer the cases to big hospital for proper management.

Though the majority of the TB cases in this study had pulmonary TB with 642 (59.7), Extra-Pulmonary TB cases should not be undermined as it is the kind of TB that causes mortality in children. Children are more vulnerable to TB meningitis and military TB the forms of Extra-Pulmonary TB [1] hence need put much attention on this area as well. Extra- Pulmonary TB can be prevented if children can be the most targeted group in managing tuberculosis. Data was reviewed on the bacteriology confirmation that is Xpert MTB/RIF which allows the detection of both MTB and Rifampicine Resistance, microscopy, culture among others, the majority 90.90% of children had their TB test results negative. This may due to limitation in diagnosing children TB as they have difficulties in producing sputum. The diagnosis of TB in children relies on the

thorough assessment of the disease starting with the history of exposure, clinical examination and relevant investigations [11].

### 4.1. 2 Risk Factors for Mortality

This study revealed that the treatment outcomes among children enrolled for treatments were favorable in the sense that more than half of the TB patients had completed their treatment and 7.2% had cured from the disease though a small proportion. On the other hand, those that died from the disease are few (5.4%). Despite having hope that the TB treatment is working we still need to minimize the number of deaths to zero in order to get to the target of having TB free country.

WHO and the stop TB partnership are working by having all public health programs and health care providers to transform the approach to TB case finding so that all children with TB get high quality care that can help the world move towards Zero TB deaths among children [5,23] which is achievable even here in Malawi . WHO and partners brought in various measures to put in place in order to achieve the zero TB cases countries, the childhood TB to be viewed as a family illness; every child be infant or other age showing typical signs and symptoms of TB and who live with a person who has TB should be treated for TB infection [1,5]. Secondly, conducting TB case identifying campaigns to find all people affected by TB and efforts to be made to actively look for people with TB in the communities that are at risk and assist them to get diagnosis and care. Thirdly, prioritizing the outreach in children living with HIV, screening programs should provide testing for both infections to all children. Those who test positive for HIV should be tested for TB and if TB diagnosis is confirmed then they need to start TB treatment immediately. Lastly,

integrating maternal and child health services, HIV care and TB care into a seamless package, all pregnant women who are HIV positive should be examined for TB and provide with treatment if needed or preventive therapy. Children who are malnourished or HIV positive should be examined for TB [5,56].

The study has observed that there is no difference in risk of mortality between male children and female children. We have found no difference in risk of mortality from TB between those that are HIV negative, positive and unknown. There have been contrasting results within Malawi where it was found that children on ART who are diagnosed with TB in routine setting die at higher rates than patients who newly initiate ART [12]. Other studies also observed increased hazards of death in patients with HIV who were not on treatment [58].

The study has also found that the risk of death is the same among all age groups of children. Much that other studies found that HIV is a well-known risk factor for TB and that children with vulnerable immune systems, such as the very young, HIV-infected or severely malnourished are most at risk for falling ill or dying from TB [5,54]. This study has further found that there is no difference in risk of dying from TB between those that are HIV negative, positive and not known, while other studies observed increased hazards of mortality in patients with HIV who were not on treatment [58]. The risk of mortality from TB was the same among all children dying from all hospitals thus no difference in mortality risk among children who had been treated at health centers, private hospitals and a big Hospital. This means that children suffering from TB receive equal treatment in all levels of health facilities. During the study it was also observed that the risk of mortality from TB is the same among pulmonary and extra-pulmonary patients as the P-value

=0.918. This entails that children suffering from pulmonary TB are not different from those that are suffering from Extra-Pulmonary TB on the risk of mortality hence require same attention on TB prevention and management.

## 4.2 Knowledge Attitude and Practice of TB Transmission

### 4.2.1 Knowledge of TB Transmission

We have found more than half of the participants did not know that TB cannot be spread through sharing clothes and interacting with TB patients on treatment. Knowledge has been shown to be an important factor for quality of TB care. These factors influence the quality of care in TB treatment and care. In line with these findings, other studies in Africa have shown that the quality of care in TB treatment and care is poor and it is influenced by certain factors, for example lack of knowledge on how TB is spread, attitude and practice [58]. Children are affected most acutely in areas where adult TB is poorly controlled [34].

The study observed that the majority of respondents 40.7% had sound knowledge on TB transmission which is similar to the findings by a study done in Lesotho, Nigeria and India [59–61]. There was difference between gender, level of education and monthly income and most respondents knew that TB is not spread by exchanging clothes. The study showed that secondary education was associated with reduced odds of poor knowledge, attitude and practice Univariate OR 0.21, 95% CI (0.06- 0.78) and Multivariate OR 0.17 95% CI (90.04-0.67) and P-value 0.01 compared to those that did not have any form of education. This therefore means having attended secondary or primary education improves knowledge, attitude and practice on the TB disease. This was also showed by Palash Das et al where the study assumed that literate were better

informed and were more aware about various aspects of TB as compared to illiterates [61]. In this study most respondents were able to know that TB can be transmitted by TB patients mixing with others though on treatment. Surprisingly, most respondents agreed that only poor people can be infected with TB and mostly poor people are at greater risk of being infected with TB.

The study shows that knowledge on TB does not depend on age as people of all ages indicate that they did not know issues about TB diseases. The overall TB knowledge of respondents was poor as only 4.7% demonstrated good knowledge on the disease, which is contrary to the studies done in Ethiopia as 54% and 92.0% of participants had good knowledge about TB in North Mech and Holeta town respectively [49,64].

### 4.2.2 Attitude of Guardians towards TB Patients

The study revealed that of the total respondents, 78.7% showed that were not comfortable to mix with TB patients. More than half also showed that they cannot try to touch TB patients, 74% answered that they will stay away from their spouse if s/he is confirmed to have with TB because they are afraid of being infected. This brings stigma and discrimination within family members resulting into the patient getting depressed hence deteriorating of the condition. These results are similar with the study done in Kenya [51]. There is a need to engage the affected households to programs of health promotions and intensify Health Surveillance Assistants site visits to provide TB awareness campaign. Most participants in this study have been observed to have had an unfavorable attitude towards TB patients contrary to the study done in Malaysia where more than half had positive attitude towards TB [41]. This has a negative effect in TB management as most

patients rely on their guardians to remind and monitor them when taking medication, it can result into patients missing treatment hence chances of transmitting it to others.

### 4.2.3 Guardian Practice towards TB

The study has observed that most respondents (guardians) had good practice regarding TB and this was observed in 107 (71.3%) that expressed that they will go to hospital if have chronic cough, 112 (74.7%) will go to hospital if have other TB related symptoms and 121 (80.7%) will encourage other household members to go for medical checkup. These results are similar to another study done in Malaysia [41]. Seeking medical care will help improve people's health as they will get proper medication for the TB disease and this will reduce TB cases and its spread will be minimized.

The key predictors of good practice for TB were being married, having at least primary school level education, having a job, good TB knowledge and favorable attitude towards TB. However, over half (64.7%) of the respondents said that they prefer buy medication from grocery whenever they have prolonged cough. Self-medicating can delay seeking medical care and can contribute to antimicrobial resistance which can result into a patient having prolonged suffering of TB disease. As a good health practice, it is expected for patients to have presented first and seek medical attention in a nearby hospital or clinic before using over-the-counter (OTC) medication without a prescription. The OTC drugs are safe if used at recommended doses and can result into serious body damage including microbial mutation when taken long drugs. Abusing of OTC drugs can lead to problems like memory loss, kidney failure, heart problems and death depending on what drug and how much is consumed without following the recommended doses.

In the present study, the overall knowledge and attitude was poor as out of 150 participants interviewed 54.7% scored poor in knowledge, they did not know how TB disease can be transmitted while only 4.7% demonstrated full knowledge about TB and its transmission. The lack of knowledge makes it difficult in assisting the TB patient as most guardians will not pay much attention to the needs of the patient and what measures to put in place to prevent TB spreading. Out of 150 participants 68.7% of the respondents had poor attitude on the TB disease. This results TB mismanagement as people pay little attention to TB disease hence more cases of TB and MDR-TB. This study found that overall practice among respondents was poor as 31.3% only had shown good practice towards TB lower that the study done in Ethiopia [47]. This tells us that there is lack of attention in as afar as prevention and management is concerned amongst the community members. Awareness campaigns can help sensitize the community on issues to do with TB.

### 4.3 Limitations

It was difficult to meet some TB patients that are on treatment during the time of study due to luck of some important information like phone numbers and proper address from the TB registers.

# CHAPTER 5: SUMMARY, CONCLUSION AND RECOMMENDATIONS

## 5.1 Summary

This study analysed secondary data from HNTI that was collected from Blantyre district health facilities that includes; health centres, private hospitals and the country's biggest referral hospital and primary data from Ndirande Health Centre. Children of less than 15 years had their data reviewed, and parents and guardians of children seeking medical care at Ndirande health centre. The study found that having HIV positive does not pose a risk to TB deaths, children can get cured if they are given good medication, management and disease awareness and attending primary or secondary education improves knowledge about the TB infection compared to those who do not attend school at all.

## 5.2 Conclusions

Despite observing no difference in risk of TB mortality between those that are HIV positive, negative and those that their HIV status was not known this study recommends that the ministry of Heath should intensify TB diagnosis in all newly identified HIV children. Having HIV positive does not pose a risk to TB deaths, children can get cured if they are given good medication, management and disease awareness. As the risk of mortality from TB was the same among all children dying from all levels of health facilities, the Ministry of Health should focus much on the provision of medication in primary care where most people access health services. Though there was no significant difference in risk for death in Extra-pulmonary and Pulmonary TB, case detection in children is of paramount importance.

The knowledge is paramount for the prevention, control and management of the TB disease, this means having past primary or secondary education improves knowledge, attitude and practice on TB disease. This study suggests that the Ministry of Health should join with ministry of education in strengthening TB-related lessons in all levels of education to help impart knowledge and have good upbringing of children.

## 5.3 Recommendations

According to the findings of this study, it is important for the government scaling up testing for HIV all children presenting with TB and or signs that they might have TB.

It is important to ensure that there is continued mentorship on the cadres that work on the management and initiation of ART and TB treatment to manage any drug interaction in the HIV and TB treatment.

We recommend that policy makers should develop standards/guidelines to intensify TB screening using GeneXpert MTB/RIF assay technology in clinics to increase TB case finding among HIV infected children to identify drug resistant TB.

The Ministry of Health to conduct health awareness campaign in communities emphasizing the effects of TB transmission.

## 5.4 Further Research

More research needs to be conducted to establish better ways of diagnosing TB in children and also ways to reduce the risk of mortality in TB pediatric patients.

## 5.5 Conflict of Interest

We declare that there was no conflict of interest for our study.

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# APPENDICES

## Appendix 1. Informed Consent Form English

## Factors associated with deaths among paediatric tuberculosis patients in Blantyre, Malawi

### Introduction

You are being invited to take part in our research study investigating the factors associated with deaths among paediatric tuberculosis here at Ndirande Health Centre. This form explains what the study is all about, and what will happen if you agree to take part in the study. Please ask us if there is anything that you don't understand. You will be given a copy of this information to keep.

### What is the purpose of this study?

Globally, little has been done to establish factors associated with death in children who has tuberculosis. Countries with the highest TB burdens have limited diagnostic capacity, usually relying on sputum microscopy, a test with low sensitivity in the few children who can produce specimens. In Africa, only one third of the estimated one million cases of TB in children that occurred in 2010 were reported. This is due to challenges with TB diagnosis in children among which is limited ability of the children to produce sputum and paucity of TB bacilli in samples produced, little or no access to rapid detection and treatment initiation.

The study is responding to the recommendation by a survey done by R.J. Flick and colleagues in 2016 on "burden of disease and risk factors for death among children treated for tuberculosis in Malawi" The study discovered gaps on the topic, therefore, recommended further investigations on the factors associated with deaths in tuberculosis children in the country. Findings of this study

may influence policy makers to revise or come up with some proper measures to help in rapid detection and management of children tuberculosis.

**Why am I being invited to take part?**

You have been selected to participate in this survey because you have a patient child suffering from coughing for more than a week and some, your children have TB and being managed here at Ndirande Health Centre. The study participants are parents/guardians of children 6 to 15 years of age. We therefore believe that your contribution to this research will be valuable.

**What is going to happen?**

If you don't have any problem taking part in the study, the researcher of the study will ask you some questions using a questionnaire prepared. The interview will take approximately 15-20 minutes. The responses you give will be recorded on the questionnaire to make sure we don't miss anything. The questions will focus much on knowledge, attitude and practice on TB disease but we may also ask your personal background e.g. your highest level of education, your occupation and household monthly income.

**Will I benefit and are there any risks?**

There are no immediate benefits for participating in this survey but the results to this study will be wide reaching to the whole society. We believe that results from this survey will help the government coming up with good strategies on how best TB in children can be detected and managed at an early stage to avoid child deaths from the disease. The interview will take up some of your time, but we will arrange a time for the interview with you so that you can choose a time that minimizes any inconvenience.

**How confidential is the information I give you?**

Please be assured that the information you give will be kept confidential and your name will not be used anywhere nor mentioned when disseminating the results of this study. Files will be accessible by the investigators only and there will not be any link to trace a questionnaire. We may use quotes from what you have told us in reports on the study, but we will not use your name.

**How will the research findings be shared?**

Results of this project will be presented in research dissemination meeting. A copy of the final report outlining the findings will be submitted to College of Medicine Research and Ethics committee, Helse Nord Tuberculosis Initiative, College of Medicine Library, Blantyre District Hospital Office and The Ministry of Health. In all this dissemination, quotes from individual interviews may be used, but your name and the names of specific research projects will not be shared.

**Do I have to take part?**

Taking part in the study is entirely voluntary, you are free to change your mind and withdraw at any time you may feel uncomfortable. Withdrawal from the study will not affect the child TB treatment, however, we will appreciate if you decide to take part and answer our questions. You will be given this sheet to keep and we will ask you to sign a consent form.

**What if I have questions?**

If you have any questions or need for any clarification regarding this study please contact the principal investigator, Mable C. Kisyombe on +265 999 07 51 40, or email: mablekisyombe@ymail.com

**What if I have complaints to make about the study?**

If you have questions about your rights as a research participant or any concerns about the study, please contact Chairman, College of Medicine Research and Ethics Committee (COMREC) (phone: 01 871 911 ext. 334) will be happy to answer them. Concerns may also be forwarded to COMREC at: +265 1 874 377. Fax: +265 1 874 740 College of Medicine, 3rd Floor, John Chimphangwi Learning Resource Centre, Private Bag 360, Chichiri, Blantyre 3, Malawi or email: comrec@medcol.mw

**Consenting**

If you are willing and free to participate please sign/print your thumb below and we will ask you a number of questions using the following questionnaire.

| | |
|---|---|
| Participant ID ……..…… | Principal Investigator…… |
| Signature/Thumb print..... | Signature …… |
| Date..... | Date…… |

**Appendix 2. Informed Consent Form (Chichewa)**

# Zifukwa zimene zimapangitsa kuti ana odwala nthenda ya Chifuwa chachikulu azimwalira mu boma la Blantyre

## Malonje

Inu mwasankhidwa kutenga nawo mbali mu kafukufuku amene tikuchita okhudza zinthu zimene zimapangitsa imfa za odwala chifuwa chachikulu cha TB pa chipatala cha Ndirande. Form iyiyi ikulongosola kuti kodi kafukufuku ameneyi ngotani ndipo chidzachitike ndi chani mudzakatenga nawo mbali mu kafukufukuyu. Chonde funsani mafunso ngati pena sipanamveke bwino.

## Cholinga cha kafukufukuyu ndichani?

Maiko omwe ali ndi chiwelengero chachikulu cha anthu odwala TB ali ndi kuthekera kochepa kopeza matenda a TB mwa munthu kaamba kakusowa kwa zida zamphamvu makamaa kwa ana ang'onoang'ono omwe sangakwanitse kutulusa makhololo. Chifukwa chakusowa kwa zidaku, mwa ana oposa 1000 omwe anali ndi matenda a TB, ana osaposela theka okha ndiamene anakwanisidwa kupezedwa ndi matendawa chifukwa cha kuchepekedwa kwa zida zoyezela.

Zotsatira zakafukufukuyu zidzathandiza boma kuti apeze njira zamakono zoyesera matenda a TB zimene angakhale ana aangono akhoza kuyeseredwa.

## Mchifukwa chiyani ndasankhidwa

Mwasankhidwa chifukwa choti muli ndiodwala amene akudwala wakhala akukhosomola kwa mopitilira mulungu umodzi kapenawodwala wanu ali ndi TB ndipo iyeyo akulandila chithandizo kuno ku Ndirande. Inuyo ndinu woyenera kutenga nawo mbali chifukwa mwana wanu ali ndi

zaka zosachepela zisanu ndi chimodzi (6) komanso zosaposela khumi ndi zisanu kuti atha kuyankhula bwini bwino. Kutengapo kwanu mbali mkafukufukuyu kudzakhala kwamtengo wapatali.

**Chidzachitika ndichiyani?**

Mukavomereza kutenga nawo mkafukufukuyu, opanga kafukufukuyu adzakufunsani mafunso amene mukuyenera muzidzayankha. Muzidzafunsidwa mafunso kwa mphindi pafupifupi makumi awiri ndipo mayankho anu azidzalembedwa mu chipepala cha mafunso chomwe chakonzedwa. Mafunsowa kwambiri adzakhala okhudza zomwe mukudziwa zokhuza matenda a chifuwa cha chikulu cha TB komanso tikhoza kudzafunsa zaumoyo wanu makamaka maphunziro anu, ntchito yomwe mumagwira komanso chuma chimene mumapeza ngati banja lanu pa mwezi.

**Kodi ndizapeza phindu lanji, nanga pali zoopsa zanji?**

Palibe phindu lapompopompo koma zotsatira za kafukufukuyu zidzakhala zothandiza dera lonse. Tikukhulupilira kuti zotsatira za kafukufukuyu zidzathandiza boma kupeza njila zabwino zopezela matenda a TB mwa ana ang'onoang'ono. Mafunsowa atengako kanthawi ndithu chotero tikupemphani mutiuze nthawi imene mungakwanise.

**Kodi uthenga mukutengawu ngotetezeka bwanji?**

Uthenga uwuwu ndiotetezeka kwambiri ndipo sudzapelekedwa kwa wina aliyense kupatula owe akutenga nawo mbali mkafukufukuyu. Mauthenga ena omwe mutiuze adzagwilitsidwa ntchito polemba ma repoti koma sitizatchula dzina lanu.

**Kodi zotsatira za kafukufukuyu zidzagawidwa bwanji?**

Zotsatilazi zidzafalisidwa mu misonkhano yaza sayansi. Zotsatilazi zidzapelekedwanso ku sukulu yaukachenjede ya zaudotolo ya College of Medicine komanso bungwe la Helse Nold TB Initiative, ma office a chipatala cha Blantyre komanso ku boma la Malawi ndi zina mwa mfundo zanu zidzagwilitsidwa ntchito ngakhale dzina lanu silidzatchulidwa.

**Ndikuyenera kutenga nawo mbali?**

Kutenga nawo mbali mkafukufukuyu ndikosakakamiza ndipo mukhoza kusiya nthawi iliyonse ngati mwafuna. Kusiya kutenga nawo mbali sizingapangise kuti mwana wanuyu asathandizidwe komabe tidzakhala othokoza mukatenga nawo mbali mkafukufukuyu. Tidzakufunsani kulemba dzina lanu pa form yi.

**Ndikhoza kufunsa mafunso?**

Mukakhala ndifunso lirilonse funsani ochita kafukufukuyu a Mable C. Kisyombe pa 0999075140 kapena tumizani uthenga pa mablekisyombe@ymail.com.

**Nanga ngati nditakala ndi madandaulo ndingawapeleke kwa ndani?**

Mutakhala ndi dandaulo lirilonse, yankhulani ndi wapampando wa bungwe loona za Umoyo wanu la COM research ethics committee (COMREC) pa: 01871911, kapena lembani uthenga pa comrec@medcol.mw.

**Kutenga chilolezo**

Ngati mwavomela kutenga nawo mbali mkafukufukuyu lembani dzina lanu kapena dindani chala chanu mmusimu.

| | |
|---|---|
| Participant ID ……..……. | Principal Investigator…… |
| Signature/Thumb print..... | Signature …… |
| Date..... | Date……. |

**Appendix 3. Questionnaire (English)**

**KNOWLEDGE, ATTITUDE AND PRACTICE OF TB DISEASE QUESTIONNAIRE FOR PATIENTS/GUADIANS**

**Name of Heath Facility** _____

**Participant ID** _____ **Date** _____

Kindly answer by ticking ☑ in the boxes for the best response to which you agree or disagree, yes or no and the best answer with the following statements where applicable to you.

**Social Demographic Information**

1. Sex: Male ☐ Female ☐
2. Gender <15Years ☐ 15-25 Years ☐ 26-35Years ☐ > 35 Years ☐
3. What is your marital Status?

   A. Single ☐ B. Married ☐ C. Divorced ☐ D. Widowed☐
4. What is your highest level of education?

   None ☐ Primary ☐ Secondary ☐ Tertiary ☐
5. What is your occupation?

   A. None ☐ B. Student ☐ C. Farmer ☐ D. Private institutions/NGO ☐

   F. Business☐ Others specify ……
6. How much is the household in a month?

   <45,000 ☐

   45,00-100,000 ☐

>100,000 ☐

7. How many people are there in your household? Children <15 years……. Adult of 15 and above …….

**Knowledge on TB**

Knowledge on TB transmission

8. TB can be spread through sharing of cloths

   Strongly agree ☐ Agree ☐ Unsure ☐ Disagree☐ Strongly disagree ☐

9. TB can be spread through coughing droplets

   Strongly agree ☐ Agree ☐ Unsure ☐ Disagree☐ Strongly disagree ☐

10. TB patients should not mix with others even though they are under treatment because they can spread the infection

    Strongly agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strong disagree ☐

11. Only poor people can be infected with TB

    Strongly agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly disagree ☐

**Attitude**

12. I'm not comfortable to mix with TB patients

    Strongly agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly disagree ☐

13. I will not mix or mingle with TB patients because I do not want to be infected

    Strongly agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly disagree ☐

14. I try not to touch TB patients because I fear I might be infected

Strongly agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly disagree☐

15. I will not marry people who have TB because he/she will infect me

Strongly agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly disagree ☐

16. I will stay away from my spouse if he/she has been confirmed to have TB because I am afraid of being infected

Strongly agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strong disagree ☐

17. I will still take care of the patients despite having TB

Strongly agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly disagree ☐

**Practice**

18. I will quickly go to the hospital or health centers if I've prolonged cough

Strongly agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly disagree ☐

19. I will quickly go to the hospital or health centers if I have other TB-related symptoms

Strongly agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly disagree ☐

20. I will encourage other household members to go for medical checkups whenever showing signs of TB

Strongly agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly disagree ☐

21. I will buy medication from a grocery if I have prolonged cough

Strongly agree ☐ Agree ☐ Unsure ☐ Disagree ☐ Strongly disagree ☐

**Appendix 4. Questionnaire (Chichewa)**

**MAFUNSO A ZA CHIDZIWITSO, KUVOMEREZA NDI MACHITIDWE PA MATENDA A CHIFUWA CHACHIKULU (TB) KWA ODWALA NDI ACHIBALE OSAMALIRA ODWALA**

**Dzina la chipatala** _____

**Nambala yachinsisi ya odwala** _____ **Date** _____

Yankhani pochonga mu kabokosi motere ☑ , **eya** kapena **ayi** kusonyeza kuvomereza kapena kutsutsana ndi funso, kapena mfundo yomwe yafunsidwa, molingana ndi maganizo anu mwaufulu.

**Mbili ya munthu.**

1. Mamuna ☐ Mkazi ☐
2. Zaka kuchepela 15 ☐ pakati pa 15 ndi 25 ☐ pakati pa 26 ndi 35 ☐ kudutsa 35 ☐
3. Mbili ya banja Osakwatila ☐ Okwatila ☐ Banja linatha ☐ Wamasiye ☐
4. Mbili ya maphunziro. Sindidaphunzile ☐ Pulayimare ☐ Sekondare ☐ Ukachenjede ☐
5. Mbili ya ntchito Sindigwira ntchito ☐ Mwana wasukulu ☐ Mlimi ☐ Bungwe loima palokha ☐ Wamalonda ☐
6. Mapezedwe a chuma pabanja lanu pamwezi?

   Kuchepela 45,000 ☐

   Pakati pa 45,00 ndi 100,000 ☐

   Kupyola 100,000 ☐

7. Mulipo angati pabanja panu? Ana ochepera zaka 15…… Akulu opitilira zaka 15…….

**Chidziwitso pa matenda a TB**

8. TB ingafalitsidwe pobwelekana zovala

   Kuvomereza kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana ☐ kukanitsitsa ☐

9. TB ingafalitsidwe kudzela mu malovu otuluka pokhosomola

   Kuvomereza kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana☐ kukanitsitsa ☐

10. Odwala TB asamakhale pamodzi ndi anthu ena ngakhare akulandila mankhwala a TB chifukwa angathebe kufalitsa TB.

    Kuvomereza kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana☐ kukanitsitsa ☐

11. Ndi anthu osauka okha omwe angadwale TB

    Kuvomereza kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana☐ kukanitsitsa ☐

**Maganizidwe pa za TB**

12. Sindili omasuka kukhala pamodzi ndi odwala TB

    Kuvomereza kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana☐ kukanitsitsa ☐

13. Sindingasakanikilane kapena kuyandikana ndi odwala TB chifukwa angandipatsire

    Kuvomereza kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana☐ kukanitsitsa ☐

14. Sindimayelekeza kumukhudza odwala TB chifukwa ndimaopa angandipatsile TB

    Kuvomereza kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana ☐ kukanitsitsa ☐

15. Sindingakwatilane ndi odwala TB chifukwa angandipatsire TB.

Kuvomereza kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana ☐ kukanitsitsa ☐

16. Ndidzamupewa okondedwa wanga akadzati amupeza ndi matenda a TB

Kuvomereza kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana ☐ kukanitsitsa ☐

17. Ndidzamusamalirabe odwala wanga angakhare atamupeza ndi TB

Kuvomereza kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana ☐ kukanitsitsa ☐

**Machitidwe a zinthu pa nkhani ya TB**

18. Ndingathamangire kuchipatala nditazindikira kuti ndakhala ndikukhosomola Kwa nthawi yotalika.

Kuvomereza kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana ☐ kukanitsitsa☐

19. Ndingathamangire kuchipatala nditazindikira kuti ndikuonetsa zizindikiro zogwilizana ndi matenda a TB

Kuvomera kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana ☐ kukanitsitsa ☐

20. Ndidzalimbikitsa apabanja panga kupita kuchipatala kukayezetsa akaonetsa zizindikilo za matenda a TB

Kuvomera kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana ☐ kukanitsitsa ☐

21. Ndingathe kugula mankhwala ku sitolo nkazindikira kuti ndakhosomola kwanthawi yotalika

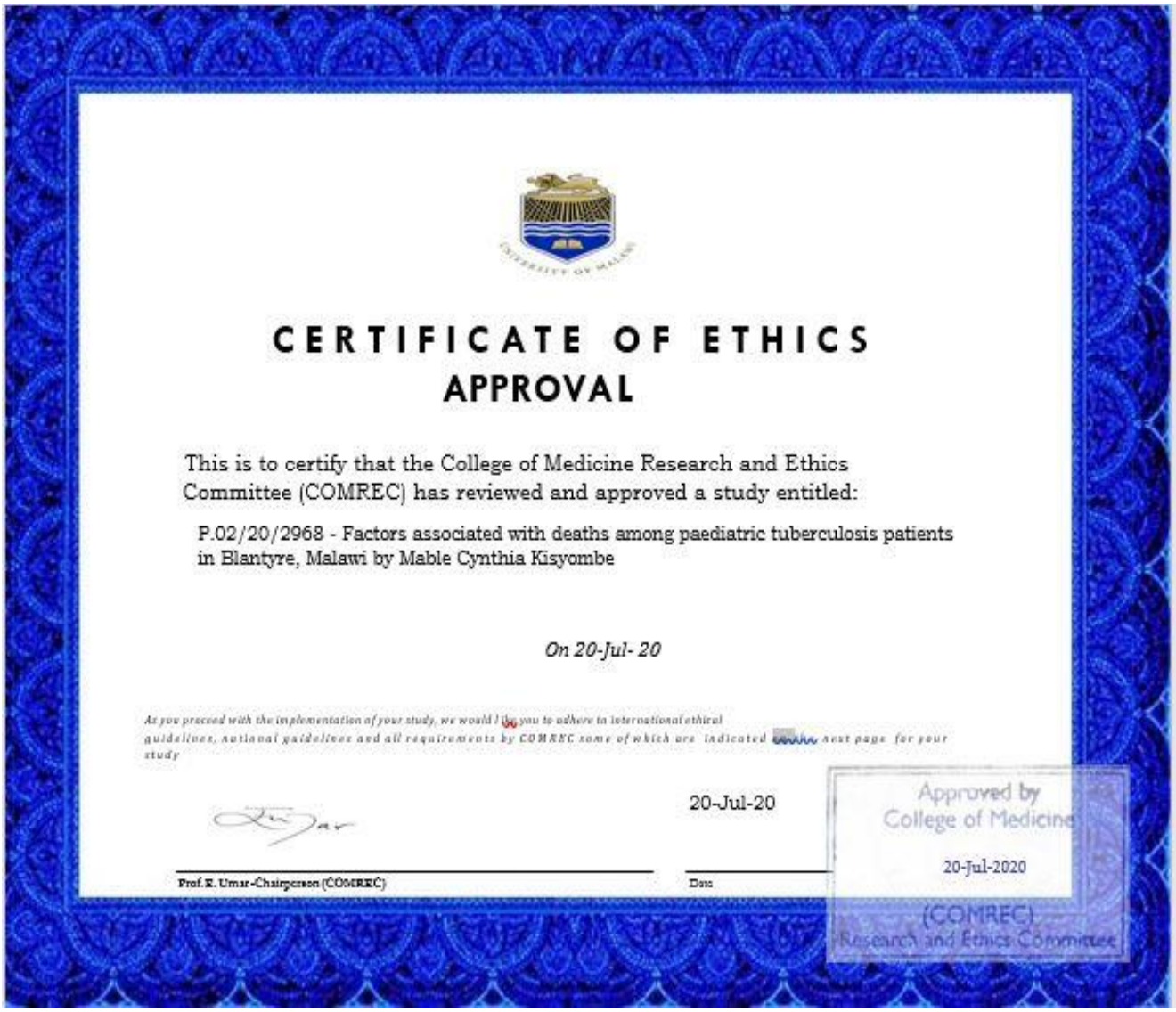
Kuvomereza kwambiri ☐ kuvomereza ☐ sindikudziwa ☐ kukana ☐ kukanitsitsa ☐

**Appendix 5. Evaluation checklist**

**Factors associated with deaths among paediatric tuberculosis patients in Blantyre**

| **Variable** | **Category** | | |
|---|---|---|---|
| Sex | Male | | |
| | Female | | |
| Age | 13-20 | | |
| | 21-30 | | |
| | >30 | | |
| Education | None | | |
| | Primary | | |
| | secondary | | |
| | Tertiary | | |
| Employment | None | | |
| | Self employed | | |
| | Employed | | |
| Health Facility Type | Health Centre | | |
| | Private Hospitals | | |
| | Hospital | | |
| Diagnosis type | Smear positive | Yes | |
| | | No | |
| | Smear Negative | Yes | |
| | | No | |
| | X-ray | yes | |
| | | No | |
| | GeneXpert | positive | |
| | | Negative | |
| | TB Clinical (LAM) | Yes | |
| | | No | |
| TB type | Pulmonary | | |
| | Extra Pulmonary | | |
| | MDR | | |
| | Recurrent | | |
| HIV | Positive | | |
| | Negative | | |
| Observed outcomes | Cured | | |
| | default | | |
| | Lost to follow up | | |
| | Died | | |
| | Treatment failure | | |

## Appendix 6. COMREC Approval Certificate



CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.02/20/2968 - Factors associated with deaths among paediatric tuberculosis patients in Blantyre, Malawi by Mable Cynthia Kisyombe

*On 20-Jul- 20*

*As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC some of which are indicated next page for your study*

20-Jul-20

Prof. K. Umar-Chairperson (COMREC)

Date

Approved by College of Medicine

20-Jul-2020

(COMREC) Research and Ethics Committee

## Appendix 7. Approval Letter from the Public Health Department


**COLLEGE OF MEDICINE**

**DEPARTMENT OF PUBLIC HEALTH**

**Principal**

**M. H. C. Mipando, MSc, PhD**

**College of Medicine**
**Private Bag 360**
**Chichiri**
**Blantyre 3**
**Malawi**
**Telephone: 01 871911**
**01 874107**
**Fax: 01 874 700**


13th January 2020

The Chairman
COMREC
P/Bag 360
Chichiri
Blantyre 3

Dear Sir/Madam

**RE: Factors associated with deaths among peadiatrics tuberculosis patients in Blantyre, Malawi**

We are writing to introduce **Mable Cynthia Kisyombe** who is a Masters in Epidemiology student in the second year in the department of Public Health. She is working on her research proposal titled as above and she would like to submit this for Ethical Review. This proposal was developed by the student and was supervised by a senior member of the department.

Kindly assist her with all the necessary support required for her to start working on his research.

Yours Sincerely

COLLEGE OF MEDICINE
PUBLIC HEALTH DEPARTMENT
13 JAN 2020
PRIVATE BAG 360
CHICHIRI, BLANTYRE 3

**Dr Fatsani Ngwalangwa**
**Masters in Epidemiology Coordinator**

**Appendix 8. Letter of Permission to Use Data (HNTI)**


**COLLEGE OF MEDICINE**

To : The COMREC Chairperson

Date : 20 December 2019

**Support letter for Mable Kisyombe --- MSc Epidemiology student**

I would like to support the submission for ethical review by the above named candidate. I am her supervisor for the dissertation which is entitled "*Factors associated with death among paediatric tuberculosis patients in Blantyre, Malawi*".

I would like to confirm that Mable will be able to use secondary data collected by us in the tuberculosis surveillance system for Blantyre city. There will also be adequate support for the primary study where she intends to conduct a knowledge, attitudes and beliefs study on paediatric tuberculosis.

I hope her submission will be considered favourably.

Dr Marriott Nliwasa

**Postdoctoral Research Fellow**
**Helse Nord Tuberculosis Initiative**

**Appendix 9. Letter of Permission to Use Data (BT DHO)**

Telephone: Blantyre 0 1875332 / 01 877 401
Fax: 01 875 430 / 01 872 551

Communication should be addressed to:
**The District Health Officer**

UNITY AND FREEDOM

In reply please quote No. .....

DISTRICT HEALTH OFFICE
P/BAG 66
BLANTYRE
MALAWI

**REF. No: BT DHO/MED/9**

10th February, 2020

The Chairman
College of Medicine
Private Bag 360
**BLANTYRE**

Dear Sir,

**LETTER OF APPROVAL FOR ACADEMIC RESEARCH TITLED "FACTORS ASSOCIATED WITH DEATHS AMONG PAEDIATRIC PATIENTS IN BLANTYRE"**

---

I write to approve of the above named study by MSc in Epidemiology at College of Medicine, Mable Kisyombe. She will use both primary and secondary data at Ndirande Health Centre and COM respectively.

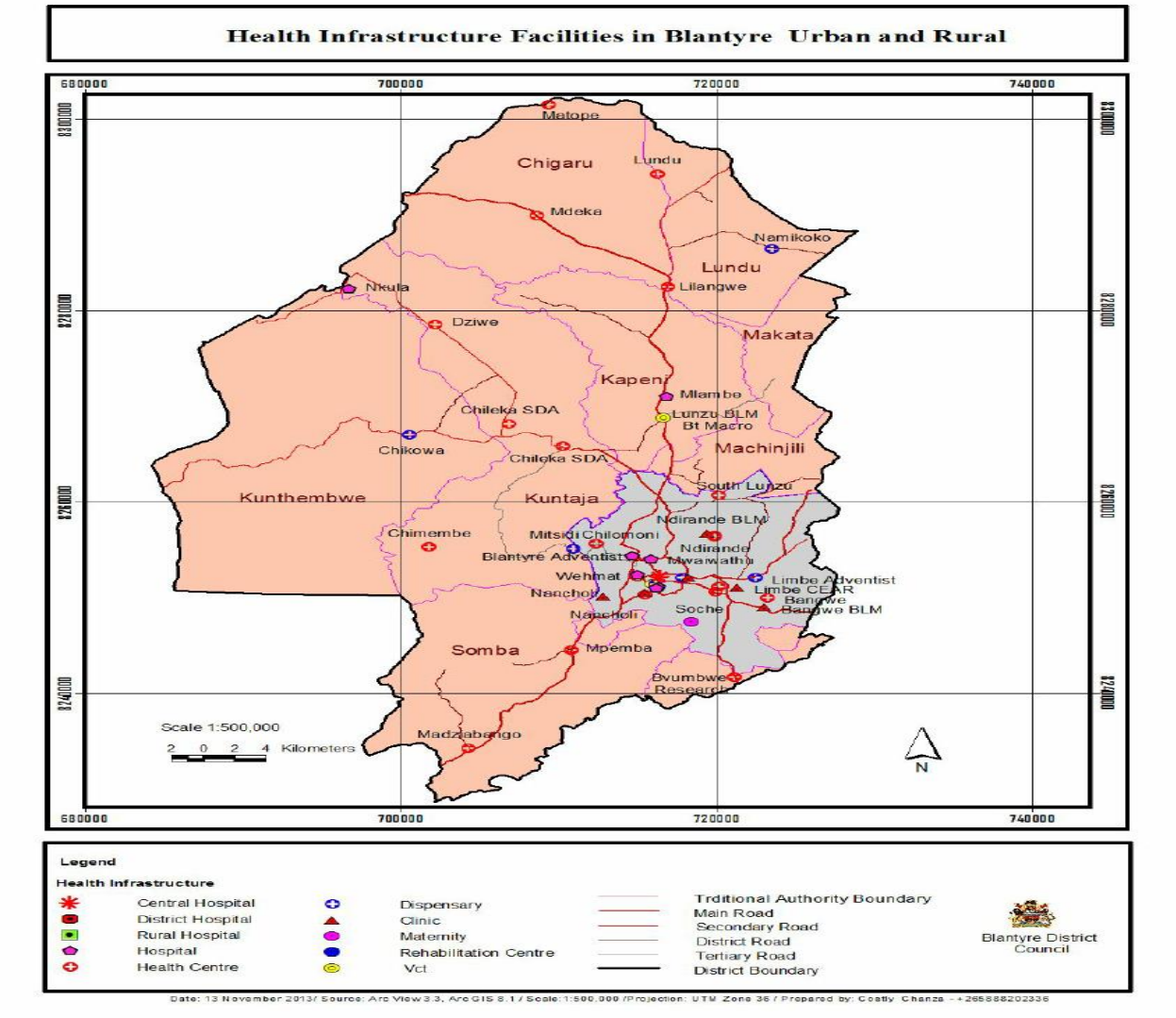
Your assistance is highly appreciated.

Yours faithfully,

Blantyre District Council
Director of Health & Social Services
17 FEB 2020
Private Bag 66
Blantyre

Dr. Gift Kawalazira
**DIRECTOR OF HEALTH AND SOCIAL SERVICES**

## Appendix 10. Map of Blantyre District Health Facilities



**College of Medicine**

# Factors associated with Mortality among paediatric tuberculosis patients in Blantyre Malawi

**By**

**Mable Cynthia Kisyombe**

**(201870104781)**

**A Manuscript submitted in partial fulfillment of the requirement of the**

**MSc of Science in Epidemiology**

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**With Malawi Medical Journal Format**

# Factors associated with Mortality among paediatric tuberculosis patients in Blantyre Malawi

Mable C. Kisyombe, Dr Marriot Nliwasa

## Abstract

Although there is highly effective treatment, tuberculosis (TB) remains a leading cause of death in children. In 2018, 1.2 million deaths from TB among HIV-negative individuals and 251,000 deaths among HIV-positive people were estimated. Identifying patients at risk of death during TB treatment should be a priority for proper management. It helps in assessing the needs and identifying potential interventions that contributes to the End TB Strategy of reducing TB mortality by 95%. The study assesses factors associated with mortality amongst paediatric TB patients in Blantyre and knowledge, attitude and beliefs of TB disease transmission among parents/guardians of children. This was a cross-sectional study using retrospective records review of data extracted from Helse Nord Tuberculosis Initiative (HNTI) for different health facilities in Blantyre district and a primary data collection in assessing the knowledge, attitude and practice of the parents/guardians of children with TB and those with cough for more than a week at Ndirande Health Centre in Blantyre. The proportion of deaths was similar among males and females (5.1% compared to 5.6% respectively, with a P-value of 0.73). The death was higher among children of age group of 1 to 5 years with a death proportion of 6.9% compared to older children of 5-14 years (5.0%) although the results were not statistically significant P-value 0.374. Deaths numbers was higher among HIV positive children as 6.6% HIV positive children died comparing to 4.1 HIV negative patients who died with a P-value of 0.194. For the KAP study, parents/guardians had poor knowledge, attitudes and practices towards TB disease as of 150 participants interviewed in the primary data, 54.7% scored poor in knowledge, 68.7% had poor attitude and 22.0% displayed poor practices towards TB disease. There is a need to develop some

effective techniques to educate the public on TB and improve the detection and management of tuberculosis in children.

## Introduction

Tuberculosis (TB) is a major and often recognized cause of morbidity and mortality globally [1]. In 2020, 1.5 million people died from TB disease among which 214,000 had HIV [2]. In 2017, 233,000 children aged 0-14 years died of TB among which 17% died with HIV globally [3]. While the number of TB-HIV mortality rises, up to 74,000 HIV-uninfected children die of TB every year[4]. In Africa, 20%-40% of TB case load is borne by children[1,5]. 36% of global tuberculosis deaths in children infected with HIV were in sub-Saharan Africa [6]. In 2016, Malawi registered 16,959 TB cases of which childhood TB made up to 8.6% of these cases [7]. Catalysing Paediatric (CaP) TB targets to identify approximately 2000 paediatric cases, treat at least 1,700 paediatric TB cases and initiate at least 2,400 children on preventive treatment [7] but this will not benefit all Malawian children with TB infection because projects have their targeted locations leaving others unreached.

### Risk factors

People who are HIV positive are up to 20 times more likely to develop active TB disease [2]. Children with vulnerable immune systems, such as the very young, HIV infected or severe malnourished are most at risk for falling ill or dying from TB disease [8], taking advantage of their body immunes system which is under developed [1]. Children not been treated for HIV during TB treatment significantly increase the risk of poor outcomes. Disseminated TB and TB meningitis are also associated with high mortality and are more common in young children [9].

Weight loss is also found to be a contributing factor to TB death in children. Age group of 5-14 years is also found to have highly contributing to early childhood TB death. Most disseminated TB and central nervous system TB occur at the age of 1-4 years while the age of 5-10 has least morbidity but increase mortality [10]

**Prevention**

Treatment of people with TB infection (TB preventive treatment), prevention of *M. tuberculosis* through infection prevention and control and vaccination of children with the Bacillus Calmette-Guerin (BCG) vaccine are the current health interventions in place [1]. Although BCG vaccine has a documented protective effect against meningitis and disseminated TB in children, it does not prevent primary infection [11]. Lack of access to TB preventive therapy contributes to having more TB infections in children. TB awareness campaigns emphasizing on prevention and control measures must be undertaken to prevent TB in children [12]. Isoniazid Preventive Therapy (IPT) is intended to prevent recent TB infection from progressing to active TB disease and to prevent Latent TB infection (LTBI) from reactivation [13]. Contact screening and management has enormous potential to prevent children exposed to and infected with TB from developing TB disease [2].

Many countries have challenges with TB diagnosis in children due to the limited ability of children to produce sputum and paucity of TB bacilli in samples produced. In Malawi there is lack of information for what has been done to establish factors associated with mortality in children who are on TB treatment. This study was responding to the recommendation by a survey done in central region of Malawi on “burden of disease and risk factors for death among children treated for TB in Malawi [14].” A study referred was conducted in Ntcheu district in

Malawi, in which gaps were discovered on the same topic and their findings were for a district with low population size, therefore, the results of their study could not be generalized hence recommended further investigations on the factors associated with mortality in children with tuberculosis in the country on a large scale.

## Methods

### Study design and data collection

This study was a cross-sectional study design that focused on retrospective records review of secondary data obtained from the previous studies conducted by Helse Nord Tuberculosis Initiative (HNTI) at different health facilities in Blantyre district. The HNTI is a collaborative programme between the Kamuzu University of Health Sciences (KUHeS), the Malawi-Liverpool-Wellcome Trust Clinical Research Programme (MLW) and the Herse Nord RHF of the University of Tromso in Norway.

Data was extracted using checklist on the following variables: sex, age, education status, employment, health facility type, type of diagnosis, type of TB, HIV status and observed outcomes. HNTI collected data for all patients registering for TB treatment using a standard procedure as TB is a notifiable disease. The information was recorded in electronic format in addition to paper records (TB registers) in a system maintained by the Malawi-Liverpool-Wellcome Trust. This electronic dataset was made available for purpose of this analysis

### Study setting and population

HNTI collected data from different health facilities in Blantyre district to give a representation of both rural and urban settings. Blantyre is a commercial city situated in the Southern Region of

Malawi covering an area of 2,012 Sq.km with the population size of 800, 264 in 2018 [15]. The health facilities where data was collected are: Health Centres; Bangwe, Ndirande, Chilomoni, Zingwangwa, Limbe and South Lunzu health centre. Private Hospitals; Blantyre Adventist Hospital, Chitawira Hospital, Mlambe Hospital, Mwaiwathu Hospital and the biggest referral Hospital Queen Elizabeth Central Hospital which saves patients from health centres, private health care facilities and neighboring districts health facilities.

The study reviewed the electronic data for the TB patients who were less than 15 years of age that were enrolled in the HNTI study from 2014-2018. In data analysis, children were categorized depending on their age.

**Study sample size**

Sample size was calculated using the risk of death as main outcome. The key risk factor being investigated was HIV status. The proportion of death among TB patients were 14.0% among those HIV positive and 7.4% among those HIV negative. We needed 373 HIV positive patients and 373 HIV negative patients to demonstrate this difference at 80% power and alpha 0.05. STATA software was used for the calculation of the sample size. The available dataset had 512 HIV positive patients and 512 HIV negative patients, which is adequate for the comparison.

**Inclusion and Exclusion**

Subjects were all children of less than 15 years of age who were on TB treatment during data collection and had all their data available. Children with missing data were excluded from the study.

**Data Management and analysis**

Coded data was entered and analysed using statistical programmes; Microsoft Excel spreadsheet and STATA version 14.0 respectively. Data cleaning and cross-checking for missing variables was performed before conducting the analysis.

A multivariate logistic regression analysis with socio-demographic characteristics as covariates were used to determine factors associated with Tuberculosis in children. A Chi square test were used to test for associations between mortality and some covariates. A logistic regression was used to model the relationship between categorical variables. Graphs and tables have been used to present the summarized data.

**Ethical Consideration**

Before commencement of the study an ethical approval was obtained from University of Malawi, College of Medicine Research Ethical Committee (COMREC). Permission was sought from Helse Nord Tuberculosis Initiative where secondary data was reviewed. No participant identifier was used.

**Results**

Out of 1,077 children that had their data reviewed for the target period of 5 years -*Table 1,* there were 525 females and 552 males representing 48.8% and 51.2% respectively. The study had a representation from age groups of 0-1 years 191 (17.7%), 1-5 years 289 (26.8%) and 5-14 years 597 (55.4%). Data was also reviewed based on HIV status, it was observed that there was no difference in number between children with HIV negative and HIV positive both with 512 (47.5%), the rest had HIV status not known. Among the health facilities that had data reviewed, it was noted that a minimum number 73 (6.9%) of TB children were from private hospitals. Data was reviewed depending on the TB type a child suffered from and it was observed that among

the reviewed data 642 (59.7%) children had Pulmonary TB and the rest had Extra Pulmonary TB. Biological samples were analyzed for the TB diagnosis by smear microscopy, culture and GeneXpert MTB/RIF, the collective results showed that of 1,077 children who had their data reviewed 98 (9.1%) were found to be positive for TB disease.

**Table 1: Baseline characteristics of the study participants**

| Variable | Category | Total Number (1,077) N (%) |
|---|---|---|
| Gender | | |
| | Male | 552 (51.2) |
| | Female | 525 (48.8) |
| Age in years | | |
| | 0 – 1 years | 191 (17.7) |
| | 1 -5 years | 289 (26.8) |
| | 5-14 years | 597 (55.4) |
| HIV Status | | |
| | Negative | 512 (47.5) |
| | Positive | 512 (47.5) |
| | Unknown | 53 (5.0) |
| Health Facility Type | | |
| | Hospital | 832 (77. 1) |
| | Health Centre | 172 (16.0) |
| | Private | 73 (6.9) |
| TB Type | | |
| | Pulmonary | 642 (59.7) |
| | Extra-Pulmonary | 434 (40.3) |
| Bacteriology | | |
| | Negative | 979 (90.9) |
| | Positive | 98 (9.1) |
| Treatment Outcomes | | |
| | Cured | 78 (7.2) |
| | Completed | 833 (77.3) |
| | Died | 58 (5.4) |
| | Lost to follow up | 108 (10.0) |

The figure 1 below shows the trend of TB in children from 2014 to 2018. There were more TB cases in children in 2017.

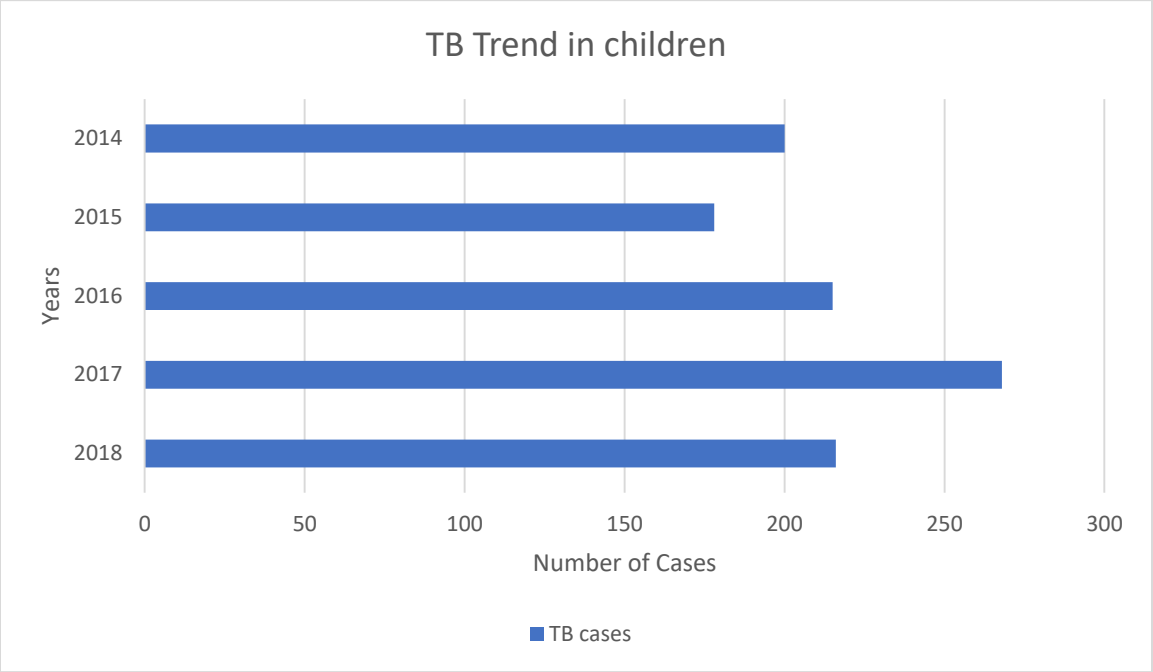


**Figure 1: Trend of children with TB cases**

Data was further reviewed depending on the treatment outcomes, the study found that of 1,077 children enrolled in the study, only 58(5.4%) died of the disease, 78(7.2%) cured, 833(77.3%) were cured and 108(10.0%) were lost to follow up.

**Table 2. Risk factors for mortality in children with TB**

| Variable | Category | Dead Percentage N (%) | Risk Ratio | P-value |
|---|---|---|---|---|
| Sex | Female | 27 (5.1) | 1 | 0.731 |
| | Male | 31 (5.6) | 1.09 (0.66-1.80) | |
| Age | 0-1 | 8 (4.2) | 1 | 0.374 |
| | 1-5 | 20 (6.9) | 1.65 (0.74-3.67) | |
| | 5-14 | 30 (5.0) | 1.26 (0.56-2-57) | |
| HIV Status | Negative | 21 (4.1) | 1 | 0.194 |
| | Positive | 34 (6.6) | 1.62 (0.95-2.75) | |
| | Unknown | 3 (5.9) | 1.38 (0.45-4.35) | |
| Facility Type | Health Centre | 8 (4.7) | 1 | 0.789 |
| | Hospital | 45 (5.4) | 1.60 (0.56-2.42) | |
| | Private Hospitals | 3 (6.9) | 1.47 (0.50-4.35) | |
| TB Type | Extra-Pulmonary | 35 (5.4) | 1 | 0.918 |
| | Pulmonary | 23 (5.3) | 0.97 (0.58-1.62) | |

Table 2 shows risk factors for mortality. The study found that the odds of mortality is the same among all age groups of children. For HIV status the risk ratio (RR) of death was 1.62 (95% CI: 0.95 to 2.75, p=0.194) for HIV positive children compared to HIV negative. HIV is not considered a risk for death. The RR for facility type was 1.60 (95% CI 0.56 – 2.42) for hospital and 1.47 (95% CI 0.50 – 4.35) for private hospital compared to health Centre. The type of TB also did not pose an increased risk to dying RR 0.97 (95% CI: 0.58 -1.62, P-value=0.918), that means there is no difference in death risks for children dying from Extra-Pulmonary and Pulmonary.

## DISCUSSION

The study found that there were more children with TB cases in 2017 as the number of cases were 268/1,077 representing 24.9% and the least was in 2015 with 178/1,077 (16.5%) children TB cases. From the TB cases trend, it was observed that Malawi is far away from the STOP TB target of having 100% TB free country. The trend is not consistent and not decreasing as expected with WHO and stop TB partnership [16,17]. This is in line with WHO findings That states that the TB incidence rate is falling, but not fast enough to reach the 2020 milestone of a 20% reduction between 2015 and 2020 [1]. This could be due to the lack of effort put towards TB in children that could result in having fewer cases as we go with years. The increasing trend of TB cases need to be reversed by adopting the zero combating of tuberculosis strategies that were put in place.

Much that strategies are developed that can be implemented to identify, diagnose and treat infants, under-five and children with TB, Malawi seem to be way behind in implementing these strategies. Children are at higher risk of contracting TB infection and with their underdeveloped immune system they can develop a disease that can result into deaths if not treated immediately hence need to be fast targeted group. Of the 1,077 children with TB, the study observed the majority being male 552 (51.2%) and this is consistent with other studies [18–20]. When Malawi is implementing the STOP TB strategies, much consideration should to be put to children. More

TB cases were observed among older children of age 5-14 years. The study found that among the total number of TB children the proportion between HIV Positive and HIV Negative were the same 47.5%. This means that the probability of contracting TB infection is the same whether a child is HIV positive or not, hence proper measures must be followed to prevent children of either age from getting exposed to TB infection. Despite provision of HIV Testing Services (HTS) to almost every TB case 53 (5%) had their HIV status not known. This could be due to; unwillingness of the parents to consent for their children to get tested, quality of counselling being offered to parents. However, studies can be done to determine the reasons in future. The majority of the TB children were from the biggest referral hospital QECH with 832 (77.1%). This was so may be because many cases are left unattended to while at home thinking they will get better at some point, when the condition worsen is when many decide to seek medical care and due to the stage at which the condition is many health Centres refer the cases to big hospital for proper management.

Though the majority of the TB cases in this study had pulmonary TB with 642 (59.7%), Extra-Pulmonary TB cases should not be undermined as it is the kind of TB that causes mortality in children. Children are more vulnerable to TB meningitis and military TB the forms of Extra-Pulmonary TB [2] hence need put much attention on this area as well. Extra- Pulmonary TB can be prevented if children can be the most targeted group in managing tuberculosis. Data was reviewed on the bacteriology confirmation that is Xpert MTB/RIF which allows the detection of both MTB and Rifampicine Resistance, microscopy, culture among others, the majority 90.9% of children had their TB test results negative. This may due to limitation in diagnosing children TB as they have difficulties in producing sputum. The diagnosis of TB in children relies on the

thorough assessment of the disease starting with the history of exposure, clinical examination and relevant investigations [21].

**Risk factors for mortality**

This study revealed that the treatment outcomes among children enrolled for treatments were favorable in the sense that more than half of the TB patients had completed their treatment and 7.2% had cured from the disease though a small proportion. On the other hand, those that died from the disease are few (5.4%). Despite having hope that the TB treatment is working we still need to minimize the number of deaths to zero in order to get to the target of having TB free country.

WHO and the stop TB partnership are working by having all public health programs and health care providers to transform the approach to TB case finding so that all children with TB get high quality care that can help the world move towards Zero TB deaths among children [5,23] which is achievable even here in Malawi . WHO and partners brought in various measures to put in place in order to achieve the zero TB cases countries, the childhood TB to be viewed as a family illness; every child be infant or other age showing typical signs and symptoms of TB and who live with a person who has TB should be treated for TB infection [2,17]. Secondly, conducting TB case identifying campaigns to find all people affected by TB and efforts to be made to actively look for people with TB in the communities that are at risk and assist them to get diagnosis and care. Thirdly, prioritizing the outreach in children living with HIV, screening programs should provide testing for both infections to all children. Those who test positive for HIV should be tested for TB and if TB diagnosis is confirmed then they need to start TB treatment immediately. Lastly, integrating maternal and child health services, HIV care and TB

care into a seamless package, all pregnant women who are HIV positive should be examined for TB and provide with treatment if needed or preventive therapy. Children who are malnourished or HIV positive should be examined for TB [16,17].

The study has observed that there is no difference in risk of mortality between male children and female children. We have found no difference in risk of mortality from TB between those that are HIV negative, positive and unknown. There have been contrasting results within Malawi where it was found that children on ART who are diagnosed with TB in routine setting die at higher rates than patients who newly initiate ART [14]. Other studies also observed increased hazards of death in patients with HIV who were not on treatment [22].

The study has also found that the risk of death is the same among all age groups of children. Much that other studies found that HIV is a well-known risk factor for TB and that children with vulnerable immune systems, such as the very young, HIV-infected or severely malnourished are most at risk for falling ill or dying from TB [17,23]. This study has further found that there is no difference in risk of dying from TB between those that are HIV negative, positive and not known, while other studies observed increased hazards of mortality in patients with HIV who were not on treatment [22]. The risk of mortality from TB was the same among all children dying from all hospitals thus no difference in mortality risk among children who had been treated at health centers, private hospitals and a big Hospital. This means that children suffering from TB receive equal treatment in all levels of health facilities. During the study it was also observed that the risk of mortality from TB is the same among pulmonary and extra-pulmonary patients as the P-value =0.918. This entails that children suffering from pulmonary TB are not different

from those that are suffering from Extra-Pulmonary TB on the risk of mortality hence require same attention on TB prevention and management

## Conclusions

Despite observing no difference in risk of TB mortality between those that are HIV positive, negative and those that their HIV status was not known this study recommends that the ministry of Heath should intensify TB diagnosis in all newly identified HIV children. Having HIV positive does not pose a risk to TB deaths, children can get cured if they are given good medication, management and disease awareness. Although there was no significant difference in risk for death in Extra-pulmonary and Pulmonary TB, case detection in children is of paramount importance.

## Summary

This study analysed secondary data from HNTI that was collected from Blantyre district health facilities that includes; health centres, private hospitals and the country's biggest referral hospital. The study findings revealed that

## Limitations

Despite this study being conducted in a commercial city which includes a national referral hospital, the results cannot be generalized due to the sample size that was used. It is therefore recommended to do further investigations at a larger scale.

**Acknowledgements**

The study was made possible by Helse Nord Tuberculosis Initiative (HNTI) a collaborative programme between the Kamuzu University of Health Sciences (KUHeS), the Malawi-Liverpool-Wellcome Trust Clinical Research Programme (MLW) and the Herse Nord RHF of the University of Tromso in Norway for the provision of data. The author thanks Dr. Marriot Nliwasa for his mentorship and his critical review in developing the research concept and for the manuscript. The study was self-funded.

**Conflict of interest**

We declare that there was no conflict of interest for this study

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