THE VALUE OF HOUSEHOLD CONTACT INVESTIGATION IN CONTROL OF DRUG-SUSCEPTIBLE TUBERCULOSIS AMONG CHILDREN AGED 0-5 YEARS IN KISUMU COUNTY KENYA

BY

BARBARA K. BURMEN

A THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN PUBLIC HEALTH

SCHOOL OF PUBLIC HEALTH AND COMMUNITY DEVELOPMENT

MASENO UNIVERSITY

DECLARATION

This is my original work done during doctoral studies in public health at Maseno University.

Dr. Barbara Burmen, MBChB MPH

PG/PHD/00110/2012

Sign…… Date……

Supervisors

1. Prof. Wilson Odero, MD, MSc, PhD.

   School of Medicine

   Maseno University

   Sign…… Date……

2. Dr. martien W. Borgdorff, MD,PhD

CDC

Western Kenya

Sign…… Date……

ACKNOWLEDGEMENTS

I am eternally grateful, for robust health and abundant life from the Almighty Lord, and for constructive critique, chart and compass, from mentors, supervisors Prof Martien Borgdorff and Prof Wilson Odero. I would also wish to thank the Principal investigators of the parent study Dr Kevin Cain and Dr Mary Reichler in which this study was nested, other co-investigators, research team members, colleagues, supervisors, and research participants for their voluntary participation without which this study would not have been possible. Additionally, I wish to express my gratitude to my family and friends for their unconditional love and unwavering support. I am eternally indebted to you all.

DEDICATION

This work is dedicated to my family for your love and support.

ABSTRACT

Ninety percent (90%) of TB infections are self-limiting; 10% will progress into active or latent TB. Persons with latent TB cannot spread disease but can go on to become infectious cases later. The risk of TB infection and progression from latent infection to active infection is higher in children than in adults. A person with active TB can infect up to 15 persons yearly through close contact. Contact investigation is therefore recommended for close contacts of TB patients to identify undiagnosed cases of active and latent TB to initiate them on curative and preventive therapy respectively. The value of TB contact investigation in childhood TB control is unknown. This study determined the value of Contact Investigation in childhood TB control (persons aged< 5 years) in Kisumu County between 2014 and 2015 a period prior to the implementation of standardized contact investigation using the following methods used to address the specific objectives: To describe risk factors for TB infection among child contacts, a cross sectional survey was conducted on 183 TB index and 257 child contact using a symptom screen, Tuberculin Skin tests (TST) and Chest X rays. Cut off for TST positivity was identified using a bimodal peak for TB prevalence surveys. Hierarchical level modeling analyses, with children nested within households, was used to describe contact and index characteristics associated with TB infection. To describe Isoniazid Preventative Therapy (IPT) uptake among eligible child contacts, in a retrospective cross-sectional survey, data belonging to 337 child contacts was linked to TB program registers and logistic regression analyses used to describe individual characteristics associated with IPT initiation. To compare the value of contact investigation (intervention arm) to contact invitation (control arm) in contributing to childhood TB control, a cluster randomized trial was employed to compare TB cases diagnosed and children receiving IPT in the pre- intervention (2012-2013) and intervention (2014-2015) years, and the intervention years using a minimum sample size of 15 per arm. A convenience sampling technique was employed for the first 3 objectives. To describe lessons learnt implementing standardized contact investigation in a setting with routine contact invitation; a mixed method design was employed. The study recruited 345 child contacts linked to 243 TB index cases. Of these 39.3% child contacts with completed TST (n=257), had TB infection based on a TST cut off of 5mm for positivity. The risk of TB infection was higher among child contacts of TB index cases aged 15-45 years (OR =2.59, 95% CI 1.1-7.2) who had a cough (OR =3.76, 95% CI 1.51-9.35) after fixing other contact and index characteristics. Eight (8; 2.3%) children had TB. The remainder (n=337) were IPT-eligible and the 15.1% that initiated IPT were more likely to be 1st degree relatives of the index case (OR =2.57, 95% CI 1.19-5.52) and to reside in a rural area (OR=2.65, 95% CI 1.37-5.09). Index cases with child contacts initiated on IPT (19.6%) were more likely have smear positive TB (OR =4.62, 95% CI 1.02-20.88) and to resides in rural area (OR 3.06, 95% CI 1.45-6.48). In the pre- and post- intervention years, TB cases increased by 20 (75% of them were from intervention arm). During the intervention years TB cases decreased by 17 (71% were from the control arm); the intervention arm contributed to 100% and 75% of the children put on IPT in 2014 and 2015. There was inadequate diagnostics, treatment and data support for contact investigation. Contact investigation enhanced childhood TB control in comparison to routine approaches and identified factors to prioritize contacts for screening, but low IPT initiation rates negated its intended benefits. Adequate investments need to be made in infrastructure to support contact investigation. Household contact investigation should target populations at high risk of infection; IPT implementation be supported using linked index-contact registers and TB contact investigation be ingrained within community health systems

TABLE OF CONTENT

LIST OF ABBREVIATIONS

AIDS	-	Acquired Immune Deficiency Syndrome
AAFB	-	Acid Alcohol Fast Bacillus
ACH	-	Air Changes per Hour
BCG	-	Bacille Calmette Guerrin
CDR	-	Case Detection Rate
CMI	-	Cell Mediated Immunity
CNR	-	Case Notification Rate
DBS	-	Dried Blood Spot
DTLD	-	Division of Leprosy Tuberculosis and Lung Diseases
HIV	-	Human Immunodeficiency Virus
HLM	-	Hierachical Level Model
IFN	-	Interferon
IGRA	-	Interferon Gamma Release Assays
IPT	-	Isoniazid Preventative Therapy
TB	-	Tuberculosis
LTBI	-	Latent Tuberculosis Infection
MTB	-	Mycobacterium Tuberculosis
SLM	-	Single Level Model
TB	-	Tuberculosis
TST	-	Tuberculin Skin Test
WHO	-	World Health Organization

OPERATIONAL DEFINITION OF TERMS

Value of Contact investigation – the value of a disease screening strategy is measured by the number of cases detected and number of cases prevented. In this study, the number of children diagnosed with TB is used as proxy for decrease in morbidity and mortality from timely diagnosis; and the number of children who received IPT is used as proxy for the number of disease cases prevented.

TB control describes a decrease in the incidence, prevalence, morbidity and mortality from TB. The number of cases of TB diagnosis found through active case finding will be used as a proxy for a decrease in morbidity and mortality from TB. The number of children put on IPT as a proxy for a decrease in incidence and prevalence from TB.

Household Contact- an individual that had spent at least 7 consecutive nights in the same household as the index case in the three months preceding the TB diagnosis date.

Contact screening-subjecting persons in proximity with a person with an infectious disease to tests so as to determine whether they have contracted the disease. This could be done by either be contact investigation or contact invitation.

Contact Investigation- the screening or evaluation of close contacts of index cases of TB. It includes active follow up of persons who have been in contact with an index case to ensure they are screened.

Contact invitation-a case finding strategy where the index case with an infectious disease is asked to bring all his close contacts to a health facility to be screened for the same disease; it does not actively follow up the index case to ensure that all contacts are screened and appropriately managed thereafter.

TB index case- The initially identified case of new or recurrent TB, in a person of any age, in a specific household or other comparable setting in which others may have been exposed. An index case is the case around which a contact investigation is centered (but is not necessarily the source case)

Latent TB-people with LTBI have been infected with TB bacteria but have not developed active TB. Persons with LTBI have positive TST and IGRA results but do not have symptoms or tests results consistent with TB e.g. Chest X-ray and laboratory tests. LTBI is not infectious.

Active TB is also known as “TB disease”. People with TB disease are usually symptomatic and have test results consistent with TB disease. Some forms of active TB disease are infectious

Drug-susceptible TB- active TB disease that is caused by bacteria that are killed or inhibited by standard concentrations of one or more TB medications

Drug resistant TB-active TB disease that is caused by bacteria that are not killed or inhibited by standard concentrations of one or more TB medications

Period of infectivity- the period prior to TB diagnosis in which a TB index case may have transmitted TB to his or her contacts. This is usually the three months preceding the TB diagnosis date

Child a person aged 0 to 5 years

LIST OF TABLES

LIST OF FIGURES

CHAPTER ONE

INTRODUCTION

1.1 Background of the Study

In developed countries, the TB incidence declined steadily between 1850 and the 1900s long before the disease became curable in 1940. This has been hypothesized to be due to changes the standards of living, sanitation, isolation of infectious cases and change in virulence of the infecting organism *Mycobacterium Tuberculosis* (Blower et al., 1995). In 2016, 10.4 million persons fell ill with Tuberculosis (TB) and 1.4 million died from TB. Twenty-five percent of these cases occurred in Africa. Africa also had the highest TB incidence rate (272 per 100,000 populations) which was close to twice the global average (140 per 100,000). The same year, a million children were infected with TB and 170,000 of them died from TB (excluding children with HIV). TB was the commonest cause of death worldwide in 2015. Kenya, a lower middle income country, was ranked among the 30 high TB burden countries that contributed to 90% of the global TB burden in 2016 (World Health Organization [WHO], 2017).

The TB program in Kenya was formally launched in 1980. The TB Case Notification Rate (CNR) in 1980 was 60 per 100,000 populations. Before the advent of HIV in Kenya, the TB CNR was falling at a rate of 4% per year. With the onset of the HIV epidemic in the 1990s, the TB CNR begun increasing at a rate of 15% per year with a peak CNR of 300 cases per 100,000 population in 2005 (WHO,2008). In Kenya, between 1987 and 2006, the TB burden increased ten-fold due to Human immune-deficiency Virus (HIV) infection (Division of Tuberculosis Leprosy and Lung Disease [DTLD], 2013a). In 2016, the TB CNR in Kenya was 170 per 100,000 populations and in Kisumu County, 228 per 100,000 populations. Over 90% (75,986) of

the TB case burden in Kenya was borne by adults. Kisumu County, one of the 47 counties in Kenya, contributed to 2,564 (3.4%) of the 75,896 TB cases notified in 2016 (National Tuberculosis Leprosy and Lung Diseases Program [NTLP], 2017a). In 2012, Kisumu County had the highest HIV prevalence in the country, 15.1% against the country‟s average of 5.6% (National AIDS and STI Control Program [NASCOP], 2014).

By 2005, Kenya had already reached the targets for TB Case Detection Rate (CDR) of 70% and cure rates of 85% (WHO,2008). From 2010, the TB program in Kenya increased expanded its focus on active case finding to screening HIV infected persons, new inmates in prisons, and household contacts of index cases of TB through the use of household or community cough monitors (DTLD, 2011a).

The theoretical framework adopted for this study was derived from the Iceberg theory of disease, first brought to attention by Last in 1963. The theory postulates that cases of disease that have been correctly diagnosed are at the tip of the iceberg, visible and easily measured. Majority of cases of disease are submerged and remain unseen, unmeasured and easily forgotten with potentially catastrophic consequences (Raj, 2016). As Kenya is still yet to achieve a TB CDR of 100%, a proportion of TB cases remain undiagnosed (DTLD, 2011a). Therefore, disease screening among those at risk of TB e.g. child household contacts of TB index cases, will enable health programs address the true burden of disease and therefore contribute to disease control.

TB is a multi-systemic disease caused by *Mycobacterium tuberculosis* with a myriad of presentations and manifestations. The majority (85%) of *M. tuberculosis* infections occur in the lungs (Herchline & Amorosa, 2017). A person acquires TB infection via inhalation or ingestion (Erkens et al., 2010). In 90% of infections, the primary infection is self-limiting and is eliminated

by the hosts‟ immune mechanism. In 5-15% of infections, healing is incomplete and viable bacteria may either spread to the blood stream leading to TB lesions in multiple organs, or be suppressed into an inactive form called Latent tuberculosis infection (LTBI) (Benjamin, Griggs, Wing, & Fitz, 2016). Tuberculosis infection can be described as either Active or Latent TB infection (LTBI). Active tuberculosis is defined as the presence of clinical signs and symptoms in an individual infected by *Mycobacterium tuberculosis*. It is distinct from LTBI which occurs without signs or symptoms of active disease (WHO, 2013b). LTBI is *Mycobacterial* infection as evidenced by a positive tuberculin skin test (TST) or Interferon Gamma Release Assays (IGRA) (Yun, Kim, Kim, Lee, & Lim, 2016). Tuberculosis can be classified depending on susceptibility of the bacilli to anti-TB drugs. Multi-drug resistant TB is that which is resistant to Isoniazid and Rifampicin while Drug-susceptible is that which the bacilli are susceptible to 1st line anti-TB drugs (DTLD, 2013b).

The dynamics of TB transmission are dependent on the rate of transmission to a susceptible host. As regards TB, the majority of persons exposed to TB (90%) never develop TB. However, susceptible individuals who are free of disease develop latent infection and active TB infection. Susceptible individuals can either have rapidly progressing TB which develops into active TB, or slowly progressing TB which develops from slow reactivation of latent TB. Active TB infection could either be infectious or non-infectious. An infected person may recover spontaneously and either relapse and develop TB, or go on to die from other causes. An adaptation of this model is given in figure 1 (Blower et al., 1995). The basic reproductive rate is the number of secondary infectious cases an infectious case generates per unit time (Clark, Riben, & Nowgesic, 2002).

Disease control is defined as a decrease in the incidence, prevalence, morbidity and mortality from a disease (Dowdle, 1998).A decrease in the morbidity and mortality from disease can be

achieved through timely diagnosis and initiation of treatment; whereas a decrease in the incidence and subsequently in the prevalence of disease can be achieved by the prevention of new cases (WHO, 2016). The effectiveness of an individual case detection method is dependent on its effectiveness to detect cases, treatment outcomes for the cases detected and the population impact of the strategy in decreasing disease incidence (Bruce, Pope, & Stanistreet, 2008).In this study, the number of cases of TB diagnosed found using a disease finding strategy will be used as a proxy for a decrease in morbidity and mortality from TB. Similarly, the number of children put on Isoniazid Preventative Therapy (IPT) for TB will be used as a proxy for a decrease in incidence and prevalence from TB.

Contacts of a TB case are defined as people who have had close contact with an infectious case of TB and are therefore at risk of TB infection and should therefore be investigated for TB infection and disease (WHO, 2012). Tuberculosis contacts could also be classified as 1st degree contacts who include household members and close non-household members who spend up to 8 hours cumulatively with a sputum positive index case and up to 40 hours cumulatively for a sputum smear negative confirmed culture positive TB case, 2nd degree casual contacts who include workplace colleagues or visitors to the home, and 3rd degree community contacts(Erkens et al., 2010). In this study, contacts will be limited to household members of TB cases who had spent at least 7 consecutive nights in the same household with a TB index case in the 90 days preceding the TB diagnosis date which defines the period in of infectivity.

Contact screening is the identification of all persons who have had contact with a case of infectious disease and screening them for disease (Armbruster & Brandeau, 2007). Contact screening can either follow a contact invitation approach or a contact investigation approach. Contact invitation is a screening strategy in which the TB index case is asked to refer all his or

her close contacts for screening(Chakhaia et al., 2014). Contact investigation refers to the screening or evaluation of close contacts of index cases with TB; a form of active case finding (DTLD, 2011b). The administration of TB treatment to contacts with TB infection prevents TB transmission from the infected contact to a third contact and thus breaking the chain in TB transmission. Similarly, the administration of preventative therapy to contacts of index cases of TB prevents the progression of LTBI to active TB. Both strategies could potentially lead to TB elimination (Anger et al., 2012). Contact screening is also done for contacts of MDR-TB. In Kenya, more focus has been directed to screening of MDR TB contacts because they are fewer; 284 MDR TB case compared to 75,896 cases of drug-susceptible TB in 2016 (NTLP, 2017a). Additionally, due to delays in diagnosis, such patients have usually had a longer duration of contact with the index case and screening will therefore yield a high number of MDR-TB cases among contacts. Furthermore, MDR TB has poorer treatment outcomes especially with delayed diagnosis (WHO, 2014). In this study, contact invitation will be used to describe the standard approach where no intervention will be implemented as patients will continue to receive TB diagnosis, treatment and prevention services as per the national guidelines. Whereas contact investigation will be used to describe study-specific procedures that will be used to identify and screen all household contacts of a drug-susceptible TB index case(Erkens et al., 2010; Guwatudde et al., 2003).

With reference to TB disease, the WHO defines a child as a person aged less than 15 years. In 2006, this definition was revised to categorize children into younger children (aged less than 5 years), and older children (aged 5-14 years) (Glaziou, Sismanidis, Floyd, & Raviglione, 2015). In this study, a child will be used to refer to the „younger children" aged less than 5 years.

Tuberculosis is highly infectious; a person with active TB can infect up to 15 persons a year through close contact (Erkens et al., 2010). The symptoms of TB can be mild for several months leading to delays in seeking care and therefore, increasing the risk of TB transmission. For effective TB control, TB programs should detect cases of infectious TB early and initiate them on treatment (WHO,2018). Even if a patient presents with advanced TB disease at the time of diagnosis, provided TB chemotherapy is used correctly and the tubercle bacilli were not drug resistant from the outset, cure rates of 95% and 40%-60% are possible for those with drug-susceptible TB and drug-resistant TB respectively. Without proper treatment, two thirds of patients with active TB will die (Herchline & Amorosa, 2017). The case fatality rate of untreated smear positive TB is 70% and that of culture positive smear negative TB is 20% (Tiemersma, van der Werf, Borgdorff, Williams, & Nagelkerke, 2011). In 2012, Kenya had attained a TB CDR of 82% with 90% of these cases being adults (aged 15 years and older); the rest of the cases remained undiagnosed and went on to spread the disease (DTLD, 2012).

One third of the world‟s population has LTBI, the majority (80%) of whom are found in WHO South-East Asia, Western-Pacific and Africa regions (Houben & Dodd, 2016). However, the current diagnostics tests (Tuberculin Skin Test (TST) and interferon-gamma release assays (IGRA)) poorly predict who will develop active disease (Esmail, Dodd, & Houben, 2018).

Persons with LTBI cannot spread TB; however, if left untreated, 5-10% of persons with LTBI will develop disease and contribute to infectious TB cases (Anger et al., 2012; Herchline & Amorosa, 2017). The rate of tuberculin sensitivity (a proxy for the prevalence of LTBI), irrespective of the BCG coverage, is related to the annual risk of TB infection(Adetifa et al., 2010). Persons with LTBI (i.e. asymptomatic infection) should therefore be screened using chest X-rays to determine whether they should receive chemotherapy or chemoprophylaxis. IPT is

given to persons with LTBI identified during contact tracing to prevent disease progression (Herchline & Amorosa, 2017). Chemoprophylaxis with Isoniazid achieves an efficacy of 70% on full completion. Among all contacts, the Number needed to treat (NNT) to prevent one case of TB is 88; however, the NNT in children aged less than 5 years is 6. This justifies chemoprophylaxis in young children (Anger et al., 2012). The WHO End TB strategy aims to achieve treatment coverage of at least 90% for LTBI treatment by 2035. However, in 2016, only 16% of eligible children received IPT in 2016 (WHO, 2016).

Nevertheless, 6 months‟ duration of IPT, may not be optimal for implementation in regions where there are a high number of contacts per TB index case (Esmail et al., 2018). The prevention of TB among contacts of TB source cases also depends on their willingness to accept and adhere to a chemoprophylaxis regimen (WHO, 2017). In Kenya, IPT administration is recommended for children aged less than 5 years who have been exposed to an open case of TB and screen negative for TB, and for HIV infected adults who screen negative for TB (DLTD, 2011b). However, it is difficult to exclude a TB diagnosis in children (World Health Organization, 2013a).

Because contacts are considered TB suspects, Contact screening is done to identify persons with asymptomatic infection or active disease (MacIntyre & Plant, 1998). Contact investigation of household members of TB patients is recommended by the World Health Organization as an approach to early TB case finding (WHO, 2018). Contact investigation achieves a high case yield (up to 7%) where it is focused on household contacts of sputum-smear positive patients, especially among those aged less than 25 years (Erkens et al., 2010). In a systematic review of Contact investigation in high- and low-income countries, the prevalence of active TB among all contacts of persons with TB was higher in low income countries compared to high income

countries (3.1% vs. 1.4% respectively); similarly, the prevalence of LTBI was higher in low income countries when compared to high income countries (51.5% vs. 28.1% respectively). There was also a higher number of contacts per TB index cases in low income countries compared to high income countries (5.1 vs. 3.8) (Fox, Barry, Britton, & Marks, 2013). Each household in Kenya is estimated to have an average of 4.2 members of all ages, 17% of whom are aged less than 5 years (Kenya National Bureau of Statistics [KNBS], 2015).

In the literature, contact invitation has been shown to be effective. However, it leaves the onus of completing the screening process of all contacts to the index case (Chakhaia et al., 2014). The TB program in Kenya conducts contact invitation. This is because contact investigation requires resources to track all contacts, screen them for TB and initiate preventive or curative therapy (Graham et al., 2004). The TB program in the Kenya also does not document the details of household and non-household contacts of index cases of TB despite the fact that they represent a population at risk of TB disease. Data on contact investigation in Kenya is limited. Of the 11,886 cases reported in the former Nyanza north in 2012, only 2% (281) were found by contact investigation. The annual TB reports do not document the number of cases of LTBI put on chemoprophylaxis and their treatment outcomes (Nyanza Province DTLD Coordinator, Personal Communication; 30th August 2012).

Childhood TB (from birth to 15 years), estimated to be approximately 10% of all incident TB cases, often goes undiagnosed. As children are often smear negative, childhood TB is ranked low on public health priorities (WHO, 2013a).Historically, global TB programs have exclusively focused on adults with smear positive TB as it was believed that this was the most cost-effective way to contain the TB epidemic. In 2006, the WHO issued guidance on the management of childhood TB which were later updated in 2014 (Marais, 2016).Accurate TB diagnosis is

challenging as many childhood diseases can present with similar signs and symptoms. TB is a continuum between exposure with or without infection, latent infection, non-severe disease and severe disease. Therefore, differentiating exposure and infection, and infection and disease is challenging. The pauci-bacillary nature of childhood TB further complicates the bacteriological confirmation of TB and specimen collection is difficult. The diagnosis of intra-thoracic TB is extremely difficult (Roya-Pabon & Perez-Velez, 2016). The risk of TB infection following exposure is higher among children (Sloot, Schim van der Loeff, Kouw, & Borgdorff, 2014). Additionally, the likelihood of developing TB infection following a positive tuberculin skin test is related to the age of an individual (this risk is highest in toddlers) and the life expectancy of the individual. i.e. a younger person with a longer life expectancy is more likely to develop TB(Erkens et al., 2010).

The willingness of a TB index case to allow for the screening for his close contacts implies the disclosure of a TB diagnosis (Oliveira et al., 2017).Furthermore, the identification of a contact is a complex phenomenon as TB infection may either result from exogenous infection from an index case, or from the reactivation of an endogenous infection (Vynnycky & Fine, 1997).

This points out to the need to conduct contact investigation in children in order to assess its value in TB control in a high TB burden, population dense setting, with a high proportion of children aged less than 5 years. The period prior to 2017, when the TB program in Kenya was only conducting contact invitation, and not contact investigation, provides a suitable period to assess the value of standardized contact investigation in comparison to contact invitation (Garg, 2016).

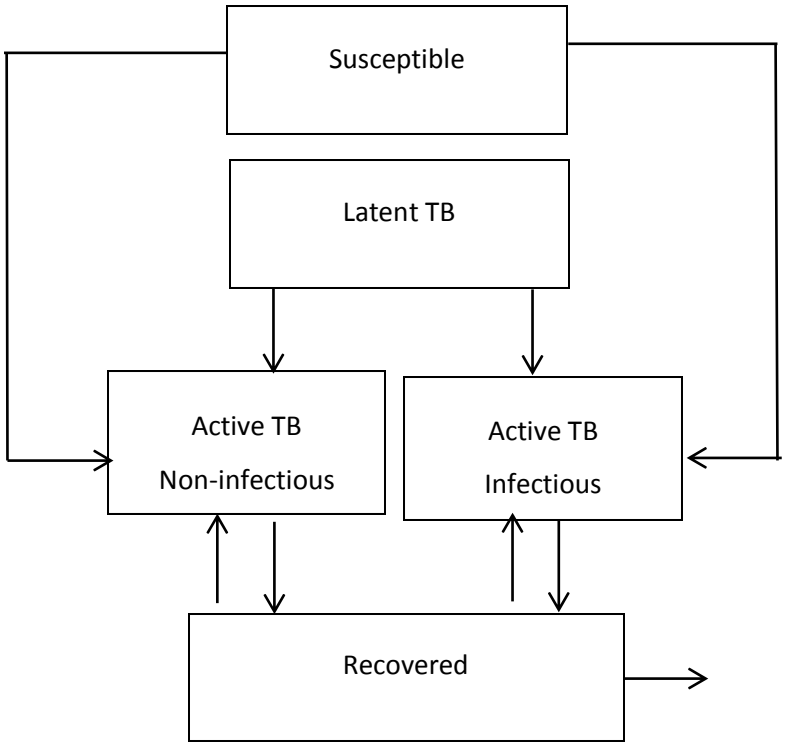


Figure 1: TB transmission dynamics

Source: Blower et al., 1995

1.2 Problem statement

For effective TB control, TB programs should detect cases of infectious TB early and initiate them on treatment (WHO, 2018). Kenya is listed among 30 high TB burden countries that contribute to 80% of the global TB burden (WHO, 2017). By 2005, Kenya had already reached the targets for TB case detection of 70% and cure rates of 85% (WHO, 2008). From 2010, the TB program in Kenya expanded its focus on active case finding to screening HIV infected persons, new inmates in prisons, and household contacts of index cases of TB through the use of household or community cough monitors (DTLD, 2011a). Following this, the guidelines then

recommended IPT administration among children aged less than 5 years who had been in contact with an index case of TB (DTLD, 2011b).

Contact investigation aims to identify and treat new cases of TB, administer preventative therapy to contacts in whom TB is ruled out, or to closely monitor household transmission (Erkens et al., 2010). Screening contacts of known TB cases is only useful if TB prevention IPT is given to persons with LTBI to prevent disease progression or TB treatment is effected for persons with active TB (MacIntyre & Plant, 1998). In Kenya, IPT administration is recommended for children aged less than 5 years who have been exposed to an open case of TB and screen negative for TB, and for HIV infected adults who screen negative for TB (DTLD, 2013b).

Household contacts are the focus of TB contact investigation as they are at an increased risk of TB infection due to prolonged exposure with a TB index case (Guwatudde et al., 2003). Among household contacts, the risk of TB infection following exposure is highest among children (Sloot et al., 2014). Similarly, the likelihood of developing TB infection following a positive tuberculin skin test higher in younger persons (Erkens et al., 2010).Although household contact investigation is included in Kenya TB Control policies, it has not been conducted in Kenya as it is resource-intensive case (Chakhaia et al., 2014). TB screening among household contacts in Kenya is non-standardized and limited in scope to contact invitation. Subsequently, the information on contribution of contact investigation to early case detection in children is scarce or non-standardized. This precludes the assessment of its impact on TB control (WHO, 2012).The absence of information on the uptake of IPT uptake following among child contacts with household exposure to TB further hampers such assessments. In addition to generating conceptual knowledge, health services research projects ought to bring about change and quality improvement by exploring barriers to improvements in disease management in the context of

existing specific guidelines (Chafe, 2017). For instance, to enhance the yield of TB screening activities, screening ought to be done among persons who are at a higher risk of infection (Zhang et al., 2007).

However, information regarding the risk factors for TB infection after household exposure is unavailable. Additionally, information that also would assist in guiding the TB control program in conducting standardized contact investigation is unavailable (Nyanza Province DTLD Coordinator, Personal Communication; 30th August 2012).

In view of this discrepancy, there is a need to assess the contribution of contact investigation to diagnosing and preventing TB in children as well as to provide information that would advise the implementation of TB contact investigation among child contacts.

1.3 Study Justification

Kisumu County located in Western Kenya, is a high TB burden, densely-populated region; it has a population of 1,097,307 of whom 17.4% are aged less than 5 years. It population's density 464.5 per square kilometer (County Government of Kisumu, 2013). In 2016, the TB CNR was 228 against a national average of 170 per 100,000 populations (National Tuberculosis Leprosy and Lung Disease Program, 2017a). The risk of TB infection following exposure is higher among children (Sloot et al., 2014). Additionally, the likelihood of developing TB infection following a positive tuberculin skin test is related to the age of an individual (this risk is highest in toddlers) and the life expectancy of the individual. i.e. a younger person with a longer life expectancy is more likely to develop TB (Erkens et al., 2010).

The WHO estimates that globally, 4 million people develop highly infectious smear positive pulmonary TB annually. If each of these patients has at least three contacts, and the prevalence of active TB among the close contacts is 2.5%, at least 300,000 early TB cases could be identified among close contacts per year (WHO, 2012). The TB program in Kenya conducts contact invitation which is a contact screening strategy that asks the index case to refer all his close contacts for screening. This is because contact investigation is resource-intensive (Graham et al., 2004). The contribution of contact investigation to TB control in children is therefore unknown. Limited data is also available on the interaction of the various known risk factors for TB infection following household exposure that would guide health workers on when to screen for TB (Becerra et al., 2005; Wood et al., 2010).

1.4 Research Purpose

The purpose of this study was to determine the value of contact investigation (defined as the yield of contact investigation in identifying household contacts of TB patients with LTBI or active TB) in the control of childhood TB, using a prospective cross-sectional survey of newly diagnosed TB patients at TB clinics and all their household contacts, with a view to providing information on the contribution of contact investigation to childhood TB control. Contact investigation entailed the screening of all children who had been in household contact with a TB index case. Specifically the study determined the contribution of this TB case finding strategy in contributing to the number of children diagnosed with TB and initiated on IPT.

1.5 Research Hypothesis

H_0: The value of Contact investigation in childhood TB control is equivalent to contact invitation

H_1: The value of Contact investigation in childhood TB control is superior to contact invitation

1.6 Research Objectives

1.6.1 Broad objective

To assess the value of household TB Contact Investigation in control of drug-susceptible TB among children aged 0-5 years who have been in household contact with an index case of TB in Kisumu County, Western Kenya, 2014-2015 a period prior to the inception of standardized contact investigation (Kisumu County TB and Leprosy coordinator, Personal Communication 10th September 2018).

1.6.2 Specific objectives

i. To determine the prevalence of TB infection and individual, index and household risk factors for infection following household exposure to a TB index case with drug-susceptible TB among children in Kisumu County

ii. To determine the IPT uptake and completion rate for TB prevention following household exposure among children in whom a TB diagnosis has been excluded in Kisumu County

iii. To compare the value of TB contact investigation to contact invitation in identifying TB cases (number of TB cases diagnosed) and preventing TB progression (number of children who received IPT) following household exposure among children in whom a TB diagnosis has been excluded TB in Kisumu County

iv. To describe the lessons learnt when implementing standardized TB contact investigation in Kisumu County, a setting with routine contact invitation

1.7 Research Questions

1.7.1 Broad Research Question

What is the value of household TB Contact Investigation in control of drug-susceptible TB among children aged 0-5 years who have been in household contact with an index case of TB in Kisumu County, Western Kenya between 2014 and 2015 a period prior to the inception of standardized contact investigation?

1.7.2 Specific Research Questions

i. What is the prevalence of TB infection and what are the risk factors for TB infection following household exposure to an index case of drug-susceptible TB among children in Kisumu County?

ii. What is the IPT uptake and completion rate for TB prevention following household exposure among children in whom a TB diagnosis has been excluded in Kisumu County?

iii. How does the value of TB contact investigation in diagnosing and preventing TB in children compare to contact invitation in Kisumu County?

iv. What are the lessons leant in implementing standardized TB contact investigation in Kisumu County, a setting with routine contact invitation?

1.8 Significance of the Study

It was anticipated that the study would be useful in providing information on the true value of TB Contact investigation in childhood TB control in Kenya. Knowledge gained from this study assisted in identifying the benefit of contact investigation (in addition to passive case finding) in enhancing TB control activities in children. Study participants benefitted from timely TB diagnosis and initiation of treatment and therefore had favorable patient outcomes. This also led to a decrease in TB transmission within communities. The study improved clinical practice by ensuring that all household contacts were screened for TB and appropriate treatment was initiated. The TB program found the study useful as it contributed to increasing the TB CDR and ultimately a reduction in TB burden and guided on the implementation of standardized TB contact investigation.

1.9 Scope of the Study

In this study, TB contact investigation was conducted among child contacts of TB index cases within Kisumu County between 2014 and 2015, a period prior to the introduction of standardized contact investigation activities, using a cross-sectional survey of newly diagnosed TB patients at 54 health facilities Kisumu County. The study was conducted among 157 child contacts of at least 243 TB index cases. Data was collected using questionnaires and each contact was screened using TST, HIV test and Chest X rays. The study specifically sought to ascertain the value of contact investigation in childhood TB control.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

This chapter discusses the literature related to the value of TB contact investigation in childhood TB control. It particularly focuses on the prevalence of TB infection following contact screening in comparison to passive case finding approaches, characteristics of persons who screen positive during contact screening, Isoniazid administration for TB contacts and lessons learnt when implementing standardized TB contact investigation.

2.2 The Value of TB Contact Screening in Childhood TB Control

Porter (2010) defines value in health care as, health outcomes per dollar spent (Porter, 2010). Volpp and Asch (2012) describe a valuable health care program as one that should improve health care outcomes at a reasonable cost, or achieve the most improvement with the resources available. This is because not all programs have a positive return on investment e.g. prevention programs across broad populations which have low yield but result in a decrease in morbidity and mortality (Volpp, Loewenstein, & Asch, 2012). Value should always be defined around results i.e. the health outcomes achieved which are usually are disease-specific and multidimensional (Porter, 2010).

Dowdle (1998) defines disease control as a decrease in the incidence, prevalence, morbidity and mortality from a disease (Dowdle, 1998). To reduce TB incidence and prevalence by 2005, the World Health Assembly set two TB control targets of 70% TB CDR and 85% TB treatment

success rate in 1991 (Dye, Hosseini, & Watt, 2007). Later, a new strategy to end TB by 2035 (defined as a TB incidence to < 10 per 100,000 populations) was set by the World Health Assembly in 2014. A milestone in this strategy (the Global Plan Targets 2015 to 2025) was to reach 90% of all undiagnosed TB cases, 90% of all key populations, and attain at least 90% TB treatment success. Key populations, who are the most vulnerable and under-serve at risk populations include children, PLHIV, indigenous peoples, healthcare workers, mobile population, PWID, rural populations, urban populations, miners, prisoners, etc. Each government would define its key populations, plan and implement appropriate services to suit them, and measure progress towards theses targets (WHO, 2016). The Kenya TB program guidelines recommend IPT for TB prevention for all children aged < 5 years who have been in household contact with a TB index case in whom a TB diagnosis has been excluded, as part of its underserved populations (DTLD, 2011b).

This study will adopt the WHO TB control targets to define TB control i.e. TB control will defined in terms of number of TB cases diagnosed among children aged less than 5 years, and number of child contacts who have been exposed to an infectious case of TB who receive IPT (Azman, Golub, & Dowdy, 2014). The TB treatment outcomes will not be assessed as no further intervention will be provided in either group (contact investigation or contact screening) outside that which is received during routine care by the national TB control program after TB diagnosis. Although the ultimate outcome of IPT use that ought to be assessed is a decrease in TB incidence among children who received IPT; this would require a longer duration of follow up and a comparator group to assess the risk reduction accorded by IPT (Golub et al., 2015).

This study will describe the value of a TB contact screening strategy (e.g. contact investigation or contact invitation) as changes in TB control achieved by that specific contact screening

strategy. Cost comparisons are only possible if the program is mature, economic costs are well quantified and comparisons can be made across groups (Issel, 2004). The TB program in Kenya has provided clear guidelines for the screening of household contacts (DTLD, 2011b). However, this is limited by the fact that contact invitation rather than contact investigation is practiced in Kenya. As contact investigation is yet to be standardized in Kenya, an economic comparison between the two strategies would not be done (Nyanza Province DTLD Coordinator, Personal Communication; 30th August 2012).

Beccerra et al (2005) assessed the yield of an active case finding among contacts of TB index cases strategy in Peru. The prevalence of TB detected in household contacts through active case finding was higher than through passive case finding (0.91% vs. 0.18%). Similar results were observed among neighbors of the index case i.e. 0.22% vs. 0.08% respectively. But diagnostic testing was limited to only those who presented with cough, and compliance to screening was low. Additionally, there were no TB cases diagnosed in children aged less than 15 years. This was attributed to challenges, in providing sputum samples, in IPT use, or could reflect a true absence of disease (Becerra et al., 2005). The yield of TB screening among children may be low because children usually have pauci-bacillary disease, the yield of sputum smears is low even with samples from induced sputum or nasogastric aspirates, and the fact that sputum cultures which are preferable, are not routinely available (Graham et al., 2004).The existing WHO policies did not have chest x-ray interpretation guidelines and TB treatment assignment policies. These guidelines asked clinicians to exercise, sound clinical judgment‟ in the interpretation of Chest x-rays without clearly defining what features to use (Bos et al., 2013). In Kenya and in Malawi, limited TB diagnostic capacity was responsible for very low rates of TB diagnosis among symptomatic patients (Bos et al., 2013; Burmen et al., 2015).

Ayles et al (2013) assessed the effect of two community-level interventions on TB control among adults aged 18 years and older. These interventions were implemented as follows; within the clinic alone (Group 1), within the clinic plus enhanced community level case-finding ECF (Group 2), enhanced community level case-finding plus household contact investigation (Group 3), and clinic plus enhanced community level case-finding plus household contact investigation (Group 4). The prevalence of TB was 832 per 100,000 populations. The adjusted prevalence ratio for ECF vs. non-ECF was 1.09 and for household vs. non-household was 0.08.The adjusted incidence ratio for a group of children followed up for 3 years for ECF vs. non-ECF was 1.36 and for household vs. non-household was 0.45. As these interventions were designed to decrease TB transmission and ultimately TB prevalence, a longer follow-up period may have been required to assess their effect. Additionally, screening limited to only sputum smear positive cases (Ayles et al., 2013). In India, among child contacts aged less than 5 years, 30% of TB cases would have been missed by focusing only on sputum positive index cases. This is because majority of sputum negative cases do not have the minimum 10,000 AFB per ml required for a positive Zeihl-Neelsen stain (M. Singh, Mynak, Kumar, Mathew, & Jindal, 2005).

Borgen et al (2008) assessed a large TB contact investigation program in the Netherlands for customers who frequented a supermarket where one employee had TB. Of 13,970 persons screened, 2.6% (359) had TB infection based on TST readings, 11 of whom had TB disease. This yield may have been higher if screening was limited to only frequent customers (who had a higher prevalence of TB), and radiographic screening (which had a zero yield) was not used. However, customers‟ socioeconomic status, which may have influenced screening results, was not assessed (Borgen et al., 2008). Chest X-ray screening is more useful in high TB endemic regions. In such regions, less than 10% patients with culture-confirmed tuberculosis infection

have normal chest radiographs. However, this proportion increases with increasing immune-suppression (Erkens et al., 2010).

Liu et al (2010) evaluated the yield of different TB contact investigation strategies in China. The yield, which ranged from 0 to 11%, varied with the type of index case, the circle of contact screened, and the protocols to followed when identifying and investigating contacts(Liu et al., 2010). In India, the yield of TB contact investigation among young children living in households of smear positive TB cases ranged from 22-34% and was higher (27-62%) among in children aged less than 10 years. Majority of TB infections among children aged <3 years occurred from household contact. Conducting household contact investigation in this age-group will therefore lead to earlier diagnosis and treatment, prevent the occurrence of complications, and reduce the pool of future LTBI cases (Banu Rekha, Jagarajamma, Wares, Chandrasekaran, & Swaminathan, 2009). Due to its potential benefits, TB active case finding is recommended in regions with high TB prevalence, low detection rates and moderate to high treatment completion rates (Murray & Salomon, 1998). In 2012, the WHO provided recommendations for investigating contacts of persons with infectious TB in low and middle income countries. However, these did not specify guidelines for specific programmatic conditions under which contact investigation should be conducted, the types of index cases to be prioritized for screening, specific protocols to be followed, or the contacts to be investigated (other than children aged < 5 years and PLHIV)(WHO, 2012).

2.2.1 Risk factors for TB infection

The World Health Organization (nd) defines a risk factor as "... any attribute characteristic or exposure of an individual that increases the likelihood of developing a disease or injury"(World

Health Organization, n.d.). Van Dyke and Sheilesh (2005) define a risk factor as an occurrence or a characteristic that is associated with an increased rate of developing a disease. They distinguish the fact that risk factors are only associated with disease but do not cause disease. Risk factors are classified as non-modifiable risk factors (also known as determinants of disease) and modifiable risk factors which are extrinsic to the individual and can be changed. Modifiable risk factors include behavior and environmental factors (Van Dyke & Sheilesh, 2005). This study will adopt a definition of 'risk factor' as a characteristic intrinsic or extrinsic to a TB index case or a child contact that predispose a child contact to developing TB infection following household exposure. This is because the development of TB infection in a child contact following household exposure is due to a combination of infectiousness of the TB index case, susceptibility of the contact to infection, and intensity of the susceptible person exposure to the index case (Lienhardt et al., 2002).

2.2.2 Infectivity of the TB index Case

2.2.2.1 Presence of Cough

In a systematic review, Erkens et al (2010) assessed the relationship between cough and infectivity of the TB index case. A TB patient who coughs is therefore more likely to transmit TB than one who does not cough; a risk that is increased if the cough is productive. However, any respiratory maneuver e.g. talking, singing etc., generates aerosols. „Cough" which has been used a proxy for the period of infectivity can be misleading since bacilli can also be expelled in any respiratory maneuver (Erkens et al., 2010). Infection with TB results from inhalation of infected aerosol droplets (1-5 micrometers in diameter). A single cough can generate up to 3000 of these droplets and each aerosol can contain 1-400 bacilli. Only 1-200 bacilli are needed to initiate the infection (Herchline & Amorosa, 2017).

Turner and Bothamley (2015) reviewed the relationship between cough and the transmission of Tuberculosis. Although cough promotes the aerosolization of infectious particles, the exact mechanisms of how this happens, the patterns and types of cough that most efficiently do this, are poorly defined. Further research into the subjective and objective nature of cough, temporal cough patterns and aerosolization of respiratory secretions is still required (Turner & Bothamley, 2014).

2.3 HIV and AIDS

Espinal (2000) examined the infectiousness of MTB in HIV patients. TST was positive in 61% and 76% of contacts of HIV positive and HIV negative patients respectively (Espinal et al., 2000). HIV infected patients have a weaker cough and lower bacillary load and are thus less effective in disseminating of *M Tuberculosis* bacilli (Elliott et al., 1993). A lower tuberculin response has however been observed among contacts of HIV positive contacts of index cases compared to contacts of HIV negative cases (52% vs. 7%). This was attributed to anergy resulting from undiagnosed HIV infection as not all contacts had HIV test results (Espinal et al., 2000).

Munthali et al (2014) assessed the effect of ART on the characteristics of pulmonary TB patients in Malawi. Sputum smear positive patients were more likely to be found among HIV negative patients than among HIV positive patients. Among HIV positive patients, positive smears were more likely to be found among those on ART compared to those not on ART. ART shifts the presentation of TB among HIV positive towards that seen in HIV negative patients. This facilitates TB diagnosis but also increases the infectivity of the patient. It is also possible that TB among patients commencing ART is due to Immune Reconstitution Inflammatory Syndrome;

although the relationship between immune status as measured by CD4 counts and smear positivity; neither was the effect of duration on ART on immune status (Munthali et al., 2014).

2.3.1 Bacillary load as evidenced by sputum smear status and chest X ray findings

Singh (2005) investigated the risk factors for TB infection among child contacts following household exposure to a TB index case. Contact with an adult with smear positive TB was associated with an increase in TB infection in child contacts. However, this study did not screen older child contacts. The exclusion of contacts of smear negative TB index cases from screening may have missed 30% of the TB cases diagnosed. This is because a sputum sample ought to have a minimum of 10,000 AAFB per ml to be detected on ZN staining. Sputum cultures however, can detect a AFB concentrations of as low as 100 ml AAFB per ml (M. Singh et al., 2005). . Sputum-smear positivity of the TB index case, an indicator of microbial case load, is associated with increased infectivity especially if there are >100 acid fast bacilli per high power field (Graham et al., 2012; M. Singh et al., 2005). Extra-pulmonary TB doesn‟t warrant contact investigation; focus should be shifted to the index case to rule out TB of the lung parenchyma. This is because tubercle bacilli are usually transmitted by persons with TB of the lung parenchyma (MacIntyre & Plant, 1998). However, commonly used tests to diagnose TB i.e. sputum microscopy and chest x ray perform poorly in HIV infected persons who commonly have smear negative and extra pulmonary TB (Getahun et al., 2011). Furthermore, HIV-infected TB patients with low CD4 counts, patients with pleural effusions obscuring the lung parenchyma, or in TB patients with mediastinal or hilar lymphadenopathy, may have sputum cultures that are positive for mycobacteria even without parenchymal lung disease (Erkens et al., 2010).

The number of bacilli expelled by a cough is also determined by underlying lung parenchyma lesions and their access to respiratory airways. Cavitary lesions on the source case‟s chest x ray are associated with a high number of bacilli; up to 100 million colony forming units (Aissa et al., 2008). However, children usually have pauci-bacillary disease; the yield of more sensitive tests such as sputum culture in identifying children with TB is also low (Graham et al., 2004).

2.3.2 Susceptibly of the child contact

2.3.2.1 Age of the child contact

In India, a third of children aged < 5 years who were in household contact with adults with pulmonary TB had TB infection and up to 5% had TB disease; however, this was not studied prospectively (M. Singh et al., 2005). In a retrospective analysis of TB contact investigation programmatic data in the US, younger age (less than 5 years) and being a household contact were associated with prevalent tuberculosis; however, the HIV status of the contacts was not assessed (Anger et al., 2012). From the period of exposure to a TB index case, infants will take up to 6-8 weeks to develop TB and children up to 1 year. Although, the majority of children infected with TB will not develop active infection, they are likely to go on to become infectious adults‟ later (Graham et al., 2004). The likelihood of developing TB infection following a positive tuberculin skin test is related to the age of an individual and the life expectancy of the individual. Younger children i.e. toddlers have the highest likelihood of developing TB following a positive Tuberculin skin test. A younger person with a longer life expectancy is also more likely to develop TB. For this reasons, children are the focus of WHO TB‟s contact investigation (Erkens et al., 2010). Due to repeated exposure to *Tuberculosis*, the risk of TB infection increases with age (Aissa et al., 2008). IGRA are the preferred test for TB infection for children aged 5 years and older because the sensitivity of TST decreases with age (Kay, Islam, Wendorf, Westenhouse, & Barry, 2018).

2.3.2.2 Immunization status of the contact

BCG confers individual protection of 40%-70% against Tuberculosis for 10-15 years and prevents approximately 80% of disseminated TB disease(Medicins Sans Frontier [MSF], 2014). Its absence correlates with a two-fold increase in the risk of TB infection (M. Singh et al., 2005). Although Ganmaa et al (2018) did not find a relationship between the presence of a BCG scar and a positive quantiFERON TB Gold test, it is important to note that some children who receive BCG never develop a scar (Ganmaa et al., 2018).

TB programs in endemic regions should therefore aim for BCG vaccine coverage of at least 80% among children aged less than 2 years. BCG may however interfere with surveillance efforts especially when conducting contact investigation using Tuberculin Skin Tests (TST) (MSF, 2014). For this reason, various methods have been proposed to identify a suitable cut off for TST positivity (Rieder, Chadha, Nagelkerke, van Leth, & van der Werf, 2011). In Kenya, a TST cut off of 5 mm is recommended for the malnourished or HIV infected child, and 10mm for the well-nourished and or HIV negative child (DTLD, 2011b).

2.3.2.3 HIV and AIDS

HIV and other immunosuppressive conditions are associated with an increased risk of progression from LTBI to active TB. Children with HIV infection are also more likely to have rapid progression of new TB infection to disease, reactivation of latent TB infection, recurrence of TB after treatment, and increased risk of death (DTLD, 2011b).

A positive TST in a HIV-infected patient (with or without AIDS) increases the risk of progression from LTBI to active TB disease. Over 2-5 year duration, among untreated persons with a positive TST, 10-23% of HIV positive persons will develop TB compared to 2 % of HIV

negative persons (Erkens et al., 2010). This justifies chemoprophylaxis for HIV-infected person with no evidence of TB disease and a positive TST (DTLD, 2011b). Lower tuberculin responses observed among contacts of HIV positive index cases in comparison to contacts of HIV negative cases (52% vs. 71%) may have been due to undiagnosed HIV-infection. This is because only 20% of the contacts had been tested for HIV (Espinal et al., 2000).

2.3.2.4 Nutritional Status

Protein Energy Malnutrition (PEM) increases the risk of infections; malnutrition contributes to every 2nd death in children from infectious illnesses (Schaible & Kaufmann, 2007). A severely malnourished child is more likely to develop TB disease after TB infection than a well-nourished child. Severe malnutrition has been associated with a four-fold increase in the risk of developing TB among children in household contact with adult patients with TB (Erkens et al., 2010). Singh et al (2005) illustrated a dose response relationship between malnutrition and TST sensitivity has been illustrated in the literature with a higher proportion of children with a positive TST among those who are severely malnourished (M. Singh et al., 2005).The immune responses in a malnourished child mimic the responses that occur in HIV/AIDS infection (Shashidhar & Grigsby, 2017). Primary and secondary immune responses to infection are reduced in malnutrition (Schaible & Kaufmann, 2007). Cell Mediated Immunity (CMI) remains unchanged in well-nourished children with TB regardless of the severity of TB, whereas it is impaired in malnourished children with severe forms of TB (Vijayakumar, Bhaskaram, & Hemalatha, 1990).

2.3.3 Intensity of the exposure between the TB index case and a susceptible contact

2.3.3.1 Household contact

Marais et al (2004) in a systematic review of literature in the pre-chemotherapy era (before 1960) found that contact with household sputum positive source case was the single most

important risk factor for TB infection children. This also remained an important contributor to infection until the child was 5–10 years of age especially for children aged less than 2 years. However, there was no clear definition of TB disease. Furthermore, TB cases in children were underreported (Marais et al., 2004). Most cases of childhood TB (under 5‟s) in low income countries usually have been in contact with a „resident‟ adult with TB in the child‟s home (Wood et al., 2010). Conversely, the prevalence of TB among contacts decreases with more remote exposure. This supports household contact investigation, in preference to non-household contact investigation (Fox et al., 2013).

2.3.3.2 Closeness of contact between index case and contact

Because they spend considerable amounts of time in the home, pre-school children aged 0-4 years are at a higher risk of TB infection from a resident adult infected with TB. When a child‟s social mobility increases, his likelihood of acquiring TB infection from a resident adult decreases, while his likelihood of acquiring infection form a non-resident adult increases even with limited social interaction with non-resident adults with TB infection. An increase in the number of households visited by children increased the risk of TB infection from 4% to 6% (Wood et al., 2010). Children aged 5 years and older, who are of school-going age, have reduced periods of exposure to an infected adult in the home (Aissa et al., 2008). TB infection has been shown to be more prevalent among contacts of female TB index cases that spend considerable amounts of time in the home than male TB index cases (Tornee et al., 2005).

2.3.3.3 Duration and frequency of contact between index case and contact

Prolonged duration in contact with an index case of TB increases the likelihood of TB infection in children who are household contacts of patients with sputum smear-positive TB. The chances of this are increased when this contact occurs at night (Aissa et al., 2008). The risk of TB disease is related to the cumulative time of contact during the period of infectiousness (DTLD, 2013b).

2.3.3.4 Housing state, ventilation and sleeping arrangements

TB transmission is unlikely outdoors since bacilli are dispersed or killed by sunlight. Transmission outdoors is only possible if the source case and his or her contact are at talking distance. However, indoors, bacilli are trapped and may remain suspended in the air for prolonged periods (Erkens et al., 2010). Air changes per hour (ACH) is the ratio between the air added to or removed from a room divided by its volume; higher values corresponding to better ventilation. A standard 12 ACH is recommended by the WHO to prevent airborne transmission of disease. A change in ventilation from 2 ACH (poor ventilation) to 6 ACH (moderate ventilation) occurring over a duration of 120, 90, 60 and 30 days during the period of infectivity, would reduce TB transmission from 3% to 2.5%, to 2.2%, 1.8% and 1.1% respectively. This corresponds to limiting daily exposure time by less than 8 hours by having separate sleeping rooms for the index case and the child contact. Increasing the ACH is only useful when infectiousness of the index case is reduced e.g. by initiating TB treatment. This model illustrated that clinic-based control programs may not be very useful in the absence of environmental control strategies. However, the number of infective quanta used in this model was based on published studies which may have been inaccurate, and the incidence of smear-positive TB used may not have reflected the true notification rate (Wood et al., 2010).

2.3.3.5 Crowding in the home environment

Crowding in the home environment can be measured by dividing the number of persons in the home by the number of rooms in the home (Espinal et al., 2000). Crowding increase the likelihood of contact as well as the intimacy of contact between source cases of TB and susceptible persons (Lienhardt, 2001). Clark et al (2002) investigated the association between TB and housing density, isolation and household income among indigenous populations in

Canada. An increase in TB CNR was found with an increase in housing density, an increase in isolation and a decrease in household income. However, limited data on other factors that may have been responsible for the occurrence of TB restricted this analysis (Clark et al., 2002). Multiple factors of the „poverty complex" act together to increase risk of disease, although none of them may lead to disease directly. These may include overcrowding, malnutrition and poor access to health care (Lienhardt, 2001). To reduce TB disease burden, its" basic reproductive rate (i.e. the number of secondary infectious cases an infectious case generates per unit time) ought to be reduced. The basis reproductive rate can be reduced by reducing contact between a source case and potential secondary cases (Clark et al., 2002).

2.3.3.6 Exposure to cigarette smoke

Both passive and active inhalation of cigarette smoke increases the risk of TB infection by 20% (Aissa et al., 2008). This implies that there are substances inherent to the cigarette smoke which increase the risk of acquiring TB infection. Ganmaa et al (2018) found a dose response relationship between the number of smokers per household and the number of children with a positive quantiFERON TB Gold test. However, they did not assess the relationship between HIV status and a positive quantiFERON TB Gold test; as this was a cross sectional study their findings may have also been confounded by unknown factors (Ganmaa et al., 2018). Contacts of sputum positive smokers had higher infection rates than contacts of sputum positive nonsmokers; smoking may impair pulmonary immune defense mechanisms or reflect poor health related habits that predispose one to infection (M. Singh et al., 2005).

2.4 Isoniazid Preventative Therapy

The WHO Stop TB strategy defines TB preventative therapy as, chemoprophylaxis with isoniazid to reduce the risk of latent TB or the risk of a first episode of TB occurring in people exposed to an infectious case of TB who have LTBI. It further states that the greatest risk in reduction is observed in HIV negative persons and in TST positive HIV individuals (WHO, 2006). The Kenyan TB control guidelines describe Isoniazid Prophylactic Therapy (IPT) as a six months course of Isoniazid recommended for children aged less than 5 years who have had a recent exposure (within the past 12 months) with an adult ,or an adolescent with pulmonary TB provided the contact has no evidence of TB disease. IPT is also recommended for other populations e.g. HIV infected adults who screen negative for TB (DTLD, 2011b).

For this study, a description of IPT for TB control will be adapted from the two descriptions as follows; the administration of a six months‟ course of isoniazid to child contacts of TB index cases who have shared living quarters with the index case for a period of at least 3 months preceding the TB diagnosis date in who screen negative for TB. This is because screening contacts of known TB cases is only useful if TB prevention with IPT is given to prevent disease progression or TB treatment is effected (MacIntyre & Plant, 1998). This definition confines itself to the period of infectivity in which TB infection in the child contact is likely to have been as a result of household contact (Erkens et al., 2010). This definition also overcomes the challenges in accurately diagnosing LTBI (Esmail, Barry, Young, & Wilkinson, 2014). IPT completion will be defined as the completion of a six months course of uninterrupted course of IPT to limit the chances of developing IPT resistance (Teklay, Teklu, Legesse, Tedla, & Klinkenberg, 2016).

Tadesse et al (2016) assessed the programmatic uptake and completion rate of IPT among children in Ethiopia. They found an IPT uptake rate of 64% and a completion rate of 80%. Although among those who completed IPT, 80% interrupted IPT, none of them developed TB during treatment. Their assessment was limited by missing data and a short follow up period in which to assess the impact of IPT on TB prevention. Despite IPT completion being a key indicator of TB prevention, they also did not evaluate factors that would promote unsupervised completion of IPT (Tadesse et al., 2016).

Anger et al (2012) assessed TB prevention among a cohort of contacts exposed to an infectious case of TB in New York. During a four-year follow-up period, the maximum follow-up period for all contacts in New York‟s‟ TB registry, IPT completion rates were 61%. TB was diagnosed in 0.4% of contacts who initiated chemoprophylaxis and 1.5% who did not. Chemoprophylaxis afforded a risk reduction of 1.1% leading to an estimated 88 contacts treated to prevent 1 tuberculosis case. Nevertheless, the allocation of contacts to treatment or control groups was not randomized. The prevalent cases of TB were limited a 9 month period following the TB index case‟s diagnosis date. This period reflected the time it took to complete contact screening. It is possible that some prevalent cases (diagnosed within 9 months of the index case) may have been classified as incident cases (diagnosed 9 months after the TB index case) if there were delays in diagnosis (Anger et al., 2012). IPT provides protection for period of up to 7 years in medium TB incidence countries like Brazil; a duration that is shorter in high TB incident regions (Golub et al., 2015).

Singh et al (2017) investigated the impact of IPT administered to children living with TB patients in India. They found a screening rate of 37% among child contacts aged <6 years, an IPT uptake rate of 22% and a completion rate of 20%. However, their investigation relied on

programmatic data and the duration of IPT could not be verified from medical records. In the same study, health workers who were interviewed cited IPT shortages and had directed some patients purchase it. There were also challenges in monitoring IPT (A. Singh et al., 2017).

In Kenya, only 18 child contacts of 28 smear positive cases reported in one quarter in 2012 at a busy regional referral hospital in Kisumu County had been screened for TB and 5 of them received IPT. There was no documentation of the total number of eligible household members that were screened (Clinical Services Coordinator, KEMRI, Personal Communication, 30th June 2012). The components of the WHO Stop TB strategy to dramatically reduce the global burden of TB include standardized supervised treatment, effective drug supply and the monitoring and evaluation of performance and impact (WHO, 2006).

Gomes et al (2013) assessed the impact of IPT on mortality in children aged less than 5 years following household exposure to TB in Guinea Bissau. Exposed children who received IPT between 2005 and 2008, had 70% lower all-cause mortality than exposed children who did not receive IPT between 1996 and 1998, when IPT was not available (Gomes et al., 2013). Nonetheless, comparing data from two time periods is not straightforward as many conditions may have changed. Similarly, „disease-specific mortality" is preferred over „all-cause mortality" when making comparisons as the cause of death can be ascertained (W. Black, Haggstrom, & Gilbert Welch, 2002).

The prevention of TB among contacts of TB source cases depends on their willingness to accept and adhere to a chemoprophylaxis regimen. However, worldwide only 16% of eligible children received IPT in 2016 (WHO, 2017). Gomes et al (2011) assessed adherence rates to IPT among child contacts of TB index cases in Guinea Bissau. They measured adherence rates as completion

of 6 months of consecutive doses of IPT with at least 80% adherence (Gomes et al., 2013). Nevertheless, different investigators have employed different measures of adherence e.g. Shayo et al (2011) defined it as consumption of 90% or more, of the monthly dose (Shayo, Moshiro, Aboud, Bakari, & Mugusi, 2015).

2.5 Lessons learnt when implementing Standardized TB Contact Investigation

The project management institute defines „lessons learnt" as learning gained from the process of performing a project. This can happen either at the end of a project or during the course of implementation of a project (The Project Management Institute, n.d.). Whereas „The Project Definition" describes lesson learnt as significant knowledge or understanding gained by experience that is technically correct and is impactful on operations. This knowledge, which may either be positive or negative, reduces potential for mishaps and reinforces a positive results (The Project Definition, n.d.).

This study adapted the two definitions to define „lessons learnt" as positive or negative information gained during the implementation of a project that would be impactful on operations i.e. would aide in producing positive results. This was because, the goal of many health services and research policy projects is not only to increase conceptual knowledge, but to also bring about change and quality improvement by exploring barriers to further improvements in disease management that may still exist despite the presence of specific guidelines (Chafe, 2017).

Liu (2010) reviewed the literature that assessed contact investigation activities in China between 1997 and 2007; a period during which there were no guidelines for contact investigation. This review showed that there was no standard definition of contacts, no prioritization of contacts to be screened and different investigations were used leading to different yields. Some studies

defined contacts as persons living in the same household with or without a stated duration of contact. In the absence of a specific set of guidelines, the quality of contact investigation conducted then was deemed low (Liu et al., 2010). In 1998, MacIntyre and Plant reviewed the appropriateness of TB screening guidelines, adherence to these guidelines and their impact on TB control in Victoria, Australia. They found the guidelines for contact investigation to be outdated. The guidelines were also not adhered to; eligible were not appropriately screened and neither did eligible contacts receive IPT. However, it was not possible to provide an accurate impact on TB control (MacIntyre & Plant, 1998). For disease screening to be effective, there should be a standard definition of the target population, prioritization of this population to be screened and guidelines on the types of investigations to be used(Bruce et al., 2008).

Regular monitoring and evaluation of activities facilitates effective implementation of TB programmatic activities (Marais, 2017). Information on trends in childhood Tuberculosis is limited in sub-Saharan Africa. Therefore, better methods for surveillance, and research into optimal methods of conducting contact investigation in children, risk factors for TB infection and adverse outcomes are recommended (Nelson & Wells, 2004). BanuRekha et al (2009) conducted a situational analysis in India prior to the implementation of the WHO guidelines for TB contact investigation. The TB treatment cards of index cases lacked details of household contacts, and health care workers were not aware of contact investigation polices. Even where policies were being implemented documentation was weak (Banu Rekha et al., 2009). Similar challenges have been observed in Kenya (Nyanza Province DTLD Coordinator, Personal Communication; 30th August 2012).

Aissa et al (2008) evaluated a model that would enhance the efficiency of TB contact screening in France among contacts of all ages. They were able to reduce the number of contacts to be

screened to 75% and still maintain a false negative rate of 9%. However, they did not adjust the false negative rate to be equivalent to or to be lower than the background TST positivity rate (Aissa et al., 2008). Similarly, Mancuso et al (2011) assessed the use of a risk score to target the screening of army recruits using IGRA in the US, a low prevalence population. The risk score was shown to reduce testing by more than 90%; however, this was limited to persons who had not received BCG and to a low TB incidence setting(Mancuso et al., 2011). As only 5-15% of those exposed to TB cases will develop TB, only those who are symptomatic or at most risk of HIV infection should be investigated for TB (Cain et al., 2010). This should be done in a rational and systematic manner to prevent missed opportunities for TB prevention (Aissa et al., 2008; MacIntyre & Plant, 1998).

Porskrog et al (2011) evaluated TB suspects who had initially screened negative for TB in Guinea-Bissau. At month one of follow up, 42% of participants were still symptomatic and 12% of them were diagnosed with TB. A HIV diagnosis and a positive TST was predictive of TB disease within one month of an initial negative TB test (Porskrog et al., 2011). In Victoria in Australia in 1991, among contacts with an initial negative skin test, 15% tested positive (MacIntyre & Plant, 1998). It takes a period of up to 12 weeks for an infection to induce a cellular immune response that can be elicited through Tuberculin Skin Testing (TST). During this period, a TB suspect would screen negative for TST (Herchline & Amorosa, 2017). In a review of observational studies, the incidence of TB among close contacts of an index case with TB was highest during the first year of exposure; this justifies repeat screening among contacts that initially screen negative (Fox et al., 2013). Since the rate of reactivation of latent TB is unknown, the appropriate rescreening rate of contacts is unknown. Nevertheless, withholding

effective preventative therapy would be unethical for contacts who initially screen negative for TB (Linas, Wong, Freedberg, & Horsburgh, 2011).

Dowdy et al (2013) modeled the population-level impact of TB case-finding strategies in the presence of subclinical or pre-diagnostic disease. The subclinical phase was shown to limit the impact of current diagnostic strategies for TB (Dowdy, Basu, & Andrews, 2012). Whereas case presentation occurs 2-3 months prior to diagnosis, culture positive TB disease has been shown to last for up to 18 months prior to case presentation. Therefore, there is on-going TB transmission for several months before TB case presentation (Esmail et al., 2018). The period of infectivity, should be considered when identifying the contacts of a source of case of TB. This period lasts from the onset of cough or any respiratory symptom, to two weeks after the onset of TB treatment. The period of infectivity could begin 3 months prior to TB diagnosis for patients with sputum smear-positive TB, and one month prior to TB diagnosis for patients with smear negative culture positive TB. The period of infectivity is closed when either smear positivity on microscopy decreases, or effective treatment (as evidenced by MTB susceptibility) has been administered for at least 2 weeks, or when symptoms are diminished. The period of screening should therefore include a 2 week period after TB treatment initiation when a TB patient is still infectious, and be extended a further 6 weeks to cover for the infection incubation period in the contact (Erkens et al., 2010).

Contact investigation in the Netherlands and the rest of Europe and the US follows the „stone in the pond" principle, where contacts around an index case are grouped according to frequency and intimacy of contact. Each concentric circle around the index case is screened starting at the innermost circle until the prevalence of infection in the circle is comparable to the age-specific background prevalence (Verdier, de Vlas, Kidgell-Koppelaar, & Richardus, 2012). If the TB

prevalence in the highest priority innermost circle is higher than the age-specific background prevalence, it means the source case was highly infectious and screening should continue to lower priority circles (Reichler et al., 2002). Although widening the circle of contacts to be screened to social contacts may lead to a higher yield, it is resource intensive or may detect remote cases that are not related to the source case. Additionally, it may have an infinitely smaller yield. The prevalence of LTBI, or the expected number of contacts to be screened to detect one case of LTBI or active TB, should guide on when to extend contact investigation to less exposed contacts (Borgen et al., 2008).

2.6 Theoretical framework

The study was modeled on the Iceberg theory of disease, first brought to attention by Last in 1963. The theory postulates that cases of disease that have been correctly diagnosed are at the tip of the iceberg, visible and easily measured. The majorities of cases of disease are submerged and remain unseen, unmeasured and easily forgotten with potentially catastrophic consequences. The iceberg is divided into 5 blocks; the 1st surface block represents cases of disease that have been diagnosed and controlled, the 2nd surface block represents cases of disease that have diagnosed and but are uncontrolled, the 3rd submerged block represents cases of disease that undiagnosed or wrongly diagnosed, the 4th submerged block represents the population at risk of disease and the 5th and deepest submerged block represents the population that is free of risk factors. To manage the 1st surface block only requires clinical vigilance, the 2nd surface block clinical review, the 3rd submerged block, targeted or population screening, the 4th submerged block, screening or health education and the 5th submerged block, primary prevention (Raj, 2016) (Figure 2).

The theory was used by Last and Adelaide (2013) to estimate the number of undiagnosed cases of different illnesses in England and Wales. They used data from community surveys and the number of patients with different diseases diagnosed at a fictitious clinical practice based on prevailing morbidity statistics. They were able to demonstrate that the proportion of persons that were „submerged" already had risk factors for disease that could have been identified without the need for additional clinical skills (Last & Adelaide, 2013). Similar to this, child household contacts of a TB index case aged less than 5 years who are at an increased risk of TB infection, can undergo screening using existing TB diagnostic tests (DTLD, 2011b).

The theory has also been used by Rubio-Tapia & Murray (2010) to describe the celiac iceberg. For each case of Celiac disease diagnosed, up to 10 cases remain undiagnosed. Celiac disease case finding strategies were described as insufficient (i.e. passive case finding) and favorable (i.e. the use of diagnostic tests and screening of symptomatic persons) (Rubio-Tapia & Murray, 2010). Currently, majority of TB cases in children are undiagnosed (WHO, 2013b). Furthermore, existing screening may only be useful in persons who are symptomatic (Eisenberg & Pollock, 2010).

This Iceberg theory is preferred over the „socio ecological model" which explores disease control at individual, relationship, community, and societal levels. This is because this study focuses on individual and household levels only (Kumar et al., 2011). The Iceberg theory is also preferred over the theory for chronic disease screening; chronic diseases have a long incubation period between possible exposure and disease ranging from years to decades whereas infectious diseases like TB have a shorter incubation period during which an infected person can be identified using diagnostic tests. Acute diseases like Tuberculosis also have pertinent clinical information e.g. a clinical history or exposure history (Raj, 2016).

As applied to this study, the iceberg theory of disease holds that screening among those at risk, or the undiagnosed, will enable health programs address the true burden of disease and therefore contribute to disease control. A proportion of TB cases among persons that are at risk of infection, e.g. child household contacts of TB index cases usually remain undiagnosed (World Health Organization, 2013a). In the application of the iceberg theory to this study, Contact screening will be defined as either contact investigation or contact invitation, and TB control will be defined as a decrease in the prevalence, incidence, mortality and morbidity from disease. However, this theory is limited in that the proportion of disease cases that are diagnosed will be dependent on the type screening tests used (Cavanaugh et al., 2016).

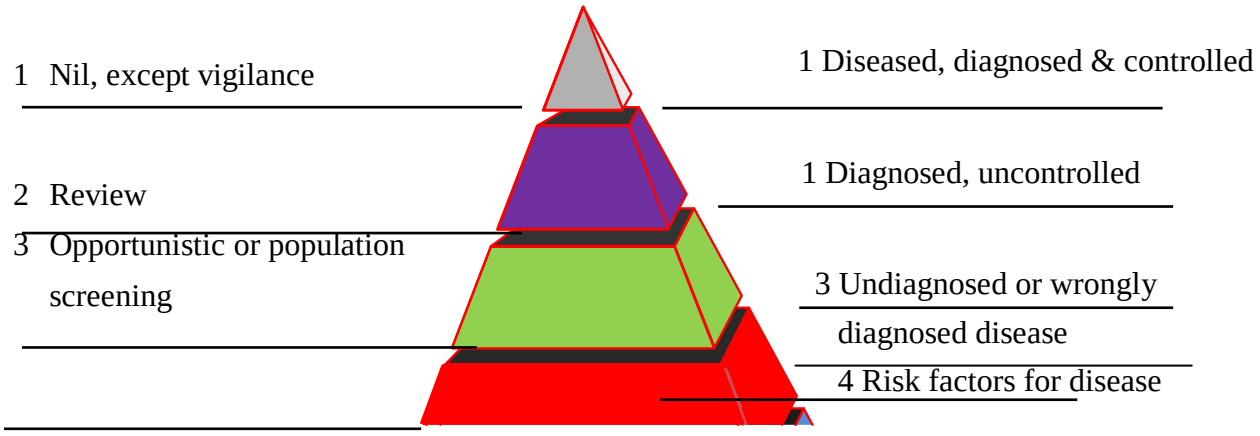


Figure 2: Iceberg Theory of Disease

Source: Raj, 2016.

2.7 Conceptual Framework

In the conceptual framework depicted in Figure 3, contact screening is hypothesized to influence TB control in children who have been exposed to a known case of TB. Contact screening is described as either contact investigation or contact invitation and TB control as a reduction in the morbidity, mortality, incidence and prevalence of TB. The framework postulates that the type of contact screening directly affects TB control; however, this relationship is influenced by index, housing and contact characteristics.

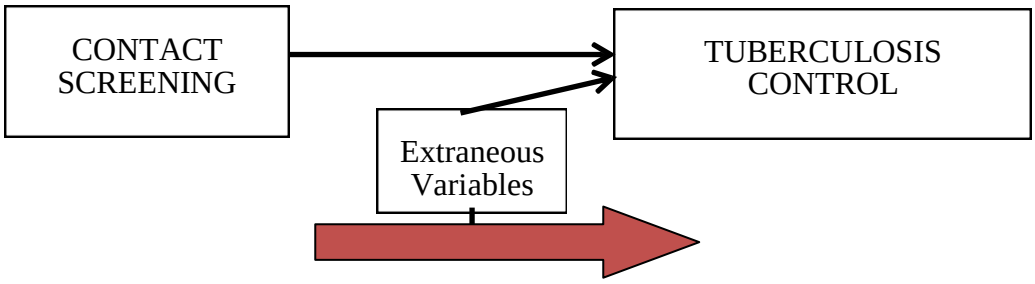


Figure 3: Conceptual framework: Relationship between contact screening & TB control Source: Bruce, Pope and Stanistreet, 2008.

CHAPTER THREE

METHODOLOGY

3.1 Introduction

This section begins with an introduction to the study, and then summarizes study approaches that were used to address each objective. It then illustrates in detail what methodology was used to answer each study objective. It ends by summarizing the data management processes and ethical considerations for this study.

3.2 A multi-methods study design

Multi methods study design was employed to address the broad research question, " What is the value of prospective household TB Contact Investigation in control of drug-susceptible TB among children aged 0-5 years who have been in household contact with a TB index case in Kisumu County, Western Kenya, 2014-2015, a period prior to the inception of standardized contact investigation?" Prior to 2017, the TB program in Kenya had only been conducting contact invitation, and not contact investigation. This provided a suitable period to assess the value of standardized contact investigation (Garg, 2016). This method, which offers the distinct advantage of quick, close coordination and comparison of different methods and their findings (Brewer & Hunter, 1989) was employed as follows

Specific objective 1: To determine the prevalence of TB infection and individual, index and housing risk factors for TB infection among child contacts following household exposure, a cross-sectional survey was conducted among all child contacts of TB index cases at facilities randomized to a TB contact investigation strategy within a larger TB case detection study. This design was selected for its powerful means of investigating associations as it is designed to collect information exactly as specified (Bruce et al., 2008).

Specific objective 2: To determine the IPT uptake and completion rate following household TB exposure after a TB diagnosis has been ruled out, a cross sectional survey was done among all IPT-eligible child contacts drawn from the TB contact investigation study based on the current Kenyan TB guidelines (DTLD, 2011b).

Specific objective 3: To compare the value of TB contact investigation to TB contact invitation in contributing to TB control, a cluster randomized trial (RCT) was conducted within 18 distinct geographical regions in Kisumu County. This RCT aimed to determine the increase in TB case detection achieved through different TB case detection strategies (Bruce et al., 2008). Cluster randomized trials provide evidence for the effectiveness of TB CDR in comparison to passive case finding (Fox et al., 2013). They should therefore be used to provide evidence to support decision making (Ayles et al., 2013).

Specific objective 4: To documents lessons learnt when transitioning to standardized contact investigation in a setting with routine contact invitation, an integrated convergent mixed methods study design was employed (Guetterman, Fetters, & Creswell, 2015). This uses both qualitative data and quantitative data to answer one research question in order to increase confidence in the research findings through the confirmation of a proposition using two or more independent measures (Heale & Forbes, 2013).

3.3 Study setting

The study was conducted at 4 of the 7 subdivisions (which now approximate the new sub-counties) of Kisumu county (Kenya Law, 2010). (3 urban and 1 rural) and within 85 of its 204 health facilities that include 146 level II, 46 level III, 21 level IV and 1 level V health facilities. The rural region was Kombewa and urban regions were Kisumu East, West and Central. The regions were selected based on having 6 contiguous locations that contained approximately

25,000 persons based on the 2009 Census. The urban regions contained 12 units while the rural unit contained 6 units (County Government of Kisumu, 2013; Ministry of Health, 2017).Kisumu County located in Western Kenya, is a high TB burden, densely-populated region; it has a population of 1,097,307 of whom 17.4% are aged less than 5 years. It population‟s density 464.5 per square kilometer (County Government of Kisumu, 2013). In 2016, the TB CDR was 228 against a national average of 170 per 100,000 populations (NTLP, 2017a). Figure 4 shows health facility distribution in Kisumu sub-counties with different counties represented using different colors.

The study was conducted within TB clinic run by the Division of Leprosy, Tuberculosis and Lung disease in Kenya. The county has 80 TB diagnostic sites, 109 treatment sites for drug-susceptible TB, and 75 treatment sites for drug-resistant TB. Records maintained in the TB clinics relate to, patient management, laboratory testing, drug supplies and grouped data. Patient management records include the TB patient record card, the TB patient appointment card, the TB treatment facility register, the TB treatment district registers, the TB patient pack control card, referral to TB clinic form, referral to other care providers form, patient defaulter tracing chart and transfer forms. Records relating to laboratory management include, request forms for sputum smear examination and culture and sensitivity, and the laboratory AFB register. Records relating to grouped data include, facility supervision tools, patient interview schedules, quarterly case

finding report forms, cohort report forms and quarterly AFB report forms (DTLD, 2013b).

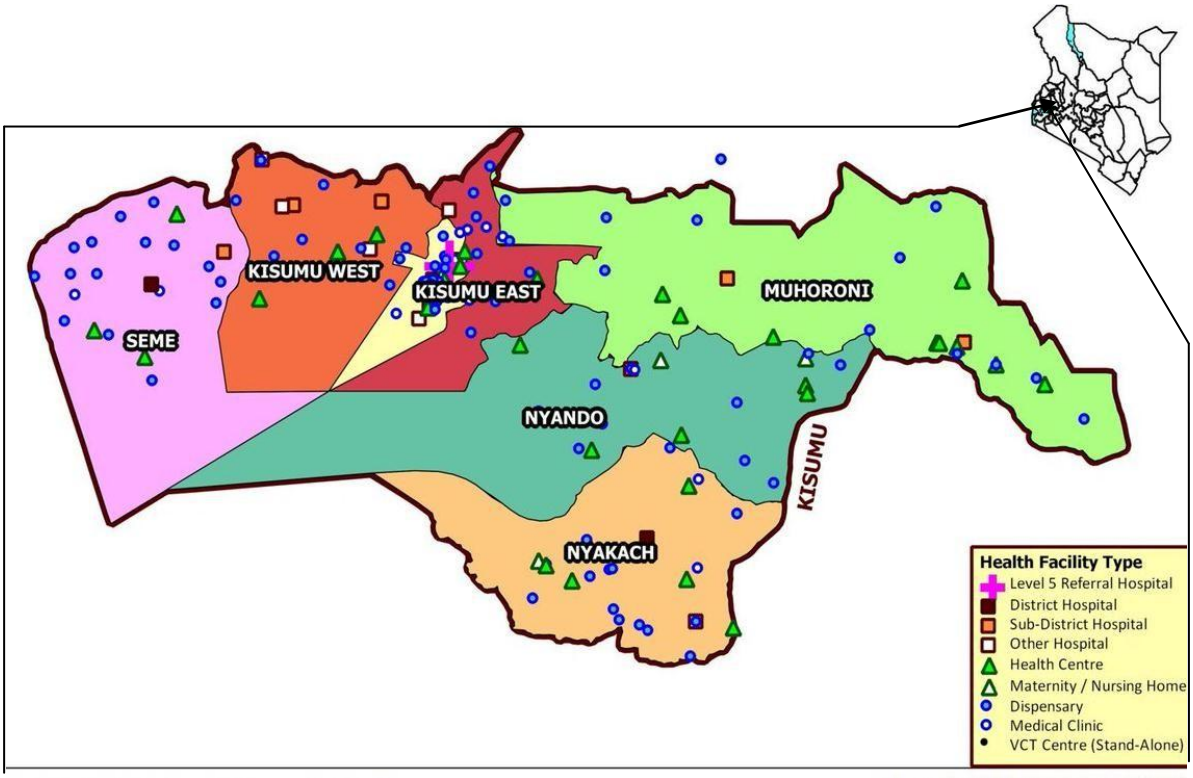


Figure 4: Kisumu sub-counties showing facility distribution

Source: Ministry of Health, 2017.

3.4 The prevalence and risk factors for TB infection

3.4.1 Study design

A cross-sectional study design was employed to describe the prevalence and risk factors for TB infection among child household contacts (aged <5 years) of TB index cases within health facilities in Kisumu County (Appendix 1: IRB approval for KEMRI SSC # 2408; Appendix 2: Memorandum of Understating with participating health facilities). This design was selected for its powerful means of investigating associations between exposures and outcomes at the same time. It is designed to collect information exactly as specified (Bruce et al., 2008).

3.4.2 Study population

The target population consisted of all children aged less than 5 years who had been in household contact with a TB index case living in Kisumu County, a high TB burden population-dense area (NTLP, 2017a).

3.5 Inclusion and Exclusion criteria

3.5.1 Inclusion criteria

A potential subject was recruited into the study if he or she met all of the following inclusion criteria:

- Be a household member of a TB index case diagnosed with TB at a participating health facility. Household members were also more likely to have spent a longer duration (a period that increases the risk of infection) in contact with the TB index case than non- household members (Coetzee, Hilderbrand, Goemaere, Matthys, & Boelaert, 2004).
- Be aged less than 5 years; children in this age group are at an increased risk of TB infection and progression of infection once infected (DTLD, 2011b).
- Have lived with the index case for at least three months preceding the TB diagnosis date which aligns to the period of infectivity (Erkens et al., 2010).
- Meet the criteria for household contacts of index cases of TB in the selected health facilities i.e. had spent at least 7 consecutive nights in the same household as the index case during the three months preceding the TB diagnosis date (Guwatudde et al., 2003).

3.5.2 Exclusion criteria

A potential subject that met one or more of the exclusion criteria was ineligible to participate in the study:

- was domiciled or lived outside the study district
- was diagnosed with TB at the time of interview
- had parents or guardians who were unwilling to consent to study participation (Appendix 3: Informed Consent document & Appendix 4: Consent Cover Sheet)

3.6 Sample population and sampling technique

The sample population consisted of 157 child household contacts of at 243 TB index cases from Kisumu County. This number was proportionally allocated to rural and urban areas in the ratio 2:1. The minimum sampled size (N) required was determined using the formula developed by Fisher et al 1998 (Pourhoseingholi, Vahedi, & Rahimzadeh, 2013).

Where, Z = Critical value for 95% confidence level / interval = 1.96

P = Prevalence of TB among children aged 0-5 years. In the absence of data on prevalence of TB with the same age group in Kenya, data from a survey in Malawi for children aged 0-4 years was employed. Malawi compares to Kenya in terms of sensitization to environmental mycobacterium(Katoch, 2004); and a high BCG coverage (Ministry of Public Health and

Sanitation, n.d.). Between 2012 and 2014, the prevalence of TB infection among household contacts of TB cases aged 0-4 years in Malawi ranged from 0.7% to 11.5% (Khan et al., 2017). The higher prevalence, the higher the sample size (Martínez-Mesa, González-Chica, Bastos, Bonamigo, & Duquia, 2014). A prevalence of 11.5% was selected to achieve the largest sample size and higher power (Bruce et al., 2008).

Q =1-P=0.885

d = the margin of error = 0.05. n= $(1.96^2*0.115*0.885)/0.05^2$

n=156.4

Therefore the minimum sample size, N required for this study = 157

Assuming an attrition rate of 5%, the minimum sample size of children would be 165. It was anticipated that each household would have approximately 4.2 household members including the index case and 17% of them would be aged <5 years i.e. approximately 68 children in 100 households (KNBS, 2015). The study therefore aimed to recruit 157 child household contacts of at least 243 TB index cases from Kisumu County.

The study employed a convenience sampling technique that collects information based on the availability and willingness of participants. This method is useful as participants were recruited from participating clinics prospectively and there were constraints on time and costs of conducting the study (Speak, Escobedo, Russo, & Zerbe, 2018).

3.7 Procedures for identification and screening of household contacts aged less <5 years

3.7.1 Procedures for identification of household contacts

When a TB case was diagnosed at a participating health facility, project personnel were notified. The TB case was interviewed and if he or she consented to participate, he or she was enrolled into the study. TB index cases were interviewed by project personnel within 7 days of diagnosis, to identify household contacts and to collect clinical, exposure, and risk factor information. Details regarding the index case and all contacts listed were entered in the study database. Household members identified by the TB patient were then asked to report to the clinic for TB screening within 7 days. A follow-up visits to the household were made within 14-30 of TB diagnosis to identify and invite household contacts that did not present to the clinic or were not named by the TB patient for screening.

3.8 Screening procedures for household contacts aged less than 5 years at health facilities

All household members of enrolled TB patients were interviewed to collect symptom, exposure, and risk variable information. Additional data was abstracted from laboratory and medical records of household contacts of TB index cases following screening procedures as follows. All child household contacts were then subjected to a TB symptom screen, after which they underwent tuberculin skin test (TST) screening using standard procedures. All TSTs were placed using the Mantoux method with 5 TU PPD, (5 Tine Units of Purified Protein Derivative) and assessed 72 hours after placement. TST indurations were measured by two independent readers who were trained nurses and experienced in TST readings. In the event of non-agreement, a third reader (the study clinician) assessed the in duration. As per the existing TB guidelines, chest radiograph examination was done for all contacts that either screened positive for TB symptoms or had a positive TST results. Child household contacts with unknown HIV status were tested

for HIV (DTLD, 2011b). (Appendix 5 and Appendix 6 illustrate the Participant appointment schedules and Participant Activity checklists).

3.9 Clinical management of household contacts

All new cases of active TB detected, all HIV+ contacts and all household contacts children <5 years of age in whom TB had been excluded (who were IPT eligible as per the existing TB treatment guidelines), were referred to the local TB control program for further evaluation and consideration for treatment. Decisions on treatment, treatment regimen, and clinical management during treatment were carried out by the TB program according to national policies and guidelines, and were not a part of this project. For this reason, the documentation of IPT initiation and completion were also not within the confines of this study.

3.10 Data Collection

3.10.1 Data collection tools

Data was collected from participants using interviewer-administered electronic data collection tools. Data was also collected from medical record review and household visits. All data were then uploaded to a central institutional server.

3.10.2 Index information

The main data elements collected during TB index case interview were demographic information of the index, birthplace, when TB was diagnosed, the presence or absence of TB symptoms, TB symptom duration, occupational information and history of incarceration, alcohol and tobacco use, use of recreational drugs, prior HIV testing and ART drug history.

The main data elements collected from medical records were the type of TB, details regarding TB treatment, and results of any prior testing for HIV. The main data elements collected from diagnostic testing records were results sputum smear, chest radiography, and HIV test results.

The main data elements collected during the follow-up household visit (to invite contacts that had not presented to the health facility for screening and identify additional contacts) were the number of inhabitants, number of smokers in the house, the building style, and the total number of rooms, the total number of bedrooms, ventilation and heating characteristics (Appendix 7: Data collection tools).

3.10.3 Index information

The main data elements collected during TB index case interview were demographic information of the index, birthplace, when TB was diagnosed, the presence or absence of TB symptoms, TB symptom duration, occupational information and history of incarceration, alcohol and tobacco use, use of recreational drugs, prior HIV testing and ART drug history.

The main data elements collected from medical records were the type of TB, details regarding TB treatment, and results of any prior testing for HIV. The main data elements collected from diagnostic testing records were results sputum smear, chest radiography, and HIV test results.

The main data elements collected during the follow-up household visit (to invite contacts that had not presented to the health facility for screening and identify additional contacts) were the number of inhabitants, number of smokers in the house, the building style, and the total number of rooms, the total number of bedrooms, ventilation and heating characteristics (Appendix 7: Data collection tools).

3.10.4 Database description

A relational database was used during the study. Each TB index case had eight data tables namely: Patient eligibility, Patient information, Patient interview, TB index HIV test results, and TB index Lab results, TB index Chest X-ray results, Household contact identification and

Household visit. Each contact had eight data tables; these were Contact tracing, Contact eligibility, Contact interview, Contact TST, Contact lab results, Contact HIV test results, Contact Chest X-ray results, Contact follow-up interview.

A TB index case was identified by a unique number linked to the screening center. E.g. "KI", for Kisumu County followed by a four digit code (index identifier), a hyphen, and another two digit code (contact identifier). For instance, "KI-0001-0" would be the first index case recruited in Kisumu County. All household contacts would subsequently be identified with a suffix added to the index identification number e.g. for index case "KI-0001-0", contacts would be listed as "KI-0001-1", "KI-001-2", ""KI-0001-3"…… "KI-0001-n"

3.11 Data analysis

3.11.1 Descriptive statistics

A descriptive analysis was used to summarize socio demographic characteristics of TB index cases and their contacts (Bruce et al., 2008).

3.12 Assessment for the presence of TB infection in the child contact of the TB index case

The guidelines for Tuberculosis prevalence surveys were used to identify the trough between the two modes on a graph that plotted the number (or percent) of individuals with TST measurement on the y axis and the TST readings in millimeters in the X-axis. The anti-mode was the point that distinguished individuals with reactions due to either non-tuberculous mycobacteria or previous vaccination with BCG (anterior mode) from those with actual TB infection (posterior mode). Individuals to the right of this anti-mode were described as TST positive (Rieder et al., 2011).

Terminal digit preference

To assess for terminal digit preference for TST readings, Chi square statistics for goodness of fit were used (Broeck & Brestoff, 2013). In the presence of terminal digit preference, 5-point moving averages were used to smooth the graph and reassess the TST cut (Rieder et al., 2011).

Measurements of parameters of interest The outcome variable' (Dependent variable)

The presence of a positive TST in a person who is a recent contact of a TB Index case is considered evidence of recent infection (United States Department of Health and Human Services, 2013).

Therefore, if a child household contact of a TB index case had a positive TST, this was evidence of the ***presence of TB infection***. Similarly, if a child household contact of a TB index case had a negative TST, this was evidence of the absence ***of TB infection.*** The prevalence of TB infection was the proportion of contacts with positive TST.

The independent variables (Risk factors for TB infection)

Individual :To assess the predictors of TB infection in child household contacts of TB index cases, the dependent variable was TB infection and the independent variables were socio-demographic characteristics and exposure (age, sex, rural or urban residence, relationship to index case, duration of contact with index case in days and hours, whether contact had shared a bedroom with the index case) and clinical characteristics (BCG vaccination status, HIV status, the presence or absence of symptoms).

Household: To assess the predictors of TB infection in child contacts of TB index cases, the dependent variable was TB infection in at least one child contact. The independent variables

were socio-demographic characteristics (age, gender, urban or rural residence, whether the index case smoked, number of child contacts), clinical characteristics (presence or absence of cough, TB type, chest X-ray findings, sputum smear grade, HIV status) and characteristics of their living quarters (house floor size, number of rooms, number of bedrooms, number of household members who lived in the house during the infectious period and among them how many smoked, where cooking was done, whether kitchen was separate from other rooms, whether windows were kept open during the infectious period, whether cross-ventilation was present).

To limit the chances of collinearity, one variable was selected from highly correlated variables at the same level while the others were excluded e.g. daily duration of contact and daily number of contact hours for the contact, and household size, number of rooms, and number of bedrooms, and the presence of cough and TB type for the index case (Bruce et al., 2008).

Missing case analysis

The dataset was trimmed so as to exclude persons that had incomplete information on TST readings and household characteristics from 345 to 257. Little‟s test confirmed that the variables with data were missing completely at random and therefore a complete case analysis was used (Roderick, 1988).

Conventional Single level Logistic regression analysis

Although the data collected for this study were defined at two levels i.e. one level for the household (i.e. index case) and the other for the child contacts (Yang, Zhao, Li, Krewski, & Wen, 2009). For this analysis, group level measures were assigned to individual members of groups and used as if they were individual measures (Nezlek, 2008).

A binary logistic regression, a suitable method when the dependent variable is dichotomous, was conducted to assess if the independent variables predicted the dependent variables. This type of analysis can be used when the independent variables (predictors) are continuous, discrete, or a combination of the two. This analysis permits the evaluation of the odds of membership in one of the two outcome groups based on the combination of predictor variable values. The assumptions of binary logistic regression is that the outcome must be dichotomous, there should be no multicollineartiy among independent variables, there should Using backward elimination, a final model was developed by retaining variables that have a $p< 0.05$ be no outliers and there should be a linear relationship between the odds ratio and the independent variables (Statistics, 2016a).

Univariate logistic regression was conducted to describe the relationship between individual variables and TB infection. Variables that achieved a p value of <0.25 in the single level univariate model were selected for inclusion in the multivariate model. The value 0.25 was purposefully used to select variables to include in the multivariate analysis. Purposeful selection methods are useful in risk factor modeling and not mere prediction. The help retain important confounding variables in addition to significant covariates resulting in a possibly richer model. Using backward elimination variables that had a p value of less than 0.1 were retained for inclusion in the multivariate model (Bursac, Gauss, Williams, & Hosmer, 2008). Univariate logistic regression was conducted to describe the relationship between individual variables and TB infection. Variables that achieved a p value of <0.25 in the single level univariate model were selected for inclusion in the multivariate model. The value 0.25 was purposefully used to select variables to include in the multivariate analysis. Purposeful selection methods are useful in risk

factor modeling and not mere prediction. The help retain important confounding variables in addition to significant covariates resulting in a possibly richer model. Using backward elimination variables that had a p value of less than 0.1 were retained for inclusion in the multivariate model (Bruce et al., 2008).

The reference group selected for each variable was that which was known to have a smaller probability on the outcome (Sperandei, 2014). For contact characteristics, older children, who were non-first degree relatives of the index case who had spent a shorter daily duration of contact with the index case (<8 hours) and had not shared a bedroom with the index case, had received BCG vaccination, screened negative for TB symptoms and were HIV negative were less likely to have TB infection and were therefore selected as reference groups. Similarly, older and younger adults (> 45 years or < 15 years respectively), who lived in rural areas, did not present with cough, had smear negative TB, were HIV positive, lived in a house with floor space of ≥25 square meters with cross ventilation, with less than 5 household members, who also did not smoke were less likely to have child contacts with TB infection and were therefore selected as the reference groups. Cross ventilation was described the ability of air to move across the room through doors, windows, etc. The cut off points used to group continuous variables into categorical variables were based on the literature (Yang et al., 2009).e.g. children aged less than 2 years (toddlers) being at a higher risk of TB infection, a minimum daily duration of contact of up to 8 hours predisposing a contact to risk of infection used to categorize daily duration of contact (Erkens et al., 2010). Age of the TB index was based on a definition of a child as < 15 years by the TB program after which 15-years age bands were used (WHO, 2013a). The number of household members was based on the average household size in Kenya of 4.2 (KNBS, 2015).

Multilevel logistic regression model

To accommodate for the hierarchical nature of the data in this study, a two-level random intercept multilevel model was used. Contacts within the same household are more similar to each other than to contacts from other households. For this reason, standard statistical analyses, like Conventional single level logistic regression models that do not take into account the fact that data of level one units (contacts) within the same level two units (household) are not independent, were not appropriate (Yang et al., 2009). Single level logistic regression also violate independence assumption (Nezlek, 2008).

A hierarchical multilevel logistic regression model, with clustering at the household level, was therefore used to quantify variation due to household characteristics (Ene, Leighton, Blue, & Bell, 2014). This method allows for baseline variation in TB infection rates across households, while assuming that the effect of each variable in the model is the same within each household (Yang et al., 2009). This model draws its strength from the fact that the 1st level parameters of fundamental interest (i.e. Relative risks conferred by individual characteristics) may share important characteristics (Capanu et al., 2008). HLM analyzes nested sources of variability taking into account variability associated with each level. Individual level characteristics are important because the outcome is important only when adjusted for individual outcomes. At household level, risks due to index characteristics are analyzed and differences between household compared. They also produce „shrunken" estimates that move higher unit levels estimates towards the population mean and increase accuracy of prediction (Dai, Li, & Rocke, 2006).

Individual level independent variables representing potential risk factors for TB infection used in this study were child contact demographic and clinical factors and sleeping arrangements. The household was chosen as cluster unit for index level variables with a single value calculated or

determined for each household. Thus all child contacts living in one household had the same value for each index risk factor. Household level (Index) factors considered in this study were demographic, clinical and house characteristics of the TB index case. These variables were selected from among other variables based on the fact that they were significant ($p<0.05$) in the univariate model (Yang et al., 2009).

Model building

The model building process was done as follows; firstly for random effects alone without predictors (Model 1), secondly for random effects and for level one predictors (Model 2), and lastly for model 2 plus level 2 predictors (Model 3) (Ene et al., 2014). Firstly, a null model that included no individual or index level risk factors was built to serve as a baseline for comparison with other models, and to estimate the intra-class correlation coefficient (ICC). The ICC, a measure of the proportion of variance explained by the presence of clusters (households) in the data between households, describes the similarity between contacts within the same household. The correlations coefficients estimated from the null model were used to compute the expected TB infection rate for a household (Bell, One, Smiley, & Schoeneberger, 2013).MLM must meet the following assumptions; linearity, homogeneity of variance and normal distribution of residuals (Statistics, 2016b). A series of univariate analyses were conducted to assess the association between each of the individual, index and housing factors and TB infection. Variables that were significant ($p<0.05$) in the univariate model were contact variables i.e. number of hours of daily contact with the index case, and index variables i.e. the of age of index, the presence of cough, and house size i.e. floor space in square meters size. The binary outcome for the study was TB infection in the contact (Austin & Merlo, 2017). All variables that were significant ($p<0.05$) in the univariate model were included as covariates in the full model, and a

backward stepwise regression method ($p<0.05$ for entry and $p>0.1$ for removal) was used to identify the significant independent variables from the initial multilevel models. Finally, results of conventional logistic regression models, with the same dependent and independent variables used in the multilevel models were compared to results from the from multi-level models (Yang et al., 2009). Analysis was done using SAS 9.2 (SAS Institute Inc, 2012).

3.13 IPT uptake and completion rate following household exposure

3.13.1 Study design

A retrospective cross-sectional survey of all IPT-eligible children, based on the TB Control guidelines in Kenya, was done in Kisumu County, Kenya between 2014 and 2015 (Appendix 1: IRB approval for KEMRI SSC # 2408). This design was selected for its powerful means of investigating associations between exposure and outcomes at the same time. It is designed to collect information exactly as specified (Bruce, 2008).

3.13.2 Study population

As per the Kenyan TB guidelines, all children aged < 5 years who have been in household contact with a TB index case are eligible to receive IPT for TB prevention for a period of 6 months after the exclusion of a TB diagnosis. During the period of IPT administration, persons on IPT should be routinely screened for TB symptoms in the event there is a need to stop IPT and commence TB treatment. Additionally, they should be reviewed for adverse events at each visit (DTLD, 2011b). Isoniazid which is bactericidal is given to this population who are at an increased risk of progression latent TB into active TB once they have TB infection (Herchline & Amorosa, 2017). This is also a population in whom the Number Needed to Treat (NNT) to prevent one case of TB is the most effective (Anger et al., 2012). The study population was therefore all children aged less than 5 years of age drawn from the TB household contact

investigation study, who had definitely been in household contact with a TB index case prior to screening, and in whom a TB diagnosis had been reliably excluded.

3.13.3 Sample size and sampling technique

The study sample consisted of 271 child household contacts drawn from the TB contact investigation study that had screened negative from TB. This number was proportionally distributed according to rural and urban areas i.e. in the ratio 2:1. The sample size calculation formula for cross sectional studies was used to determine sample size(Pourhoseingholi et al., 2013).

$N= (Z^2 P (1-P))/d^2$

Where Z is the 95% CI given as 1.96

P is the prevalence of IPT uptake; the prevalence of IPT uptake ranges from 15% to 68% (Tadesse et al., 2016). As IPT uptake in Kenya is unknown, a prevalence of 50% was employed.

d=margin of error which is taken as 5% $N= (1.96^2 X ((0.5 (1-0.5))) /0.05^2$

=384

Since it may not be possible to find all the 384 children, it is possible to lower the requirements of confidence from 95% to 90% and of precision from 5% to 10% in a prevalence study. A conservative choice of the accuracy could be one quarter (12.5%) or one fifth (10%) of the prevalence (Lwanga & Lemeshow, 1991; Pourhoseingholi et al., 2013) (Table 1). To determine IPT uptake to within 10% of the true prevalence with 90% confidence, the new sample size computed was therefore

$N= (1.645^2 X ((0.5 (1-0.5)))/0.05^2$

N=271

Table 1: Sample size with different precision and confidence intervals

Precision	Confidence interval (Z statistic)		
	99% (1.645)	**95% (1.96)**	**90% (2.576)**
0.01	6765	9604	16589
0.05	271	384	663
0.10	68	96	165

Adapted from: Pourhoseingholi et al 2013

The study employed a convenience sampling technique that collects information based on the availability and willingness of participants. This method is useful as participants were recruited from participating clinics prospectively and there were constraints on time and costs of conducting the study (Speak et al., 2018).

3.14 Procedures

3.14.1 Preparation of study databases

Demographic and clinical information of children aged less than 5 years from the TB contact investigation study who were not diagnosed with TB, were abstracted from the study‟s electronic databases. As contacts unique identifiers were linked to the index case, information regarding the TB index case to whom the IPT-eligible child was linked, was also abstracted (Database 1).(Appendix 7: Data Collection Tools).

3.14.2 Preparation of TB program databases

As the clinical management of participants (i.e. TB treatment and IPT initiation) was not part of the study, IPT registers from the TB program were reviewed to find out whether study participants had received on IPT. Clinical and demographic details including identification details, dates of IPT initiation, whether or not the participant completed IPT, and dates of IPT completion, of all persons who had been initiated on IPT in Kisumu County in 2014 and 2015 were obtained from the TB program IPT register (Appendix 8: Kenya TB program IPT registers) (Database 2). Reasons for non-initiation and non-completion of IPT had not been documented in the TB program registers.

3.14.3 Manual linkage of participant and programmatic databases

The two databases were linked using participant identification details, ages, dates of recruitment, dates of IPT eligibility and dates of IPT initiation to form a new database (Database 3). Because the index case and his or her household contact were not obliged to attend the same clinic for TB treatment and IPT respectively, the clinic names were not always used in the linking process.

3.15 Data analysis

3.15.1 Measurement of parameters of interest and assignment of IPT initiation and completion status to contacts and TB index cases

A child contacts‟ IPT status was described as ***'IPT initiated'*** if his or her name was documented in the IPT register and ***'IPT not initiated'*** if the corresponding information was not found in the IPT register. Similarly a TB index case was described as having a ***'child contact initiated on***

IPT' if the name of his or her child contact was found in the IPT register and ***'child contact not initiated on IPT'*** if the corresponding information was not found in the IPT register.

Among contacts who initiated IPT, a child contact‟s IPT completion status was described as ***'IPT completed'*** if a completion status and date of completion were entered in the IPT register and ***'IPT not completed'*** if the corresponding information was missing from the IPT register. Among TB index cases whose child contacts initiated on IPT, a TB index cases was described as having a ***'child contact completing IPT'*** if his or her child contact completed IPT and a ***'child contact not completing IPT'*** his or her child contacts did not complete IPT.

For TB index cases with more than one child contact, the assignment of IPT initiation and completion status as ***'child contact initiated on IPT'*** and ***'child contact completing IPT'*** would be based on at least one (of two or more child contacts) having either initiated or completed IPT respectively. However, the assignment of IPT initiation and completion status as „child ***contact not initiated on IPT'*** and ***'child contact not completing IPT' would*** be based on all child contacts not having initiated or completed IPT respectively.

IPT uptake was defined as the proportion of IPT-eligible contacts who initiated IPT. Whereas, among those with IPT initiated, IPT completion was defined as the proportion of IPT-initiated contacts that completed IPT.

3.15.2 The dependent and independent variables

To assess the predictors of having a child contact initiated on IPT among TB index cases, the dependent variable was „***IPT initiation in child contact'*** and the independent variables were demographic and social characteristics (age, gender, urban or rural residence, number of child

contacts), clinical characteristics (presence or absence of cough, TB type, chest X ray findings, sputum smear grade, HIV status). To assess the predictors of having a child contact completing IPT among index cases with child contacts that initiated IPT, the dependent variable was ***'IPT completion in child contact'*** and the independent variables were similar to those used to predict IPT imitation in the child contact

To assess the predictors IPT initiation among IPT-eligible child contacts, the dependent variable was „***IPT initiation'*** and the independent variables were demographic and exposure characteristics (age, sex, rural or urban residence, relationship to index case, duration of contact with index case in days and hours, whether he or she shared a bedroom with the index case) and clinical characteristics (BCG vaccination status, HIV status, the presence or absence of symptoms, prior history of TB or having received IPT). To assess the predictors IPT completion among child contacts who initiated IPT, the dependent variable was „***IPT completion'*** and the independent variables were similar to those used to predict IPT initiation.

3.15.3 Categorization of variables and Rationale for selection of reference groups

The reference group selected for each variable was that which was known to have a smaller probability on the outcome (Sperandei, 2014). The cut off points used to group continuous variables into categorical variables were based on the literature (Yang et al., 2009).

3.15.4 Categorization of variables for child contacts

Children aged less than 2 years (toddlers) being at a higher risk of TB infection (Erkens et al., 2010). The oldest age group was therefore taken as the reference group. In the literature, when the TB index case is a parent, IPT initiation rates have been shown to be higher. Therefore, non-

relative was used as the reference category for the variable „relationship to index case‟ (Birungi, Graham, Uwimana, & van Wyk, 2018). Child contacts who had a shorter duration of contact with the TB index case in terms of, daily duration of contact, length of time lived with the index, and whether or not they had shared a bedroom with the TB index case were less likely to be infected with TB and were therefore taken as the reference group (Americal Thoracic Society [ATS], 2000).

Since IPT is recommended for HIV positive persons, it is expected that child contacts who are also HIV positive will have higher IPT initiation rates; therefore HIV negative child contacts were used as the reference category (Jasmer, Nahid, & Hopewell, 2002). As symptomatic persons are supposed to be screened further for TB, it is expected that they would have less IPT initiation rates; symptomatic contacts were therefore selected as the reference group (DTLD, 2011b). Children who have received BCG are less likely to be infected and were therefore taken as the reference group (M. Singh et al., 2005). As prior TB diagnosis and use of IPT is not a contraindication to the use of IPT, there was no preference for selection of reference group (WHO, 2011).

3.15.5 Categorization of variables for TB index cases

The age and sex of TB index cases does not influence their infectiousness and therefore there was no preference for any age category or gender (Melsew et al., 2018). Age of was selected using the WHO definition of children as < 15 years as after which 15 years age bands were used(WHO, 2013a). Because rural populations are less likely to be employed than urban populations, they have less access to financial resources which would affect their health seeking behavior. For this reason, the rural regions were used as a reference group (van der Hoeven,

Kruger, & Greeff, 2012). The number of child contacts was used as a proxy for overcrowding (Espinal et al., 2000). Crowding increase the likelihood of contact as well as the intimacy of contact between source cases of TB and susceptible persons (Lienhardt, 2001). A lower number of child contacts were therefore used as reference group. Among TB index cases, the reference groups were taken as those in which the index was known to be less infectious and therefore less likely to transmit TB to their child contact and should therefore have a lower IPT initiation among their child contacts (ATS, 2000). TB index cases that did not cough, had smear negative, extra pulmonary TB, with normal chest x-ray findings and were HIV positive were taken as the reference group.

3.15.6 Logistic regression analyses

A descriptive analysis was used to summarize socio demographic characteristics of TB index cases and their contacts. Logistic regression analysis was used to assess index characteristics associated with IPT initiation and completion among child contacts. Logistic regression analysis was also used to assess contact characteristics associated with IPT initiation and completion (Bruce et al., 2008). The assumptions of binary logistic regression is that the outcome must be dichotomous, there should be no multicollineartiy among independent variables, there should be no outliers, and there should be a linear relationship between the odds ratio and the independent variables (Statistics, 2016a). Univariate logistic regression was conducted to describe the relationship between independent and dependent variables. Variables that achieved a p value of <0.25 in the single level univariate model were selected for inclusion in the multivariate model. The value 0.25 was purposefully used to select variables to include in the multivariate analysis. Purposeful selection methods are useful in risk factor modeling and not mere prediction. The help retain important confounding variables in addition to significant covariates resulting in a

possibly richer model. Using backward elimination, variables that had a p value of less than 0.1 were retained for inclusion in the multivariate model (Bursac et al., 2008). Using backward elimination, a final model was developed by retaining variables that have a $p< 0.05$ (Bruce et al., 2008). Analysis was done using SAS 9.2 (SAS Institute Inc, 2012).

3.16 Value of contact investigation in comparison to contact invitation in TB control

3.16.1 Study design

The larger TB case detection study, was a cluster randomized trial in which the TB contact investigation study was nested. This cluster randomized trial was conducted within 18 distinct geographical regions (clusters) in Kisumu County to determine the increase in TB case detection (for both drug-resistant and drug-susceptible TB) achieved through 3 different TB case detection strategies. In this study, a cluster was defined as contiguous geographic unit with a population of approximately 25,000 persons based on the Kenyan 2009 census (KNBS, 2010). The TB case detection study‟s sites were selected based on being in a country with a national TB incidence rate > 50/100,000 population, an in-country CDC office affiliated with existing TB activities which could easily be expanded to include contact investigation, a strong track record for successful collaboration with CDC, and either high HIV prevalence or high MDR-TB rates or both. (Appendix 9: IRB approval for KEMRI SSC # 2494).

Cluster randomized trials provide evidence for the effectiveness of TB case detection in comparison to passive case finding (Fox et al., 2013). They should therefore be used to provide evidence to support decision making (Schulz, Altman, Moher, & Group, 2011).

3.16.2 Study population

Health facilities within a particular location were assigned to the cluster to which the location found. The study population was comprised of all children diagnosed with TB or who received IPT within the specified health facilities randomized to a specific strategy.

To address this objective, the study population was comprised of all children aged less than 5 years who were diagnosed with TB and who received IPT at health facilities randomized to the TB contact investigation strategy and the standard approach (a.k.a. the contact invitation strategy) in the two years preceding the study period i.e. 2012 and 2013 (the pre-intervention period) and in during the two years that were designated the „study period" (or intervention period i.e. 2014-2015).

The study population was chosen as it represents what would constitute TB control i.e. the number of TB cases diagnosed as a proxy for a decrease in morbidity and mortality from TB, and the number of children who received IPT as a proxy for the number of TB cases of TB prevented and therefore a decrease in TB incidence and prevalence (Dowdle, 1998). The health facilities randomized to a specific control strategy would provide both a suitable intervention arm (e.g. the contact investigation strategy) and a suitable control arm the standard approach) because randomization balances both the known and unknown confounding factors that would influence the outcome (Bruce et al., 2008).

All persons residing within the region randomized to a particular TB case detection strategy, or presenting to a health facility within the region were eligible for inclusion in the strategy to which that unit was randomized to. This is because patients can present to a variety of health facilities for TB diagnoses within a larger area. As large areas were randomized to either receive,

or not receive an intervention, the impact of patients who went outside this area for TB diagnoses and treatment would be limited (Ayles et al., 2013). Before and after comparisons enabled the study to assess the presence of external changes that may have occurred in both the intervention and control arms during that may have contributed to changes in the outcome e.g. the introduction of new policies or practices in the TB program (Younge, Kouwenhoven-Pasmooij, Freak-Poli, Roos-Hesselink, & Hunink, 2015).

3.16.3 Sample size and sampling procedure

The sample population consisted of at least 15 children aged less than 5 years diagnosed with TB and 15 children aged less than 5 years who received IPT within the intervention and control arms. The study population of child contacts diagnosed with TB was computed as follows: To detect a 25% increase in number of TB cases between pre and post intervention period, with one sided 5% significance and a power of 80% power if any single intervention were anticipated to achieve its target.

$$n= (p_1(1-p_1) + p_2(1-p_2)) /(p_1-p_2)^2 *. f(\acute{\alpha},\beta))$$

Where p_1 is the proportion after the intervention and p_2 is the proportion before the intervention and f ($\acute{\alpha},\beta$) is a constant value for the power and significance level which at 80% power and 95% significance level is 7.9 (Whitley & Ball, 2002).

TB Patient diagnostic rate =TB case detection rate/TB prevalence was used as the proportion before the intervention (Borgdorff, 2004). TB Patient diagnostic rate =TB case detection rate/TB prevalence was used as the proportion before the intervention (DTLD, 2013a). TB prevalence

from the TB prevalence survey in 2015 was 586 per 100,000 (NTLP, 2017b). Patient diagnostic rate (p1) was therefore 0.41 and p2 0.513.

$n = ((0.513(1-0.513)) + (0.410\ (1-0.410))/\ (0.513-0.410)^2 * 7.9\ n = (0.513* 0.487 +0.410*0.590)$

$/0.103^2 *7.9$

n=14.79 n=15

A minimum sample size of 15 TB cases in each group (the pre and post intervention groups) would therefore be required to be 80% sure of being able to detect an increase in screening rates at the 5% significance level. The number of child contacts who received IPT was based on the WHO and Kenyan TB treatment recommendation of at least one child contact aged less than 5 years initiated on IPT for every index case of TB (1:1) (WHO, 2012).

The study employed a convenience sampling technique that collects information based on the availability and willingness of participants. This method is useful as participants were recruited from participating clinics prospectively and there were constraints on time and costs of conducting the study (Speak et al., 2018). This method was also chosen due to a small target population as childhood TB represents less than 10% of all TB cases diagnosed (World Health Organization, 2013a). As IPT implementation had just commenced, there was no existing information on which to base sample estimates (Nyanza Province DTLD Coordinator, Personal Communication; 30th August 2012).

3.16.4 Randomization

Four regions (two urban and two rural) were initially selected for the larger case detection study. The rural regions were Siaya and Kombewa Health Demographic and Surveillance System Area (HDSA); the urban regions were Kisumu Town East and Kisumu Town West. Kombewa‟s

HDSA is locaed within Kisumu County while Siaya‟s HDSA is located within Siaya County. Siaya and Kombewa region is constructed within previously defined DSSs, and areas within it have been well characterized, and most residential compounds geocoded (Odhiambo et al., 2012; Sifuna et al., 2014). Urban areas were selected from the most densely populated areas of Kisumu Township and residences of persons registered for TB after deployment of study interventions were later geocoded (County Government of Kisumu, 2013). Each region was subdivided into 6 units that represented contiguous locations with approximately 25,000 persons; there were a total of 24 units. Units were stratified into rural and urban and within each stratum, units were randomized to either implement or not to implement an intervention.

3.16.5 Implementation

The randomization sequence was generated by the study statistician based on these probabilities without the knowledge of the investigators prior to study implementation. A waiver of informed consent was sought from the Kenya Medical Research Institute because participation in this study, presented only a minimal risk for participants, would not alter rights of participants who would continue to receive services as per the existing policies and guidelines, would lead to timely diagnosis of TB as interventions implemented in the study would employ the use of more sensitive tests and, and it would be impractical to conduct with study with individual informed consent as the study aimed to compare the programmatic utility of different TB case detection strategies (Appendix 9: IRB approval for KEMRI SSC # 2494).

Among the 12 urban units, 6 were randomly assigned to have the 3 enhanced health-facility conditions (H, HC, HCM). In the 6 units with enhanced health-facility conditions, 2 were randomly assigned condition H, 2 were assigned condition HC, and 2 were assigned condition HCM. Among the remaining 6 rural units, 2 were randomly assigned condition S, 2 were

assigned condition C, and 2 were assigned condition M. The same allocation procedure was used to assign interventions to the 12 rural units. However, for this analyses, Siaya was excluded due to other on-going TB control activities in the region that limited the scope of the TB case detection strategy, and leading to an imbalance of randomization of strategies for the rural units (Appendix 10: The randomization strategy & Facility assignments).

3.16.6 Intervention

The TB case detection study utilized 3 different strategies to enhance TB case detection namely;

- Household contact investigation (C): all patients diagnosed with TB were asked to elaborate a list of household members who would all undergo evaluation for TB.
- Facility-based active case finding (H): this involved the identification of all patients who screened positive for TB symptoms from all outpatient and inpatient departments and screening them for TB using sputum smear and Cepheid gene expert.

Community-based active case finding using Mobile units (M): a mobile field site was established to move around selected communities to assess patients for TB symptoms and collect sputum specimens. The unit located itself within a particular area within the community for two weeks at a time and rotated throughout the community in order to be within a 2 km radius of every person within the community.

- The standard approach (S): in this group, there was no intervention. The program continued to diagnose patients as per their usual practice which was primarily based on the Directly Observed Treatment Short Course DOTS system of passive finding of patients and confirmation of TB based sputum smear microscopy. Zones in the Standard Approach i.e. Contact invitation provided a suitable control sites to compare the TB contact investigation study to.

The strategies were combined as follows: Standard of care (S), Health facility screening (H),

Community based mobile screening units (M), Contact investigations (C), Contact investigations and Health facility screening (HC), and all three the three strategies (HCM).

3.16.7 Outcomes

The outcome was measured at cluster-level. This was the number of TB cases diagnosed and persons who received IPT at health facilities randomized to a specific TB case detection strategy as reported by the TB program in the pre- and post intervention period. The outcome of interest, was the comparison of both the number of TB cases diagnosed among children aged less than 5 years and, number of children aged less than 5 years who received IPT in (i) the pre-intervention.

3.17 Data collection

Electronic data was extracted from the Kisumu County TB program databases. The following variables were collected from each arm; the number of TB cases diagnosed and the number of children put on IPT before and after the commencement of the study. This information was

obtained from the TB program registers in the year preceding the study and during the conduct of the study (Appendix 8: IPT register & Appendix 11: TB treatment registers).

3.18 Data analysis

3.18.1 Definitions of parameters of interest

The contact investigation strategy was comprised of either a contact investigation strategy in isolation (where the health facility only conducted contact investigation),or a contact investigation strategy in combination with other TB case detection strategies (where a health facility implemented contact investigation in combination with either enhanced facility case detection strategy, or community mobile units or both). The contact invitation strategy was represented by health facilities where the standard case approach was used. Health facilities that were randomized to other TB case detection strategies that did not include contact investigation

were excluded from the analysis i.e. either mobile units or enhanced facility detection in isolation or in combination. A TB case was described as an individual aged less than 5 years entered into the TB program register between the 1st of January 2012 and 31st December 2013 for the pre-intervention year, and between 1st of January 2014 to the 31st of December 2015 for the intervention years.

A child who received IPT was described as an individual aged less than 5 years entered into the IPT register between the 1st of January 2012 and 31st December 2013 for the pre-intervention year, and between 1st of January 2014 to the 31st of December 2015 for the intervention years.

3.18.2 The dependent and independent variables

The dependent variable was TB control as measured by number of TB cases detected (as a proxy for a decrease in morbidity and mortality from TB), and the number of children who received IPT to prevent TB (as a proxy for a decrease in TB incidence and prevalence).*The independent variable* was the TB contact screening strategy which was either contact investigation or contact invitation (a.k.a. the Standard approach).

The CONSORT flow diagram was used to illustrate the progress of randomized units from randomization, intervention and analysis (Schulz et al., 2011). Health facilities randomized to a contact investigation strategy were compared to those randomized to the standard approach in terms number, age group and gender of TB cases diagnosed in the pre-intervention years, type and rural and urban distribution of health facilities to assess for balance of randomization between the groups and limit chances of systematic error, using chi square statistics(Festic, Rawal, & Gajic, 2016)**.**Since the population sizes and TB case rates in the randomized populations were intended to be the same, the total number of cases reported during the intervention years was compared to the pre-intervention years. The change in detection in each

arm was also compared between arms. Fishers exact test was used to compare the number of TB cases diagnosed in the pre-intervention year by arm and in the pre- and post intervention years. Similarly analyses were conducted for the number of children who received IPT(Parab & Bhalerao, 2010).

3.19 Lessons learnt in implementing standardized TB contact investigation

3.19.1 Study design

An integrated convergent mixed methods study design was employed to document issues that would facilitate or hamper the implementation of TB household contact investigation in a setting with routine contact invitation (Guetterman et al., 2015). This was done to utilize both qualitative data and quantitative data to answer the same research question, and to increase confidence in the research findings through the confirmation of a proposition using more than one independent measures (Heale & Forbes, 2013). Specifically, qualitative and qualitative data were transformed by qualitizing quantitative data and or quantitizing qualitative data to enable them to be combined (Sandelowski, Voils, & Barroso, 2006). The results from quantitative analyses were used to triangulate findings from qualitative data wherever possible (Bruce et al., 2008).

The timing and weighing of this method are discussed subsequently. The sequence and integration (mixing or combination) is presented in the data analysis section (Wheeldon & Mauri, 2012). Both qualitative and quantitative studies were conducted during the entire duration of the study period. Priority and a higher weight was assigned to quantitative data that was used to analyze the main research question (Morgan, 1998).

A multi-methods study design was employed to assess the value of prospective household TB Contact Investigation in control of drug-susceptible TB among children aged 0-5 years who had been in household contact with an index case of TB in Kisumu County, Western Kenya, 2014-

2015 (a period prior to the inception of standardized contact investigation). This method was employed as it offers the distinct advantage of quick, close coordination and comparison of different methods and their findings (Brewer & Hunter, 1989). Specifically a cross sectional survey was used to determine the prevalence and risk factors of TB infection as well as IPT uptake and completion rates following household exposure among child contacts. A cluster-randomized trial was also used to compare the value of TB contact investigation to contact invitation in childhood TB control (Bruce et al., 2008).

Document analysis was used to systematically review qualitative data concerning experiences of the TB contact investigation study‟s research team (Bowen, 2009).

3.19.2 Study population

Quantitative data: These were all TB index cases and their child household contacts that participated in the TB contact investigation study.

Qualitative data: The target population was persons who had been directly involved in the provision of standardized TB contact investigation services. These included the research study team members and health workers at participating health facilities. This population was chosen because they had first-hand knowledge on the challenges faced and tools that would facilitate the implementation of clinical guidelines (Cabana et al., 1999).

3.19.3 Sample size and sampling technique

Quantitative: This included all index cases (183) and their child household contacts (257) that participated in the TB contact investigation study that had intended to recruit a minimum sample of 243 index cases and 157 child contacts. This also included all index cases (241) and their IPT-eligible child household contacts (337) that participated in the TB contact investigation study

that intended to recruit a minimum sample of 271 IPT-eligible child contacts. In both instances, Index and contact were recruited through a convenience sampling technique (Speak et al., 2018).

Qualitative : This included all the 46 study team members; there was an overall study coordinator, a clinic manager, 2 clinical officers, 5 nurses, 10 community interviewers (4 field based and 6 office based) and 27 community health volunteers. A convenience sampling method was employed as it was impractical to document the experiences of all health workers at TB clinics and laboratories of participating health facilities (Bruce et al., 2008).

3.19.4 Instruments and Procedures for Data collection

Quantitative data: This was drawn from participant databases and included index and contact information. Regarding the TB index case, the information following information as collected: X ray results, Household contact identification and Housing characteristics. As regards contact information, information was collected as regards Contact tracing, Contact eligibility, Contact interview, Contact TST, Contact lab results, Contact HIV test results, Contact Chest X ray results, Contact follow up interview. (Appendix 7: Data collection tools).

Qualitative data: The study employed document analysis as a stand-alone method; therefore, more than one document was reviewed to enhance the quality of data collected (Bowen, 2009). The following documents were used for document analysis; The consent cover sheets (Appendix 4: Consent Cover Sheets), schedules of appointments (Appendix 5: Appointments schedules), participant tracking sheets (Appendix 6: Participant Activity Checklist) and minutes of weekly meetings. The consent cover sheet contained participant demographic details, participant comprehension, literacy level, details of the consenting process, and any other additional details that the persons obtaining informed consent wished to document about the process. The

appointment schedule illustrated the number of visits to be made by each participant and procedures to be conducted at each visit.

The participant activity check list sheet which accompanied the participant as he or she moved from one point to another within the clinic, helped track the service delivery points where the participants had received services and all the documents that were filled at each point e.g. triage, clinician‟s desk, laboratory, pharmacy etc. During each meeting, an agenda item for "Challenges and Successes" was allocated for the study team members to discuss their experiences to support study implementation.

3.19.5 Data analysis and data integration

Quantitative data: Percentages were used to summarize the number of eligible participants that received specific services as a fraction of the total number of participants eligible for that service (Bruce et al., 2008; SAS Institute Inc, 2012).

Qualitative data: Content analysis was used to identify themes from minutes of meetings, participant consent sheets and participant tracking logs (Mays & Pope, 1995). The documents were initially read to extract decontextualized sub-themes, these were then contextualized with supporting information from each document and subsequently categorized and complied into main themes (Bengtsson, 2016).

Data integration: The sequence of data analysis was as follows; qualitative data was used to generate themes which guided the retrieval of corresponding or refuting quantitative data (Morgan, 1998).

A modified joint display was used to present the data. Themes identified from qualitative data analysis were presented in light of corresponding rates from quantitative data. The display was modified in that data was presented in paragraphs as opposed to side by side

(Guetterman et al., 2015). The presentation of results and discussion followed the same format of convergent mixed methods studies (Fetters & Freshwater, 2015).

3.20 Data management

The data collection and analysis have been described as per the study objective. As regards data cleaning, logical steps, frequency summaries and field verification was done. All data was then archived in institutional archives and would be destroyed 5 years after any publication from the study (Surkis & Read, 2015).

3.21 Ethical Considerations

3.21.1Risks of participation

The only risk of participation was the potential loss of privacy resulting from disclosing personal information which may have extended beyond that is routinely collected in medical practice. However, all data was kept securely and all study staff asked to sign confidentiality agreements (Appendix 12: Data Confidentiality Agreement Form)(National Institutes of Health [NIH], 2016).

3.21.2 Benefits of participation

Participants benefited from timely screening and diagnosis for TB and treatment initiation leading to favorable patient outcomes (Herchline & Amorosa, 2017). The TB program benefited from information provided to guide the implementation of contact investigation. As such, the potential risks of participating in this assessment were offset by the benefits to the individual

participants and the wider community (NIH, 2016).

3.21.3 Informed consent

Written informed consent was obtained from TB index cases and parental permission for child contacts to participate in the study (Appendix 3: Informed Consent document and parental permission & Appendix 4: Consent Cover Sheet). A waiver of informed consent was sought for facilities that participated in the larger TB case detection study (NIH, 2016)(Appendix 9: IRB approval for KEMRI SSC # 2494).

3.21.4 Privacy and confidentiality

Data was stored in password protected computers and anonymized. Only the principal investigator had access to the link log that could directly identify participants that retained with the sole intention of using it in the event there was a need to clarify some data. Upon study completion, electronic data would be stored in the institutional databases for a period of 5 years after that last publication. Paper copies of data were scanned; paper forms archived and images stored in institutional databases. Only study staff had access to the study data. Only grouped anonymized data was shared in publications and reports (NIH, 2016).

3.21.5 Institutional Review Board (IRB) oversight

Ethical approval to conduct the study was sought and granted by from the Kenya Medical Research Institute Science and Ethics Review Unit (KEMRI SERU 2408 & 2494 –Appendix 1, Appendix 9)(NIH, 2016).

CHAPTER FOUR

RESULTS

4.1 Introduction

The purpose of this study was to determine the value of TB contact investigation in childhood TB control. This was in light of the absence of information on the contribution of TB contact investigation to childhood TB control in Kenya. The data collected was analyzed and presented in subsequent sections.

4.2 The prevalence and risk factors for TB infection following household exposure

Introduction

The first objective of this study was to determine the prevalence of TB infection and contact, index and housing characteristics associated with TB infection following household exposure. To achieve this objective, data on demographic, clinical, exposure and living quarters‟ characteristics that would increase the risk of infection among child contacts following household exposure was collected. Additionally, diagnostic tests were done to assess for the presence of TB infection among child contacts. Data collected were analyzed under the research question, “What is the prevalence of TB infection and individual, index and housing characteristics associated with TB infection among child contacts following household exposure to a TB index case?” The results are presented in the subsequent sub-sections.

4.3 Characteristics of TB index cases

Of 1,519 contacts of 445 TB index cases enrolled into the TB contact investigation study, 345 (22%) were aged < 5 years. A total of 257 child contacts linked to 183 TB index cases that had complete documentation of results of TB diagnosis were included in these analyses.

The majority of TB index cases were of the age-group 15-29 years (44.3%), male (56.3%), from Kisumu region (68.9%) and had one child contact (62.6%). The majority of TB index cases presented with cough (81.4%); of the 136 TB patients with documentation of AAFB sputum smear results, majority had (135; 99%) a positive sputum smear; smear grading was scanty (n=2), 1+ (n=24), 2+ (n=33), 3+ (n=46), not documented (n=30). A majority of TB index cases were HIV positive (52.5%). Majority of the houses had a floor-space of 25 square meters or less (86.9%), and had housed less than 5 persons (61.2%), during the 3 months preceding diagnosis of the index case, the majority of whom did not smoke (95.1%). In the majority of the households, cross ventilation was present (57.9%). (Table 2)

Table 2: Characteristics of TB Index cases with child contacts, Kisumu County 2014-2015

Variables	Total (183) Number	%
Index Characteristics		
Age group		
<15 year	15	8.2
15-29 years	81	44.3
30-45 years	68	37.2
45+ years	19	10.3
Sex		
Male	105	56.3
Female	80	43.7
Region		
Urban Kisumu	126	68.9
Rural Kombewa	57	31.1
Cough		
Present	149	81.4
Absent	34	18.6
Smear Grade*		
Positive	135	84.4
Negative	25	15.6

HIV status		
Positive	96	52.5
Negative	87	47.5
House characteristics		
House size		
≤25 square meters	159	86.9
>25 square meters	24	13.1
No. of household members		
<5	112	61.2
5+	71	38.8
Persons who lived in the house that smoked during infectious period		
Present	9	4.9
Absent	174	95.1
Cross ventilation present		
Yes	106	57.9
No	77	42.1

*missing information on sputum Smear results for 23 participants

4.4 Child Contact Characteristics

A total of 257 child contacts with complete information on TB diagnosis were included in these analyses. Majority of child contacts were of the age-group 2.0-3.9 years (42.0%), male (52.5%), first degree relatives of the index cases (66.2%), with whom they had had a daily contact of more than 8 hours (66.9%) had shared a bedroom (60.7%)

The majority of child contacts had received BCG vaccination and a scar was seen on inspection at the time of interview (89.1%), was HIV negative (95.7%) and screened negative for TB symptoms (69.3%). (Table 3)

Table 3: Characteristics of Child Contacts of TB Index cases in Kisumu County, 2014-2015

Variables	Total (257) Number	%
Age group		
<2 years	101	39.3
2.0-3.9 years	108	42.0
4.0-4.9 years	48	18.7
Sex		
Male	135	52.5
Female	122	47.5
Relationship to index case[±]		
First degree relative (FDR)	170	66.2
Second Degree relation & non-relative	87	33.8
Contact number of hours per day		
<8 hours	85	33.1
8-24 hours	172	66.9
Shared a bedroom with index case		
Yes	156	60.7
No	101	39.3
BCG		
Given scar seen	229	89.1
Given no scar	22	8.6
Not given	6	2.3
HIV status[±±]		
Positive	10	4.3
Negative	222	95.7
TB Symptoms		
Present	79	30.7
Absent	178	69.3

[±]FDR includes siblings (n=21) and parents (n=149), Second degree relatives includes grandparents, grandchild, uncles, aunts, nieces, nephews and cousins; and 6 persons who are not related to the index case

[±±]HIV test results not documented for 25 contacts

4.5 Prevalence of TB infection

4.5.1 Tuberculin Skin Test (TST) placement and reading for household contacts

TST was placed and read for all the 257 child contacts. Chi square statistics for goodness of fit were used to assess for terminal digit preference. They revealed a terminal digit preference for 0 and 5 (Broeck & Brestoff, 2013). The TST were results plotted on a graph that revealed anterior mode at 0mm and posterior mode at 12mm with an anti-mode of 5mm. The TST results therefore had a bimodal distribution with a demarcation at 5mm. A cut of TST positivity of 5mm was therefore taken. The TST cut off was then reviewed after smoothing the graph using 5-point moving averages and it was found the selected cut off for TST positivity was not affected by the presence of terminal digit preference (Rieder et al., 2011). For this analysis, a total 101 (39.3%) of contacts had TB infection based on a TST reading of at least 5mm (Figure 5).

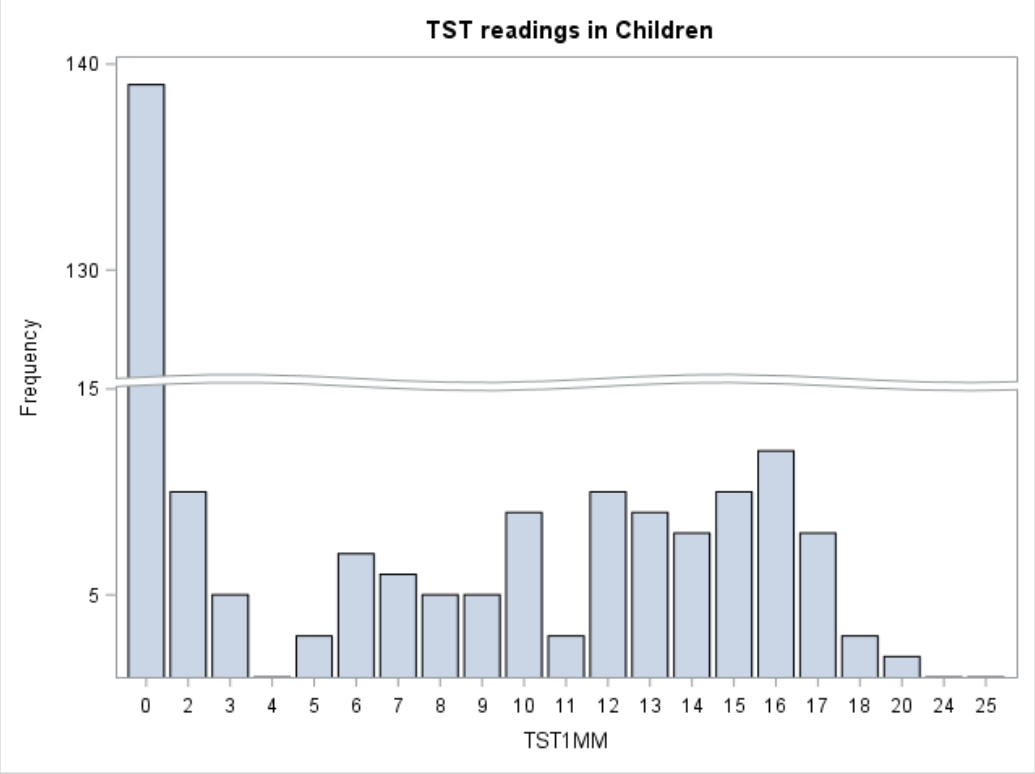


Figure 5: TST readings for child household contacts at Kisumu County, 2014-2015

4.5.2 Diagnosis of TB disease among child contacts

As per the study algorithm, chest x-rays were done where TST was positive or the child contact screened positive for TB symptoms. A total of 147 contacts met these criteria as follows; 33 screened positive using both TB symptom screen and TST, 68 screened positive using TB symptom screen only, and 46 screened positive using TST only. Chest x rays were done for 104 (70.7%) of 147 the eligible contacts as follows: 30 (90%) among those who screened positive using both TB symptom screen and TST, 56 (82%) among those who screened positive using TB symptom screen only, and 18 (39%) among those who screened positive using TST only. Seven (7; 6.7%) were diagnosed with TB; TB prevalence among all child contacts was 2.7% (7/257).

All the 7 had a positive TST and were included in the 101 child contacts with TB infection in these analyses.

4.5.3 Risk factors for TB infection following household exposure

Conventional logistic regression models (Single Level Logistic regression models SLM) for individual, index and housing risk factors for TB infection

Bi-variate analysis: TB infection showed a statistical association with more than 8 hours of daily contact with the TB index case (OR 1.78 95% CI 1.02-3.12); the TB index case being aged 15-45 years (OR 2.38 95% CI 1.18-4.83), index case presenting with cough (OR 3.23 95% CI 1.43-7.32); and a house size of ≤ 25 square meters (OR 2.44 95% CI 1.01-5.90) (Table 4)

Multivariate logistic regression model: After entering all variables that achieved a p value of <0.25 in the model and retaining only variables that had significance of $p<0.1$, the following remained in the model: the TB index case being aged 15-45 years (OR 2.67 95%CI 1.29-5.48) , presenting with cough (OR 3.78 95% CI 1.65-8.69) and having had a daily contact duration of more than 8 hours with the contact (OR 1.88 95% CI 1.05-3.28)(Table 5)

Table 4: SLM univariate risk factors for TB infection in child contacts

Variables	Total (257) Number (%)	TB infection 101 (39.3%)	Chi square	Crude OR	P value
Contact characteristics					
Age group					
<2 years	101 (39.3)	45 (44.5)	1.92	1.43 (0.86-2.39)	0.16
2.0-4.9 years	156 (60.7)	56 (35.9)		1	
Sex					
Male	135 (52.5)	51 (37.7)	0.27	0.87 (0.52-1.44)	0.59
Female	122 (47.5)	50 (40.9)		1	
Relationship to index case[±]					
First degree relative (FDR)	170 (66.2)	74 (43.5)	3.76	1.71 (0.99-2.95)	0.05
2nd Degree & non-relative	87 (33.8)	27 (31.0)		1	
Contact of hours per day					
<8 hours	85 (33.1)	26 (30.6)		1	
8-24 hours	172 (66.9)	75 (43.6)	4.04	1.78 (1.02-3.12)	0.04
Shared a bedroom index					
Yes	156 (60.7)	63 (40.3)	0.19	1.17 (0.67-1.88)	0.65
No	101 (39.3)	38 (37.6)		1	
BCG					
Given scar seen	229 (89.1)	90 (39.3)	0.36	0.88 (0.36-2.19)	0.83
Given no scar	22 (8.6)	8 (36.4)		1.54 (0.31-7.82)	
Not given	6 (2.3)	3 (50.0)		1	
HIV status[±±]					
Positive	10 (4.3)	5 (50)	0.59	1.64 (0.46-5.8)	0.43
Negative	222 (96.7)	84 (37.8)		1	
TB Symptoms					
Present	79 (30.7)	33 (41.7)	0.29	1.16 (0.67-1.99)	0.58

Absent	178 (69.3)	68 (38.2)		1	
Index Characteristics					
Age group					
<15 year &> 45 years	50 (19.5)	12 (24.0)	6.09	1	0.01
15-45 years	208 (80.5)	53 (43.0)		2.38 (1.18-4.83)	
Region					
Urban Kisumu	178 (69.2)	70 (39.3)	0.00	1.0 (0.48-1.72)	0.98
Rural Kombewa	79 (30.7)	31 (39.2)		1	
Cough					
Present	215 (83.7)	93 (43.3)	8.63	3.23(1.43-7.32)	0.003
Absent	42 (16.3)	8 (19.1)		1	
Smear Grade*					
Positive	192 (83.5)	74 (38.5)	0.01	0.96 (0.47-1.96)	0.91
Negative	15 (16.5)	15 (39.5)		1	
HIV status					
Positive	134 (52.1)	51 (38.1)		1	
Negative	123 (47.9)	50 (40.6)	0.18	1.12 (0.67-1.85)	0.67
House characteristics					
House size					
≤25 square meters	226 (87.9)	94 (41.6)	4.13	2.44 (1.01-5.90)	0.04
>25 square meters	31 (12.1)	7 (22.6)		1	
No. of household members					
<5	151 (58.7)	58 (38.4)	0.12	1	0.73
5+	106 (41.3)	43 (40.1)		1.09 (0.66-1.81)	
No. of Household members					
< 5	151 (58.8)	58 (38.4)	0.12	0.91 (0.55-1.51)	0.72
5+	106 (41.3)	43 (40.6)		1	
Persons that smoked during infectious period¶					

Present	15 (5.9)	6 (40.0)	0.00	1.02 (0.35-2.95)	0.97
Absent	240 (94.1)	95 (39.6)		1	
Cross ventilation present					
Yes	143 (55.6)	52 (36.4)	1.16	1	0.28
No	114 (44.4)	49 (42.9)		1.31(0.79-2.18)	

[±]FDR includes siblings (n=21) and parents (n=149), Second degree relatives includes grandparents, grandchild, uncles, aunts, nieces, nephews and cousins; and 6 persons who are not related to the index case

[±±]HIV test results not documented for 25 contacts 12 with TB infection and 13 without TB infection

*missing information on sputum Smear results for 23 participants with 27 child contacts

¶ Missing information for 2 participants with 2 child contacts

Table 5: Logistic regression model for risk factors for TB infection in child contacts following household exposure to a TB index case in in Kisumu County, 2014-2015

Characteristics	Crude OR (CI)	p	Adjusted OR (CI)	p
Age group of index				
<15 year &> 45 years	1		1	
15-49 years	2.38 (1.18-4.83)	0.01	2.67 (1.29-5.48)	<0.01
Cough				
Absent	1		1	
Present	3.23(1.43-7.32)	0.003	3.78 (1.65-8.69)	<0.01
Contact number of hours per day				
<8 hours	1		1	
8-24 hours	1.78 (1.02-3.12)	0.04	1.88 (1.05-3.28)	0.03

Multilevel logistic regression modeling-MLM (Hierarchical level modeling) Introduction

MLM was used to explore risk factors for TB infection in child contacts with child contacts nested within households. The data at level one (contacts) were aggregated at level two (households) and level two units were used for analysis. The study sample consisted of 257 children nested within 183 households. The number of children per household ranged from 1-4.

One contact level variables and 3 household level variables selected to be used in this analysis based on the fact they were significant in the univarite analyses in the conventional logistic regression models(Yang et al., 2009).The binary outcome for the study was TB infection in the contact which occurred in 101 (39.3%) of the contacts. The intercept, parameter estimates and standard errors for each of the models are shown in table 6.

Table 6: Estimates for the Two-level Linear Dichotomous Models of TB infection

	Model 1[¥] No predictors just random effect for the intercept	**Model 2[¥]** Model1+ level 1 fixed effects	**Model 3[¥a]** Model 2+ level 2 fixed effects
Fixed effects			
Intercept	-0.5156* (0.17)	-0.9802* (0.30)	-3.1803* (0.84)
Daily Contact (per hour increase)		0.6721 (0.35)	-0.6598 (0.38)
Index aged 15-45 years			1.1227* (0.49)
Index presenting with cough			1.5597* (0.54)
House size <25 square meters			-0.4521 (0.59)
Random effects			
Intercept	0.07906 (0.62)	0.8358 (0.66)	0.9243 (0.75)
Model fit			
Variance (-2LL)	339.27	335.24	317.21

*p <0.05

[¥]entries show parameter estimates with standard errors in parenthesis

Table 5 and 6 were used to answer the following questions by Ene et al and Austin Et al (Austin & Merlo, 2017; Ene et al., 2014)

What is the probability of TB infection in each household? Do TB infection rates vary between households? What is the relationship between different household and individual contact characteristics with TB infection while controlling for both index and contact characteristics?

What is the probability of infection in each household? (Table 6)

This question relates to model 1 that did not contain any predictors from any of the two levels and was given by the formula – $\omega_{ij} = e^{nij} / (1 + e^{nij})$. Where $\omega_{ij\ was}$ the probability of infection and e took the value of approximately 2.72, ^{nij} that represented the log odds of infection.

$\omega_{ij} = 2.72^{-0.5165} / (1 + 2.72^{-0.5165})$

$= 0.5964 (1+0.5964)$

$= 0.3736$

Thus in an average household, (whose random effect is zero on a logit scale), the probability of infection after household exposure was 0.3736

Does the probability of TB infection vary across households?

The intra-class correlation coefficient given by Bell et al 2013 (Bell BA, One M, Smiley W, & Schoeneberger JA, April 28-May 2013)(that gives covariance estimates of the intercept as 0.07556 and residual as 0.1641) was computed using the variance of housing effect level as follows

ICC= Intercept / (Intercept+ Residual)

=0.31528

It was found to be 31%. This implies that 31% of variability in the infection rate was accounted for by household factors leaving 69% to be accounted for by other contact and index characteristics. There was a statistically significant amount of variability in the log odds of infection ($p<0.01$). Therefore the probability of infection after exposure was 0.3736 but infection varied considerably across households.

What is the relationship between different index and contact characteristics with TB infection while controlling for both index and contact characteristics? (Table 6)

To select the best fitting model, a deviance test was conducted. This is a chi squared test that compared the -2LL values between two models with the degree of freedom equal to the difference in the number of parameters estimated between the models. As a deviance test can only be conducted when the models are nested, model 2 was compared to model 1, and model 3 was compared to model 2(Social Science Statistics, n.d.)

X^2_{diff}= -2LL $_{Model\ 1}$--2LL $_{Model\ 2}$

=339.27- 335.24=4.03(df 1=, p=0.044698)

X^2_{diff}= -2LL $_{Model\ 2}$--2LL $_{Model\ 3}$

=335.24- 317.21 =18.03 (df 3=, p=0.000434)

The addition of level 2 variables (index and housing characteristics) improved model fit as shown in Table 5 and this was the model selected to answer the remaining questions.

What is the relationship between contact variables (age of Index case) and TB infection while controlling for contact and household characteristics? (Table 7).

The probability of TB infection in a child contact who had been in contact with a TB index case aged 14-45 years was 2.59 times that of a child contact who had been in contact with an index case aged either <15 years or > 45 years from the OR estimates. (OR=2.59, 95% CI 1.1-7.2, p<0.05) (Table 9).The probability of TB infection in a child contact who had been in contact with an index case aged either <15 years or > 45 years was given by;

$\omega_{ij} = e^{nij} / (1 + e^{nij})$

$\omega_{ij} = 2.72^{-4.1803} / (1 + 2.72^{-3.1803})$

$= 0.04148 (1 + 0.04148)$

$= 0.039828$

The probability of TB infection in a child contact that had been in contact with a TB index case aged 15-45 years was given by;

$\omega_{ij} = (e^{nij} * 2.9) / (1 + (e^{nij} * 2.9))$

$= (0.04148 * 2.59) / ((1 + (0. 0.04148 * 2.59))$

$= 0.04404$

What is the relationship between index variables (the presence of cough) and TB infection while controlling for contact and household characteristics? (Table 7).

The probability of TB infection in a child contact who had been contact with a TB index who coughed was 3.76 times that of a child contact who had been contact with a TB index case who did not have cough from the OR estimates (OR =3.76, 95% CI 1.51-9.35, p<0.01) (Table 9). The probability of TB infection in a child contact with a TB index case who did not cough is given by;

$$\omega_{ij} = e^{nij} / (1 + e^{nij})$$

$$\omega_{ij} = 2.72^{-3.1803} / (1 + 2.72^{-3.1803})$$

$$= 0.04148 (1 + 0.04148)$$

$$= 0.039828$$

The probability of TB infection in a child contact that had been in contact with a TB index case that coughed was given by;

$$\omega_{ij} = (e^{nij} * 3.76) / ((1 + (e^{nij} * 3.76))$$

$$= (0.\ 04148 * 3.76) / ((1 + (0.04148 * 3.76))$$

$$= 0.097011$$

Interpretation of Odds ratio estimates from MLM (Table 7)

In model 2, the risk of infection did not differ between a child who had a daily contact with an index case of less than 8 hours or more than 8 hours. This model assumes that the household characteristics (and those of the index by proxy) do not influence TB infection.

In model 3, the odds of TB infection was 3.76 times for a child who had been in contact with an index case who coughed compared to a contact that had been in contact with an index case who did not cough; after fixing contact characteristics and other index characteristics. Similarly, having been in contact with an index case aged 15-45 years was associated with a 2.59 increase in risk of infection; after fixing contact characteristics and the other index characteristics.

Table 7: Estimated odds ratios for multilevel logistic regression models

	OR (95% CI)	
Independent variable	Model 2	Model 3
Contact level		
Daily Contact of more than 8 hours	1.77 (0.97-3.24)	1.75 (0.91-3.36)
Household level		
Index case aged 15-45 years		2.59 (1.13-5.91)*
Index presenting with cough		3.76 (1.51-9.35)*
Household size <25 square meters		1.47 (0.51-4.19)

*p<0.05

Comparison of MLM to Conventional logistic regression models (Single level models)

Conventional logistic regression models selected more independent variables and had narrower confidence level intervals compared to Hierarchical logistic regression models (Table 8).

Table 8: A comparison of results obtained from MLM to SLM

Characteristics	Multi-level Model		Conventional Logistic Regression	
	OR	**CI**	**OR**	**CI**
Age group of index				
<15 year &> 45 years	1		1	
15-49 years	2.59	1.13-5.91	2.67	1.29-5.48
Cough				
Absent	1		1	
Present	3.76	1.51-9.35	3.78	1.65-8.69
Daily Contact hours				
<8 hours	1		1	
8-24 hours	1.75	0.91-3.36	1.88	1.05-3.28

4.6 Isoniazid Preventative Therapy (IPT) Uptake and Completion rates

4.6.1 Introduction

The second objective of this study was to determine the uptake and completion of IPT among child contacts following household exposure to TB infection and the exclusion of a TB diagnosis. To achieve this objective, study team members identified child contacts of TB index cases that were not diagnosed with TB and attempted to link them to the TB program registers to collect information on IPT initiation and completion. Data collected under this objective were analyzed under the research question, "What is the IPT uptake and completion rate among child contacts following household exposure to TB infection and the exclusion of a TB diagnosis?" The results are presented in subsequent sections.

4.6.2 Characteristics of TB index cases with IPT eligible child contacts

A total of 243 TB index cases with 345 child contacts were recruited into the TB contact investigation study. Among the child contacts, 8 were diagnosed with TB; the remaining 337 were therefore IPT eligible as per the Kenyan TB treatment guidelines (DTLD,2011b).Of the 8 contacts diagnosed with TB, only 2 were linked to a TB index case that had a single child contact. The remaining 6 were linked to a TB index case that had more than one child contact; the other child contacts who had also been exposed with the TB index case and were not diagnosed with TB, were therefore eligible for IPT initiation. Thus 241 TB index cases linked to 337 child IPT-eligible child contacts formed the sample population used to answer the research question related to this study objective.

The majority of TB index cases were aged 15-29 years (41.9%), male (53.5%), were from urban Kisumu (69.3%), had one child contact (65.9%), presented with cough (81.3%), pulmonary TB (93.3%), which was smear positive (84.4%), with abnormal chest x rays (both cavitary 40.8% and non cavitary; 44.2%) and were HIV positive (52.3%).

4.6.3 Characteristics of child contacts

Of the 337 IPT-eligible child contacts, the majority were, aged 2.0-3.9 years (42.1%), male (51.9%), from urban Kisumu (68.3), 1st degree relatives of the index case (65.9%), with whom they had lived with for ≥90 days (68.2%), with a daily contact of ≥8 hours (69.1%), and had

shared a bedroom (61.1%). The majority also had received BCG and a scar was seen at the time of interview (89.3%), had never received IPT in the past (95.2%) nor had TB in the past (99.1%), was HIV negative (95.6%) and screened negative for TB symptoms (73.0%). (Table 10)

Table 10: Characteristics of IPT-eligible contacts in Kisumu County, 2014-2015

Characteristics	**Total Number**	**(241)**	**(%**
Age group			
<15 year		18	7.5
15-29 years		101	41.9
30-45 years		92	38.2
45+ years		30	12.5
Sex			
Male		129	53.5
Female		112	46.5
Region			
Kisumu rural		74	30.7
Kisumu Urban		167	69.3
No. of child contacts			
1		159	65.9
2		65	26.9
3		14	5.8
4		3	1.2
Cough			
Present		196	81.3
Absent		45	18.7
TB type**			
Pulmonary		224	93.3
Extra pulmonary		16	6.7
Smear Grade***			
Positive		179	84.4

Negative	33	15.6
Chest x ray results****		
Normal	22	13.0
Abnormal caviar	69	40.8
Abnormal non caviar	78	44.2
HIV status		
Positive	126	52.3
Negative	115	47.7

4.7 IPT uptake

Fifteen percent (15.1%; 51) of 337 IPT-eligible child contacts, linked to 47 (19.5%) of the 241 index cases received IPT. The child contacts were daughters (20), sons (18), nieces (6), siblings (3), grandchildren (3) and a friend (1) of the TB index case. Child contacts were linked to TB index cases as follows; 3 index cases that 2 had two child contacts each had both child contacts initiated on IPT; one index that had 3 child contacts, had two of three contacts initiated on IPT.

4.8 Factors associated with IPT uptake

TB index factors associated with IPT uptake among child contacts

Bivariate logistic regression: In bivariate analysis, IPT initiation showed a statistical association with rural residence (OR 2.14 95% CI 1.11-4.14) (Table 11).

Multivariate logistic regression analysis: After entering all variables that achieved a p-value of <0.25 in the model and retaining only variables that had significance of $p<0.1$, the following remained in the model: rural residence (OR 3.06 95%CI 1.45-6.48) and smear positivity (OR 4.62 6 95% CI 1.02-20.88) (Table 12)

Table 11: IPT initiation by index characteristics, Kisumu County, 2014-2015

Characteristics	Total (241) Number (%)	IPT initiated for child contact 47/238 (19.5%) n/N (%)	Chi squ are	Crude OR		p
Age group						
<15 year	18 (7.5)	3 (16.7)		1		
15-29 years	101 (41.9)	24/101 (23.8)		1.56	(0.42-5.84)	
30-45 years	92 (38.2)	16/92 (17.4)		1.05	(0.27-4.07)	
45+ years	30 (12.5)	4/30 (13.3)	2.24	0.77	(0.15-3.91)	0.52
Sex						
Male	129 (53.5)	27 (20.9)	0.36	1.22	(0.64-2.31)	0.54
Female	112 (46.5)	20 (17.9)		1		
Region						
Kisumu rural	74 (30.7)	21 (28.4)	5.35	2.14	(1.11-4.14)	0.02
Kisumu Urban	167 (69.3)	26 (15.6)		1		
No. of child contacts						
1	159 (65.9)	24 (15.1)	0.00	1		0.07
2	65 (26.9)	18 (27.7)		2.15	(1.08-4.31)	
3	14 (5.8)	4 (28.6)		2.25	(0.65-7.76)	

4	3 (1.2)	1 (33.3)		2.81	(0.25-	
				32.25)		
Cough						
Present	196 (81.3)	39 (19.9)	0.11	1.14	(0.49-	0.75
				2.66)		
Absent	45 (18.7)	8 (17.8)		1		
TB type**						
Pulmonary	224 (93.3)	47 (20.9)	-	-		-
Extra pulmonary	16 (6.7)	0 (0.0)				
Smear Grade***						
Positive	179 (84.4)	38 (21.2)	4.19	4.18	(0.96-	0.05
				18.2)		
Negative	33 (15.6)	2 (6.1)		1		
Chest x ray results****						
Normal	22 (13.0)	4 (18.2)		1		
Abnormal caviar	69 (40.8)	17 (24.6)		1.47	(0.44-	
				4.95)		
Abnormal non caviar	78 (44.2)	12 (15.4)	2.02	0.82	(0.42-	0.36
				2.84)		
HIV status						
Positive	126 (52.3)	23 (18.3)	0.26	1		0.61
Negative	115 (47.7)	24 (20.9)		1.18	(0.63-	
				2.22)		

Table 12: Logistic regression model for TB index factors associated with IPT initiation among child contacts of TB index cases in Kisumu County, 2014-2015

Characteristics	Crude OR (CI)	p	Adjusted OR (CI)	p
Region				
Kisumu Urban	1		1	
Kisumu rural	2.14 (1.11-4.14)	0.02	3.06 (1.45-6.48)	<0.01
Smear Grade**				
Positive	4.18 (0.96-18.2)	0.05	4.62 (1.02-20.88)	0.04
Negative	1		1	

Child contact factors associated with IPT initiation

Bivariate logistic regression: In bivariate analysis, IPT initiation showed a statistical association with rural residence (OR 1.97 95% CI 1.01-3.03); a first degree relationship with the index case (OR 2.37 95% CI 1.14-4.94) and having received IPT in the past (OR 4.72 95% CI 1.27-10.62). (Table 13)

Multivariate logistic regression analysis: After entering all variables that achieved a p-value of <0.25 in the model and retaining only variables that had significance of p<0.1, the following remained in the model: rural residence (OR 2.65 95%CI 1.37-5.09) and first degree relationship to index case (OR 2.57 95% CI 1.19-5.52) (Table 14)

Table 13: IPT initiation among child contacts within Kisumu County, 2014-2015

Characteristics	Total (337) N (%	IPT initiated 51/337 (15.1%) n/N (%)	Chi square	Crude OR	p
Age group					
<2 years	127 (37.7)	25 (19.7)	3.34	1.61 (0.70-3.67)	0.18
2.0-3.9 years	142 (42.1)	17 (11.9)		0.89 (0.38-2.11)	
4.0-4.9 years	68 (20.2)	9 (13.2)		1	
Sex					
Female	162 (48.1)	30 (18.5)	2.78	1.67 (0.91-3.03)	0.09
Male	175 (51.9)	21 (12.0)		1	
County of residence					
Kombewa (rural)	107 (31.7)	23 (21.5)	4.94	1.97 (1.01-3.59)	0.03
Kisumu (urban)	230 (68.3)	28 (12.2)		1	
Relationship to index					
1st degree relative (FDR)	222 (65.9)	41 (18.5)	5.63	2.37 (1.14-4.94)	0.02
2nd degree & non relative	115 (34.1)	10 (8.7)		1	
Duration lived with index case					
<90 days	107 (31.8)	14 (13.1)		1	
≥90 days	230 (68.2)	37 (16.1)	0.51	1.2 (0.6-2.4)	0.47
Contact number of					

hours per day					
<8 hours	104 (30.9)	14 (13.5)		1	
8-24 hours	233 (69.1)	37 (15.9)	0.32	1.2 (0.6-2.4)	0.56
Shared index' bedroom					
Yes	206 (61.1)	31 (15.1)	0.003	0.99 (0.53-1.82)	
No	131 (38.9)	20 (15.3)		1	0.96
BCG					
Given scar present	301 (89.3)	42 (13.9)		1	
Given scar absent	28 (8.3)	8 (28.6)		2.46 (1.02-5.96)	
Not given	8 (2.4)	1 (12.5)	4.31	0.88 (0.11-7.34)	0.12
Ever received IPT					
Yes	16 (4.8)	6 (37.5)	6.54	4.72 (1.27-10.62)	0.01
No	321 (95.2)	45 (14.0)		1	
Ever had TB					
Yes	3 (0.9)	0 (0.0)			
No	337 (99.1)	51 (15.3)	-	-	-
HIV status* **					
Positive	13 (4.4)	2 (15.4)		1.06 (0.23-4.98)	0.94
Negative	281 (95.6)	41 (14.6)	0.006	1	
TB Symptoms					
Present	91 (27.0)	11 (12.1)		1	
Absent	246 (73.0)	40 (16.3)	0.90	1.41 (0.69-2.89)	0.34

*FDR includes siblings (n=25) and parents (n=202), Second degree relatives includes grandparents, grandchild, uncles, aunts, nieces, nephews and cousins; and 13 persons who are not related to the index case

*******HIV test results not documented for 43 contacts 8 initiated on IPT and 32 not initiated on IPT

*entered into the multivariate logistic model, **Missing data for 43 contacts

History of prior TB treatment excluded due to no participants with prior TB being initiated on IPT

Table 14: Logistic regression model for child contact factors associated with IPT initiation among child contacts of TB index cases in Kisumu County, 2014-2015

Characteristics	Crude OR (CI)	p	Adjusted OR (CI)	p
Sex				
Female	1.67 (0.91-3.03)	0.09	1.91 (1.01-3.58)	0.05
Male	1		1	
Region				
Kombewa Rural	1.97 (1.01-3.59)	0.03	2.65 (1.37-5.09)	<0.01
Kisumu Urban	1		1	
Relationship to index case*				
Parent, sibling or grandparent	2.37 (1.14-4.94)	0.02	2.57 (1.19-5.52)	0.02
Other relation/non relative	1		1	
Ever received IPT				
Yes	4.72 (1.27-10.62)	0.01	2.89 (0.96-8.72)	0.06
No	1		1	
BCG				
Given scar present	1		1	
Given scar absent	2.46 (1.02-5.96)		2.96 (1.17-7.48)	
Not given	0.88 (0.11-7.34)	0.12	1.13 (0.12-10.33)	0.07

IPT Completion

Among the 51 (15.1%) child contacts that initiated on IPT, 10 (19.6%) completed IPT. Reasons for non-completion were not documented. Among the 10 contacts that completed IPT, 7 were children, 2 were siblings, and one was a niece of the index case. A detailed analysis of IPT completion rates was not done due to the low number of contacts who completed IPT.

4.9 The Value of TB Contact investigation in comparison to TB Contact invitation

Introduction

The third objective of this study was to compare the value of TB contact investigation to TB contact invitation in childhood TB control. To achieve this objective, data on the number of TB cases diagnosed and cases put on IPT (as a measure of TB control) in the years preceding the study period and during study period were collected. This information was collected from health facilities randomized to a TB contact investigation strategy and facilities randomized to the standard approach (Contact invitation) within a larger TB case detection study. Data collected under this objective were analyzed under this research question, "How does the value of TB contact investigation compare to that of contact invitation in childhood TB control?" The results are presented in subsequent sections.

TB case detection interventions were implemented at selected health facilities between 2014 and 2015. Of 85 facilities identified for the study, 65 facilities were randomized to a contact screening strategy. The majority (54) were randomized to a TB contact investigation strategy in isolation (n=4), in combination with health facility screening (n=19), or in combination with both enhanced facility screening and mobile units (n=31) with the remainder, (n=11) randomized to the standard approach i.e. TB contact invitation. Clinics that were randomized to other strategies (e.g. mobile units (n=6) or enhanced health facility screening (n=14) in isolation or combination were excluded from the analysis (Figure 6).

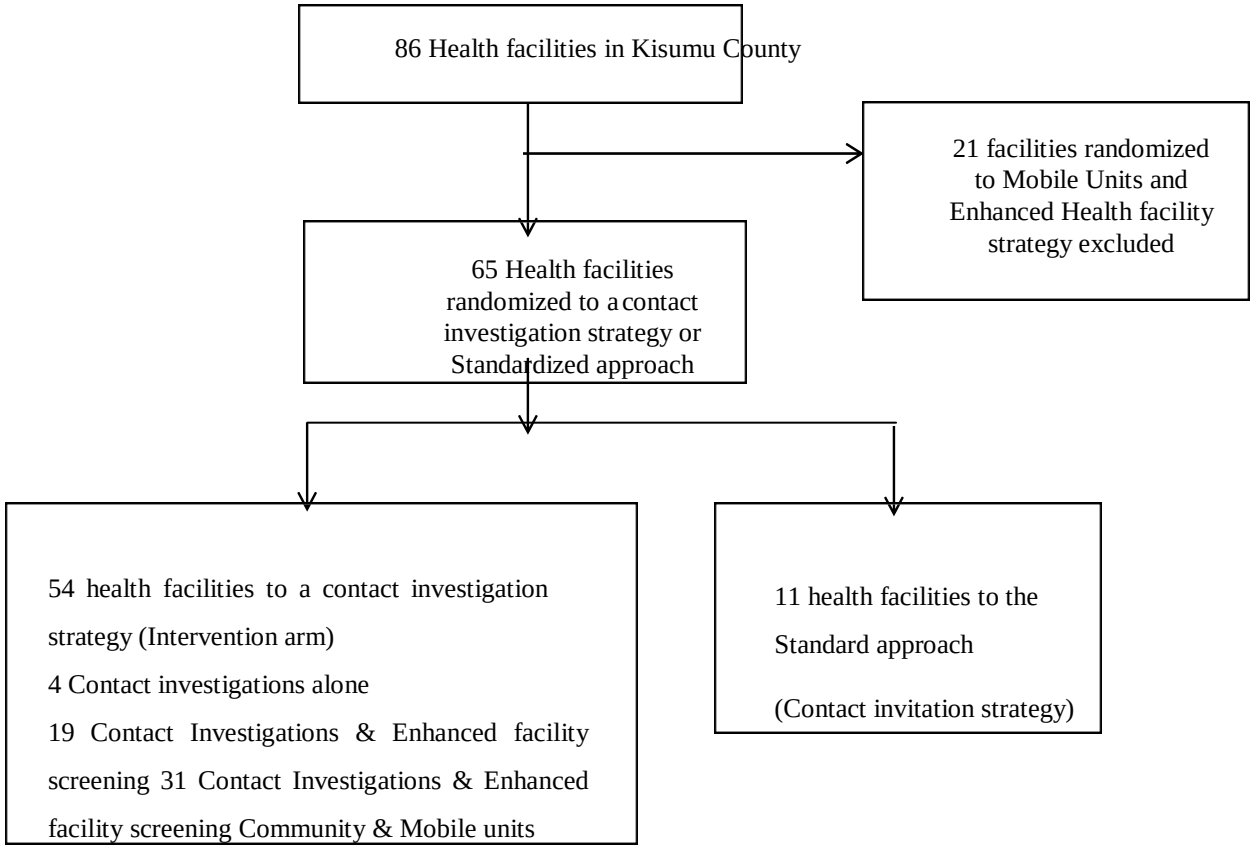


Figure 6: Randomization of health facilities to different strategies

4.10 Baseline characteristics of health facilities by strategy

Of 65 health facilities included, majority were of level 2 (69%), located in urban areas (64%) and had a majorly male (56%) adult patients (91%). No facility was randomized to the Standard approach in rural locations. Facilities distribution did not differ by category of services or patient type (Table 15).

Table 15: Health facilities distribution to TB case detection strategies

Characteristics	No. of facilities	Contact investigation	Standard approach	P value
	Total 65	54 (83%)	11 (17%)	
	N (%)	N (%)	N (%)	
Health Facility				
Facilities level				
2	45 (69)	38 (84)	7 (16)	0.18
3	16 (25)	14 (88)	2 (12)	
4 & 5*	4 (16)	2 (50)	2 (50)	
Distribution				
Rural	21 (33)	22 (100)	0 (0)	-
Urban	44 (67)	33 (75)	11 (25)	
TB cases in 2013 & 2012	N=2713	N=1879	N=834	
Age groups				
<5 years	95 (4)	62 (65)	33 (35)	0.36
5-14	123 (4)	79 (64)	43 (36)	
15+ years	2495 (92)	1738 (70)	757 (30)	
Gender				
Male	1546 (57)	1073 (69)	473 (31)	0.88
Female	1167 (43)	806 (69)	361 (31)	

*Levels grouped to eliminate cells containing zero, Contact investigation facilities have 1 level 4 and 0 level 5 facilities, and Standard approach has 2 level 4 and 1 level 5 facilities

4.11 Assessment of TB control activities

In the pre-intervention and post-intervention years

The number of TB cases increased by 20; majority were from the contact investigation arm (n=15; 75%). This increase was not statistically significant.

A before and after comparison of IPT administration could not be done since IPT implementation at all health facilities was not initiated until 2014. (Table 16)

Between 2014 and 2015, there was a decrease in TB cases by 17 (12 from the Standard approach and 5 from the contact investigation arm); but this was not statistically significant (Table 16).

During the intervention years, health facilities randomized to the intervention arm contributed to 100% and 75% of the children put on IPT in 2014 and 2015 (Table 16). Detailed contribution of each facility to the TB case detection in each year & IPT initiation is given in Appendix 13 and 14 respectively).

Table 16: TB control in children by TB case detection strategy

	Strategy					
	Contact investigation in isolation or combination with other strategies			S		
Measure of TB control	C	HC+HCM	Total		Total	P value
TB cases diagnosed						0.28†
Pre-intervention years	8	54	62 (65)	33 (35)	95 (100)	
2012	5	20	25	15	40	
2013	3	34	37	18	55	
Post Intervention years	4	74	77 (73)	28 (27)	105 (100)	0.12††
2014	1	40	41	20	61	
2015	3	33	36	8	44	
Children on IPT						
Pre-intervention years 2012 & 2013*						
Post-interventionyears **						
2014	0	2	2 (100)	0 (0)	2 (100)	-
2015	0	47	47 (75)	16 (25)	63 (100)	

C-contact investigation, HC-contact investigation+ enhanced facility screening, HCM- contact investigation+ enhanced facility screening+ Community Mobile Units, S-Standard Approach (Contact Invitation)

† P value comparing TB cases diagnosed in the pre and post intervention period by arm

†† p value comparing TB cases diagnosed in the intervention period by arm

*IPT implementation had not formally begun during the pre-intervention years

** Comparison by arm not done during intervention years as no children received IPT in 2014 in the standard arm

4.12 Lessons learnt in implementing standardized Tuberculosis Contact Investigation

Introduction

The fourth objective of this study was to identify what issues would facilitate or hamper the transition of a TB program from routine contact invitation to standardized contact investigation. To achieve this objective, a document analysis was done using participant tracking logs, consent cover sheets and meetings of minutes. Participant databases were also reviewed. Data collected were analyzed under this research question, "What are the lessons learnt when implementing standardized TB contact investigation in Kisumu County, in a setting with routine contact invitation?" The results are presented in subsequent sections.

Lessons learnt

The lessons learnt during the implementation of the study are summarized in Table 17 below.

Table 17: Key issues for implementing standardized Tuberculosis Contact investigation

Key issues for implementing standardized Tuberculosis Contact investigation
Identification and recruitment of TB index cases and their household contacts
The requirement to adhere to multiple appointment schedules
Completion of the TB screening and treatment cascade
Database management
Resource implications

4.13 Convergent validation of qualitative and quantitative data

Identification and recruitment of index cases and their household contacts

Only 554 (12%) of the 4,524 TB index cases that were diagnosed in Kisumu County during the study period 2014-2015, were recruited into the study (NTLP, 2017a). TB index cases listed a total of 1,974 household contacts. However, upon home visit, 2,068 household contacts were found. The median number of household contacts per index case was 5 (3-7). A total of 652 home visits were made in attempt to reach 1,945 (94%) household contacts. Upon tracing attempts to households of index cases who had listed at least one household contact, information was obtained about 2,114 contacts of whom 1,315 (62.2%) were interviewed, 579 (27.4%) scheduled an interview at a later date, 97 (4.6%) were not found at home, 90 (4.3%) declined participation, 18 (0.9%) had out-migrated, 14 (0.7%) were unreachable on phone, and 1 (0.0%) had died.

Upon screening of 1,918 contacts who were linked to 510 of the index cases, 1,896 (98.9%) had spent more than 7 consecutive nights in the house of the index case and were therefore eligible for enrolment. The 22 (1.1%) who were not eligible for enrolment either declined participation (n=11), did not fit the definition of household contact i.e. had not spent more than seven consecutive nights in the home with the index case during the three months preceding the TB diagnosis date (n=4), were untraceable (n=4), had out-migrated from the study area (n=2), and was mentally handicapped and therefore could not give consent to participate (n=1).

Only 1,519 (82%) household contact that were linked to 445 index cases were enrolled into the study. The 366 who were not enrolled either declined participation (n=286), could not be traced (n=48) or the reasons for non-enrolment were not documented (n=32). The majority (n=445; 80%) had at least one household contacts; of these the 243 (55%) that had at least one household contacts aged less than 5 years comprised of 44% of all the TB index cases in the study (Figure 3). Over one fifth of all contacts (n= 345/1519; 22.7%) were aged less than 5 years of age. The mean age of all TB index cases and index cases with child contacts was 32.7 (±13.9) and 30.9 (±13.1) years respectively. The ratio of the total number of TB index cases in the study to child contacts was (555: 345) 1.5: 1) (Figure 7).

The requirement to adhere to multiple appointment schedules

As a requirement for study participation, all study participants had to commit to adhere to all study procedures which included a minimum of five visits over a three month period to the health facility. During these visits, the TB index case would undergo additional tests if required and household contacts would be screened, Depending on their screening results, the appropriate treatment would be commenced. Participants had also to adhere to appointment schedules for

TST readings and to travel to higher level health facilities in the event their primary facilities did not have the infrastructure and personnel to conduct Chest x-rays and skills for TST inoculation and reading. The number of visits may have therefore exceeded the required minimum. (Appendix 6: Appointment schedule).

Completion of the TB screening and treatment cascade

There was a decrease in the number of contacts from the point of identification to completion of the screening cascade and subsequent follow-up. All participants aged less than 5 years ought to have had a HIV test done and TST inoculated, read and interpreted. Moreover, symptomatic participants and those with a positive TST should have had a chest X-ray done. However, only 82% of contacts had a TST done and of those who were eligible for Chest X ray, only 71% had a chest x-ray done. There were also challenges in completion of the TB treatment cascade for both LTBI and active TB disease. Only 15% of contacts eligible for IPT initiation were put on IPT and only one fifth completed IPT (Figure 7)

Database management

A relational database was used during the study. An index case had eight data tables; these were Patient eligibility, Patient information, Patient interview, TB index HIV test results, TB index Lab results, TB index Chest X ray results, Household contact identification and Household visit. Each contact had eight data tables; these were Contact tracing, Contact eligibility, Contact interview, Contact TST, Contact lab results, Contact HIV test results, Contact Chest X ray results, Contact follow up interview.

A TB index case was identified by a unique number linked to the screening center. E.g. "KI", for Kisumu County followed by a four digit code (index identifier), a hyphen, and another two digit code (contact identifier). For instance, "KI-0001-0" would be the first index case recruited in Kisumu County. All household contacts would subsequently be identified with a suffix added to the index identification number e.g. for index case "KI-0001-0", contacts would be listed as "KI-001-1", "KI-001-2", ""KI-0001-3"…… "KI-0001-n"... The index identifier was the unique identification number that was used on all index data tables (which contained 554 observations one for each index case), except the Household contact identification data table. In this table, study staff would enter all identification details of all the household contacts of a TB index case; this data table had 1,974 observations (one for each contact). Upon visiting the home to trace other contacts, 2,068 were identified and this was entered in the Contact tracing data table. However, upon screening, only 1,945 were found during tracing and were entered into the Contact eligibility data table. Upon interview only 1,855 met the definition of household contact and were entered in the Contact interview data table. These contacts then appeared on the Contact HIV test, Lab results, TST and Chest X-ray and follow-up data tables if they were retained in the study and completed the recommended screening tests. This implies that the final database would have a number of unique identification numbers dropped during the screening and identification cascade (Figure 7) (Appendix 8: Data collection tools).

Resource Implications

This study was conducted over a 2-year period in several facilities in Kisumu County. The study budget (that included salaries of additional staff that were hired to conduct the study, transport and screening costs, tracing costs etc.) was in hundreds of thousands of US dollars (KEMRI TB Program Strengthening section head, Personal communication, 30th June 2016). However, it was

still not possible to place a study staff at each facility. Field study personnel therefore had to shuttle between participating health facilities to implement study procedures. Additional costs were incurred to make 625 home visits to transport all the contacts from their homes to the health facilities for screening for at least 2 visits (for both inoculation and TST readings) and possibly treatment, to purchase TST kits, to pay for chest x-rays and other laboratory tests. The furthest distance the study team had to travel to transport study participants from their homes to the TB clinics was a round trip of approximately 100 kilometers. The institutional vehicle costs approximately USD 1 per kilometer. A maximum of three home visits were to be made before declaring a participant untraceable. The study team also incurred costs of telephone charges to track down participants and invite them for an .or remind them to attend a scheduled clinic appointment.

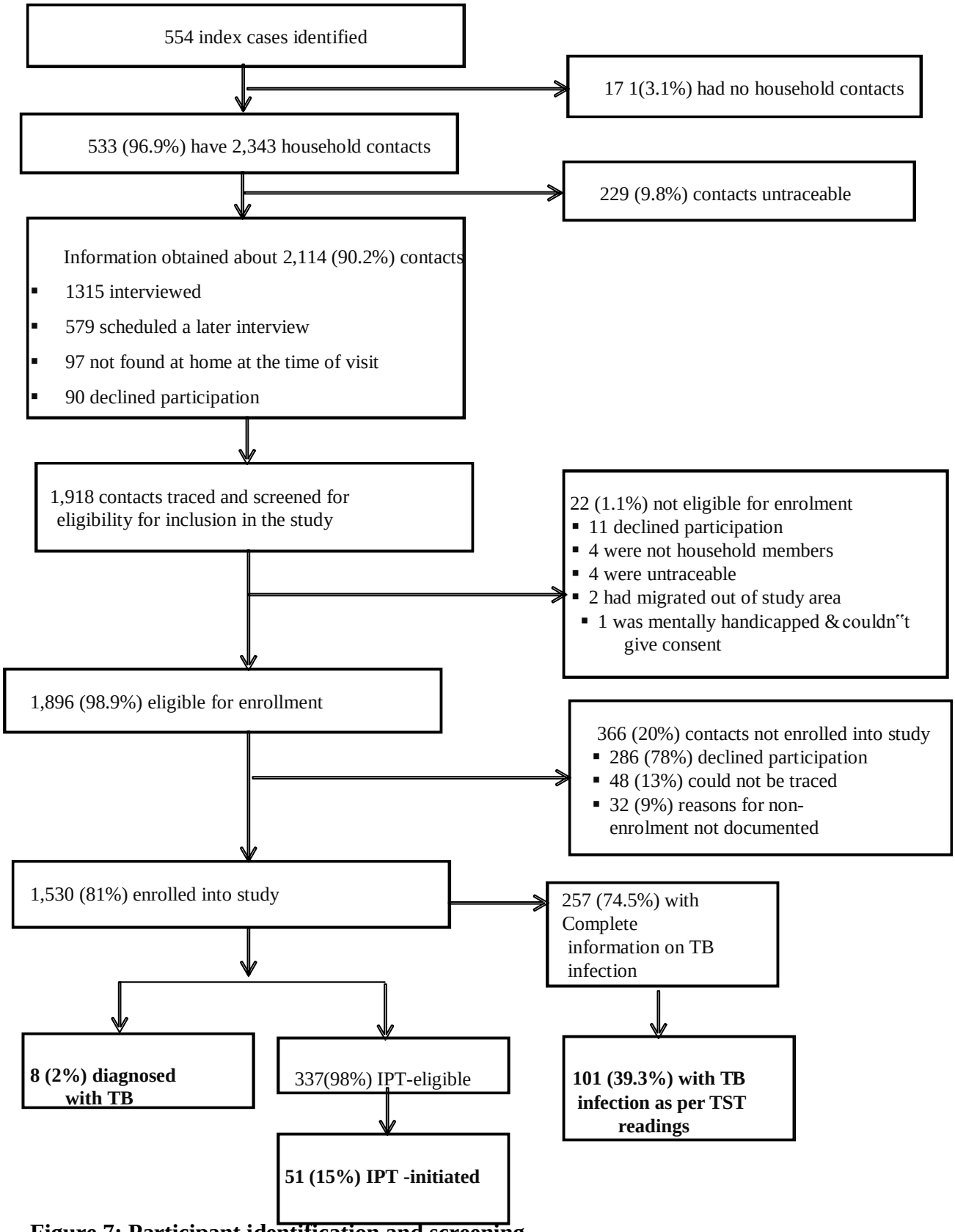


Figure 7: Participant identification and screening

CHAPTER FIVE

DISCUSSION

5.1 Introduction

This chapter discusses the results of the study. It is organized in the order to the study objectives.

5.2 The prevalence and risk factors for Tuberculosis infection among child contacts

The first objective of this study was to determine the prevalence of TB infection and contact and index case risk factors for TB infection following household exposure. Data analysis and interpretation revealed three major findings. A prevalence of TB infection of 39.3% (active and latent) was determined based on a TST cut off of 5mm. A prevalence of 2.37% of active TB was also illustrated with 37% of variability in TB infection being attributed to household factors. Hierarchical level modeling (HLM) illustrated that age of the TB index case and the TB index case presenting with cough were associated with TB infection. However, „daily duration of contact" that was significant in the single level logistic regression models, was not significant on HLM.

The prevalence of active and latent TB was 2.3% and 39.3%. In the Gambia, this was 1.6% and 15.8% for children aged less than 15 years. The Gambian study relied on microbiological diagnosis of TB infection using expectorated or induced sputum and a TST cut off of ≥10mm (Egere et al., 2017).In a prevalence survey in Malawi among high risk groups (i.e. persons who had been in household contact with a TB index case), TB prevalence was 30% using arbitrary TST cut offs of 10mm and 15mm recommended for persons who may be at risk for infection, but have no other risk factors that would increase their risk of TB infection e.g. household contact

(Khan et al., 2017). This study employed a TST cut off 5mm for positivity (Nayak & Acharjya, 2012); akin to that recommended by the American Thoracic Society for persons who are at risk of developing TB e.g. close contacts of TB patients (Taushanova, Pavlovska, & Arsevska, 2011). In Kenya, a TST cut off of 5 mm is recommended for the malnourished or HIV infected child, and 10mm for the well-nourished and or HIV negative child (DTLD, 2011b).However, not all contacts had in this study had HIV test results; neither did the study assess the effect of nutritional status.

A systematic review of contact investigation studies in low and middle income countries found a prevalence of active and latent TB of 3.1% and 51.5% respectively among household contacts (Fox et al., 2013). In New York, USA, a high income region, a systematic review of TB program data between 1997 and 2003 found a prevalence of active and latent TB of 1% and 28% respectively (Anger et al., 2012). However, routine programmatic settings in which this study was conducted reflect real life experiences and bottlenecks and therefore may provide more accurate representation of policy implementation (Tadesse et al., 2016).

There were higher TB infection rates among child contacts of TB index cases that were aged 15-45 years. Children are less contagious because they cannot generate anti-tussive force to expel microorganism (The Royal Melbourne Hospital, n.d.). Similarly, the infectiousness of TB index cases varies with the sex and age of the index case. In an assessment of the infectiousness of TB patients in the Netherlands, it was found that the infectiousness of TB index cases decreases with age. Contact investigation therefore, should not only focus on the age of the contact but also of the TB index case (Borgdorff, Nagelkerke, de Haas, & van Soolingen, 2001).

Child contacts living in households with a TB index case that had cough were more likely to have TB infection. This is because cough is promotes the aerosolization of infectious particles (Turner & Bothamley, 2014). In the literature, a longer duration of cough has been shown to increase the risk of infection in child household contacts of TB index cases (Chan et al., 2013). In an evaluation of the severity and frequency of cough and MTB strain type on TB transmission within households using a visual analogue cough scale and the Leicester Cough Questionnaire assess cough, the severity cough was associated with high transmission of TB (i.e.≥70% of contacts with TST ≥10mm). Additionally, distinct MTB strains were associated with more severe disease. The study postulated that distinct strains may cause differing patterns of cough strength and cavitation in the host leading to diverging levels of infectiousness (Salgame, Geadas, Collins, Jones-López, & Ellner, 2015).An assessment of the cough-generated aerosols for patients with Mycobacterium Tuberculosis showed that cough-generated aerosols from 25% of sputum smear positive patients were culture-positive in 25%. There was also a rapid decrease in these aerosols within the first three weeks of effective treatment. Although these aerosols showed a trend with cough frequency, this was not statistically significant (Fennelly et al., 2003). However, patients with TB generate big-aerosols during normal tidal breathing and the production of these aerosols is related to the degree of infectivity. Thus the presence of cough and smear status may not be adequate measures of infectiousness and transmission risk (Wurie, Lawn, Booth, Sonnenberg, & Hayward, 2016).

Single level logistic regression models (SLM) selected more variables that were associated with risk of infection and had narrower confidence intervals than MLM. SLM ignores the hierarchical structure of data leading to over-precision of estimates and false-positive rates (Floyd et al., 2013). It is possible for level one variable (contact variables) to vary within a cluster; however,

level 2 variables do not vary. It is possible that the effect of duration of contact will be positive in some cluster and negative in some cluster and the net effect may not be statistically significant (Sommet & Morselli, 2017). Single level logistic regression models fail to take into account that contacts are nested in homes and this may be the basis of their differences in risk of infection(Dias, Andreozzi, Martins, & Torgal, 2009).MLM improves statistical power by incorporating all information including random contact level variation and effects of the household e.g. index and contact characteristics (Yau, Lee, & Gracey, 2005). It allows for simultaneous examination of cluster level and individual level covariates (Yang et al., 2009). Variations in contact characteristics can help clinicians identify which contacts are more likely to get infected. Variations in index level characteristics can help clinicians identify from which households children are more likely to get infected. This assists in making correct inferences and valid conclusions on pertinent factors affecting the risk of infection (Yau et al., 2005).

The hierarchical model revealed a variation in risk of infection of 37% that was not attributed to any of the measured index or contact characteristics (Dias et al., 2009). This measure represents the proportion of household TB transmission that is due to between cluster variations. The higher it is, the higher the general context (Austin & Merlo, 2017). A group of contacts is exposed to the same TB index case and infectious diseases tend to cluster in space and time. Contact within a cluster also share risk factors for infection which maybe genetic, environmental or socio-economic (Floyd et al., 2013). A systematic review of household contact investigation studies conducted on children aged 0-14 years showed a variability of 20% of TB infection attributed to household infection (Martinez et al., 2017). In an investigation of age-specific risks of TB infection from household and community settings in Peru, the risk of infection increased from birth until 20 years of age. However, a large proportion of infections among children and young

adults was from household exposure. Among children aged 1 year, 10 years and 15 years, excess infection risk associated with household exposure was 58%, 48% and 44% respectively (Zelner et al., 2014). The social mobility of pre-school age children is limited to the household. As a child grows older and his social mobility increases, the likelihood of acquiring infection from non-household infection increases (Wood et al., 2010). This would argue for the importance of a targeted household contact investigation strategy in younger children (Yang et al., 2009). However, in this study"s final model, only 3.9% of infection rates could be accounted for by household factors; it is possible that the study did not collect some important index level variables that may have influenced TB transmission (Khan et al., 2017).

5.3 IPT uptake & completion rates for child household contacts not diagnosed with TB

The second objective of this study was to determine IPT uptake and completion rates of child contacts following household exposure to TB infection and the exclusion of a TB diagnosis. Data analysis and interpretation revealed three major findings. An IPT uptake rate of 15.1% and completion rate of 19.6%; IPT was more likely to be initiated where the TB index case and the IPT eligible child contact were seen at a health facility in rural region, the TB index case had sputum smear-positive TB and the child contact was a first degree relative of the index case.

The study found an IPT initiation rate of 15.1% among IPT-eligible children who had all been screened for TB, with only 20% of them completing treatment. In India, IPT initiation rates of 85% were observed child contacts in whom the index case was the parent who had received counseling from a health worker. Completion rates were not documented as IPT prescriptions had not been completed at the time of study (Belgaumkar et al., 2018). In South Africa, IPT initiation was 59% and completion was 3.7%. The low IPT initiation rates was attributed to non-

documentation of IPT as there were no formal IPT register in use and IPT card were used in its place. Low completion rates were attributed to the lack of monitoring(F. Black, Amien, & Shea, 2018). In Ethiopia, in a community health extension program, IPT initiation rates of 58% were observed due to IPT shortages. Despite this, 92% completed IPT with the main reason for non-completion being IPT shortages. The high completion rates were attributed to the delivery of IPT to homes by community health workers obviating the challenges of accessing health facilities to refill prescriptions(Datiko, Yassin, Theobald, & Cuevas, 2017).In India where IPT initiation and completion rates were 33% and 22% respectively, reasons for non-completion were long duration of treatment and stocks outs of IPT (Shivaramakrishna et al., 2014). Additionally, in this study, IPT-eligible children were recruited through a research setting and referred to the TB program for further management. Losses in the diagnostic and treatment pathway occur at any point and hamper TB control efforts (Ali et al., 2018). In the literature, poor uptake and completion rates have been attributed to attendance of different clinics by the index case and the contact, and different clinic visits schedules(Masini, Sitienei, & Weyeinga, 2013); the erratic supply of IPT and the need to adhere to a six month schedule of daily medication(Centers for Disease Control and Prevention, 2016; A. Singh et al., 2017).

IPT was more likely to be initiated where the contact was closely related to the index case (commonly a parent to the child contact). In the literature, where the index case was a parent, attendance at IPT clinics was higher. Where the index was not a parent, he or she chose not to pass the information to the parent of the child (Hall et al., 2015). In India, where65% of index cases were not informed about IPT for their child contacts by health care workers, 30% would still be unwilling to bring their child contacts for IPT since they majority (94%) were not the parent of the child and they had not disclosed their TB diagnosis to the child‟ family(Belgaumkar

et al., 2018). In Kigali, where there was 100% screening rates but only 89% IPT initiation rates, the TB index case asked the health worker to visit the home to screen the child in the absence of the parents (Birungi et al., 2018). However, in Malawi, only 8% of parents with adequate information visited the child contact clinic. This was mainly due to poor risk perception and the costs of transport and screening for the child contact (Nyirenda, Sinfield, Haves, Molyneux, & Graham, 2006).

This study revealed higher IPT initiation rates among contacts of sputum smear positive index cases. In South Africa contact screening is recommended for contacts of both smear positive and culture positive TB cases. Nevertheless, contacts of sputum smear positive TB cases had higher rates of screening compared to contacts of sputum smear negative patients (Osman et al., 2013). This is because guidelines of Kenya and South Africa countries prioritize contact screening for sputum smear positive cases who are more infectious (DTLD, Department of Health Republic of South Africa, 2014; 2011b).

IPT initiation was higher among child household contacts that resided in rural areas. Patients in high volume sites have been shown to have higher rates of pre-treatment loss to follow–up. Low volume sites are likely to be nearer patients‟ homes and patients are more likely to have a personal interaction with health workers (Thomas et al., 2018). A high patient to health worker ratio has been shown to compromise quality of care (Hughes, 2008). One of the indicators of quality of care in TB programs in the proportion of IPT eligible patients initiated on IPT (Sadaphal S, 2013). Health facilities in rural areas in Kenya have a lower patient workload than those in urban facilities and this could partly explain the better IPT initiation rates (Ministry of Health, 2017). In this study, all contacts were evaluated within a research setting and therefore did not pay for screening and transport to and from health facilities.

5.4 Yield of TB contact investigation in comparison to Contact invitation

The third objective of this study was to compare the yield of TB contact investigation to contact invitation in childhood TB control. Data analysis and interpretation revealed three major findings. The number of children diagnosed with TB increased during the intervention years compared to the pre-intervention years. During the intervention years, the number of TB cases diagnosed at health facilities that were implementing a contact investigation strategy was higher than that at health facilities implementing a contact invitation strategy. In the intervention years, health facilities implementing a contact investigation strategy had a higher number of children that were put on IPT compared to facilities implementing a contact invitation strategy.

There was an increase in number of TB cases and children put on IPT before and after the implementation of the study. In the literature, it has been established that contact investigation leads to an increase in both the number of TB cases detected among children aged less than 5 years, as well as the number of children that were put on IPT (Fox et al., 2013). Although all TB case detection strategies have also been shown increase TB case detection. Cluster randomized strategies have shown different yields between different TB case detection strategies with sometimes conflicting results. Over a four-year period, the ZAMSTAR study showed a higher decrease in TB burden among persons randomized to a household strategy compared to those randomized to a community-level enhanced case-finding strategy where health education was given (Ayles et al., 2013). Contrary to this, the DETCT TB study in Zambia showed a higher yield among persons randomized to a mobile van unit compared to a household strategy. In the literature, mobile outreach services have been known to provide a higher yield. Although the authors state that mobile unit may been associated with stigma since consultation occurs in front of others, the study did not investigate the preference for the mobile unit (Corbett et al., 2010).

A Brazilian trial also showed preference for a door-to-door strategy compared to a mobile van unit. The authors suggested that this could be due to the fact that the effect of health education may take longer to motivate community members to change their health behavior (Miller et al., 2010). These reasons apply to both household and enhanced facility screening strategies. However, it is possible that such persons may have still presented to the clinic for screening in the absence of this study (Becerra et al., 2005). A combination of these reasons may have been responsible for the increase in TB CDR in the combined strategies. However, this study was unable to track participants over a long duration to assess the impact of IPT initiation. The study did also not enquire about the preference for a specific TB case detection strategy.

The results of this study are generalizable to other TB clinics in Kenya. The clinics randomized to the intervention arm did not differ from those that were randomized to the control arm (Bruce et al., 2008). The study employed a cluster randomized controlled trial which are powerful means of measuring the effectiveness of interventions; the level of evidence generated by randomized controlled trials is ranked higher than case control or cohort studies (Fox et al., 2013). The before and after comparison allowed for an assessment of the intervention over a longer period in which changes in the TB polices and guidelines would have impacted on the outcomes in both the intervention and control arms (Younge et al., 2015). Although the difference in TB cases diagnosed did not achieve statistical significance, this was of clinical significance.

5.5 Lessons learnt when implementing standardized contact investigation

The fourth objective of this study was to document issues that would facilitate or hamper the implementation of standardized TB contact investigation in a setting with routine contact

invitation. Data analysis and interpretation revealed four major findings. Issues related to identification of contacts, completion of the TB screening cascade, database management and resource implications. These results indicate that TB programs will have to address specific issues in transitioning from routine contact invitation to standardized contact investigation.

Ninety-nine percent of contacts met the criteria for definition of household contacts and 1% (43) of potential household contacts were excluded. In Uganda, the extension of contact screening to non-household contacts that were first degree relatives of the index cases, increased the yield of contact investigation(Chheng et al., 2015). An increase in the yield of contact screening has been achieved, by extending the radius of within which to draw contacts for screening to 50 meters(Fatima et al., 2016), screening all persons sharing the same residential address and not only those who share eating arrangements(Van Wyk et al., 2012), and extension of screening to neighbors of TB index cases(Becerra et al., 2005). However, the screening of all persons who had been in contact with a TB index case in a supermarket in the Netherlands had a very low yield. Limiting the screening of contacts to those that frequented that had a longer duration of contact with the employee of the supermarket would have increased the yield of TB screening(Borgen et al., 2008). As only 5-15% of those exposed to TB cases will develop TB, only those who are symptomatic or at most risk of HIV infection should be investigated for TB (Cain et al., 2010).

Four percent (4%) of contacts declined participation. Compliance or adherence to screening among contacts in Ethiopia was only 34%. Higher compliance rates were seen among contacts who were related to the TB index case and had received health education from a health worker on TB (Gebregergs & Alemu, 2015). TB index case may have no influence on screening and treatment decisions of contacts that were not related to them (Szkwarko, Ogaro, Owiti, & Carter,

2013). In Peru, 2% of households of TB index cases declined participation (Becerra et al., 2005). In a separate study in China, 15% of contacts did not consent to participation (Nair et al., 2016).This study, as well as the study in Peru and China, did not compare those who declined to those who consented to participate. With a 4% declination rates and based on a prevalence of active TB and LTBI of 3.1% and 45% respectively among household contacts in low and middle income countries, a refusal rate of 4% (n=84) potentially translates to 3 and 39 cases of active TB and LTBI respectively who remain diagnosed (Fox et al., 2015).

The success of TB household contact investigation depends on the willingness of TB index cases and their household contact to participate(Fox et al., 2015). The willingness of a TB index case to allow for the screening for his close contacts implies the disclosure of a TB diagnosis(Oliveira et al., 2017). Declination to participate may be linked to the stigma associated with TB and the communities‟ perceived link between TB and HIV (Skinner & Claassens, 2016). Due to the high TB/HIV co-infection rate in the region where this study was conducted, disclosing a TB diagnosis is akin to the disclosure of a HIV diagnosis (Fox et al., 2015). The rights to decline participation in a research setting are well defined (NIH,2016). Contacts therefore maybe regarded as "TB suspects‟ by the TB program as they likely to have TB and are thus potentially infectious (DTLD, 2011b). There exist Laws and regulations regarding the management of persons with notifiable diseases which may be applied to compel contacts to present themselves for screening (like TB) (Gorzoni, Aguado, Pires, & Faria, 2017). However, such public health laws may infringe on individualism (Burmen, Mogunde, & Kwaro, 2017).

A high TB screening rate and low TB diagnostic rates was observed household contacts of TB index cases. The screening rates of 90% documented in this study (a research setting), were higher than those documented in a programmatic setting in Ethiopia where only 55% of the

contacts were screened(Ramos, Biru, Tesfamariam, Reyes, & Górgolas, 2013). Screening rates of over 90% with diagnostic rates of 3% have been observed in Kenya among HIV infected patients. This was due to limited diagnostic capacity at health facilities and the use of screening tests with low sensitivity and specificity (Burmen et al., 2015). Screening rates of 72% and 60% among household contacts and neighbors of TB index cases who presented with cough were seen in Peru where sputum samples were used for screening. Nevertheless, children aged less than 10 years were less likely to give sputum samples. TB programs should provide innovative case detection methods for children(Becerra et al., 2005).

The data demands for this study were huge and complex. At the time of the study there were no tools to support TB contact investigation within routine clinical care. In India, the introduction of linked IPT family cards and IPT registers, supported by health worker training, led to a three- fold increase in the proportion of contacts screened for TB. Health workers reported that the documents were easy to complete and they helped them complete their tasks according to programmatic guidelines (Banu Rekha et al., 2009). In the literature, paper-based tools having been used to implement TB contact investigation with success(Adjobimey et al., 2016). The regular monitoring and evaluation of programmatic activities has been shown to facilitate the effective implementation of TB programmatic activities(Marais, 2017). However, the use of a relational database would be preferable as it can turn disparate pieces of information into a valuable resource(Banu Rekha et al., 2009). In addition, an electronic database supported by a clinical decision support system would be more efficient and effective in monitoring this kind of data(Oluoch et al., 2015).

This study would not have been possible without external funding to support contact investigation, an activity that already exists within polices of the country‟s TB program. The

costs of tracing and screening tracking all contacts will vary based on, the TB burden and the average number of contacts per case (Yassin et al., 2013). With a TB burden of 348 per 100,000 (WHO, 2017)and most an average of 4.2 members per household in Kenya, the TB programs will have to screen a higher number of contacts than in low TB burden sparsely populated regions(KNBS, 2015). In Benin where TB contact investigation was conducted successfully, only 23% of TB index cases had a child contact compared to 44% in this study(Adjobimey et al., 2016).

This study illustrated a TB index case to child household contact ratio of 1.5:1. Investigators in India computed the ratio of sputum positive TB index cases to child contacts and found an index contact ratio of 5:1. This was done to assist in estimating the number of IPT-eligible child contacts in a region. This ratio however, has to consider the mean age of the TB index cases. The mean age of TB index cases in our study was 32 years. This was 15 years lower than the mean age of smear positive patients in India (mean age 46 years) where the majority did not have child contact aged less than 6 years (Pothukuchi et al., 2011). The WHO and Kenyan TB treatment recommend that for every TB case diagnosed, at least one child contact aged less than 5 years be initiated on IPT(WHO, 2012). It is possible that this ratio may have been higher if there was better referral and linkage between the study teams and the TB program after excluding a TB diagnosis among child contacts.

In a TB clinic in a different region in Kenya, the screening of child contacts of TB patients was hampered by the costs of transport, chest x-ray and facility registration that had to be borne by the patient. This is because such costs are higher than the daily wage of most patients in Kenya(Szkwarko et al., 2013). Although research has shown that the absence of Chest x-rays and TST should not be a deterrent to screening and management of children(Adjobimey et al., 2016).

This will require clear guidelines on long term monitoring of contacts who initially screen negative for TB(Moore, 2016). Contact investigation is resource intensive (Ramos et al., 2013). It also requires a huge investment in infrastructural support (Adjobimey et al., 2016).

5.6 Study Limitations

It is possible that the yield of screening this study may have been higher if we were able to recruit more TB index cases and all their household contacts into the study, including those who declined to participate or were untraceable, or had migrated outside the study area. An inability to screen persons who migrated out of the study area or declined participation, may have contributed to a lower yield.

Because we had to rely on programmatic data to identify child contacts that were received IPT, difficulties were experienced in matching the research study database to those in the TB program registers and matching may have been incomplete. TB IPT initiation had just been launched within the TB program; the program personnel may have not included all the names of persons on IPT in the registers. This implies that IPT initiation and completion rates may be under-estimated.

Due to the limited numbers of children diagnosed with children within each specific strategy, we were unable to make a direct comparison of the yield of different TB case detection strategies when compared with the standard approach. Although the health facilities were not balanced in terms or rural and urban distribution, this was not a basis for comparison of study outcomes. Therefore further analysis on the effect of balance was not conducted(Festic et al., 2016).

Although document analysis draws its strength from countering concerns related to reflexivity, as the information recorded is not under the researchers control; the information collected may have been incomplete and the study was unable to triangulate qualitative findings through other qualitative data collection methods that would have enriched study findings (Bowen, 2009). However, priority and a higher weight was assigned to quantitative data that was used to analyze the main research question (Morgan, 1998).

CHAPTER SIX

SUMMARY OF FINDINGS, CONCLUSIONS AND RECOMMENDATIONS

6.1 Summary of findings

A prevalence of TB infection of 39.3% with a higher prevalence among contacts of TB index cases aged 15-45 years who presented with cough. Among contacts who were not diagnosed with TB, 15.1% received IPT with 19.6% completing IPT. IPT was more likely to be initiated where the TB index case and the child contact were seen at a health facility in rural region, the TB index case had sputum smear positive TB and the child contacts was a first degree relatives of the index case. The number of children diagnosed with TB increased during the intervention years compared to the pre-intervention years. During the intervention years, health facilities that were implementing a contact investigation strategy had a higher number of TB cases diagnosed and children who receiving IPT. TB programs ought to consider issues related to identification of contacts, completion of the TB screening cascade, database management and resource implications in transitioning from routine contact invitation to standardized contact investigation.

6.2 Conclusions

TB household contact investigation identified children in need of TB preventive and curative Therapy. Through Hierarchical level modeling, the study identified pertinent risk factors with clustering and the household level that increased the risk of TB infection that could be targeted for contact investigation. This supports household contact investigation as a good strategy for TB control in children.

There is a large number of child contacts who are exposed to TB index cases. With 39.3% having LTBI and the TB guidelines recommending IPT initiation for all contacts who screen negative for TB, low IPT uptake & completion rates negated intended benefits of identifying children in need of preventative therapy

Contact investigation provided the dual benefit of increasing TB case detection & opportunity to provide IPT and therefore impacting the burden of TB in childhood in Kisumu County. Timely TB diagnosis contributes to better treatment outcomes and therefore a decrease in morbidity and mortality from TB. TB prevention therapy contributes to a decrease in TB incidence and prevalence. Together, these two contribute to TB control in childhood.

Considerable resource investment required to implement contact investigation. This includes costs of tracing a large number of household contacts in high-TB burden densely populated settings; availing all the necessary point of care diagnostics and continued supply of preventive medication. These costs would also include costs of supporting the monitoring and evaluation of this program which is vital to the success of TB program. TB programs are faced with a large number of household contacts eligible for TB screening in this high TB burden setting who may not only be difficult to trace but also may be unwilling to undergo screening or adhere to preventive medication prescribed.

6.3 Recommendations

6.3.1 Recommendations from this study

TB programs should implement TB Contact investigation among child household members; a targeted approach may be employed using specific characteristics that are associated with a

higher risk for infection as shown in this study. Clinicians may opt for watchful waiting with patient education among child household contacts that are at a lower risk of TB infection.

Due to a high proportion of LTBI in this population, in the absence of TST, IPT administration should be recommended among child household contacts among whom TB has been excluded. Health education should be provided to TB patients and their families, and the general population, understand the increased risk of contracting TB among children, and the increased risk of TB progression once infected, and the importance of IPT prophylaxis.

To optimize the effectiveness of household TB contact investigation, the TB program ought to avail of all the required infrastructures at all points of the screening and treatment cascade (point of care TB diagnostic facilities and continuous supply of Isoniazid at no cost) based on the TB burden and number of persons in households in different regions. The TB program also ought to avail job aids and monitoring tools to support contact investigation and initiation of preventive or curative therapy.

Contact investigation may be implemented within existing community health systems that already have existing household registers, with a possibility of home screening and delivery of isoniazid to limit costs programmatic costs. Health workers should be provided with job aids to facilitate the completion of the TB screening cascade. An electronic relational database, with linked IPT and TB registers, ingrained with a clinical decision support system should be used to aid the monitoring of index case-contact dyads that should have synchronized clinic appointment schedules. Retrospective contact investigation could also be employed due to the possibility of finding incident cases of TB. This would address the large number of household contacts eligible for TB screening.

6.3.2 Recommendations for further research

Further research should be conducted to: Determine specific characteristics of cough that increase infectiousness of the TB index case; Conduct long-term monitoring and evaluation of IPT uptake rates, completion rates and treatment outcomes among child household contacts; Investigate acceptable and high-yield TB case finding strategies; and assess the actual costs of contact investigation incurred by patients and their families and the TB program.

REFERENCES

Adetifa, I. M., Ota, M. O., Jeffries, D. J., Hammond, A., Lugos, M. D., & Donkor, S. (2010). Commercial interferon gamma release assays compared to the tuberculin skin test for diagnosis of latent Mycobacterium tuberculosis infection in childhood contacts in the Gambia. *Pediatr Infect Dis J, 29*. doi:10.1097/INF.0b013e3181cb45da

Adjobimey, M., Masserey, E., Adjonou, C., Gbénagnon, G., Schwoebel, V., Anagonou, S., & Zellweger, J. P. (2016). Implementation of isoniazid preventive therapy in children aged under 5 years exposed to tuberculosis in Benin. *Int J Tuberc Lung Dis, 20*(8), 1055-1059. doi:10.5588/ijtld.15.0493

Aissa, K., Madhi, F., Ronsin, N., Delarocque, F., Lecuyer, A., Decludt, B., . . . Group, C. G. S. (2008). Evaluation of a model for efficient screening of tuberculosis contact subjects. *Am J Respir Crit Care Med, 177*(9), 1041-1047. doi:10.1164/rccm.200711-1756OC

Ali, S. M., Naureen, F., Noor, A., Fatima, I., Viney, K., Ishaq, M., . . . Aamir, J. (2018). Loss-to-follow-up and delay to treatment initiation in Pakistan's national tuberculosis control programme. *BMC Public Health, 18*(1), 335-335. doi:10.1186/s12889-018-5222-2

American Thoracic Society. (2000). Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. *Am J Respir Crit Care Med, 161*(4 Pt 2), S221-247. doi:10.1164/ajrccm.161.supplement_3.ats600

Anger, H. A., Proops, D., Harris, T. G., Li, J., Kreiswirth, B. N., Shashkina, E., & Ahuja, S. D. (2012). Active case finding and prevention of tuberculosis among a cohort of contacts exposed to infectious tuberculosis cases in New York City. *Clin Infect Dis, 54*(9), 1287-1295. doi:10.1093/cid/cis029

Armbruster, B., & Brandeau, M. L. (2007). Contact tracing to control infectious disease: when enough is enough. *Health care management science, 10*(4), 341-355.

Austin, P. C., & Merlo, J. (2017). Intermediate and advanced topics in multilevel logistic regression analysis. *Stat Med, 36*(20), 3257-3277. doi:10.1002/sim.7336

Ayles, H., Muyoyeta, M., Du Toit, E., Schaap, A., Floyd, S., Simwinga, M., . . . team, Z. (2013). Effect of household and community interventions on the burden of tuberculosis in

southern Africa: the ZAMSTAR community-randomised trial. *Lancet, 382*(9899), 1183- 1194. doi:10.1016/S0140-6736(13)61131-9

Azman, A. S., Golub, J. E., & Dowdy, D. W. (2014). How much is tuberculosis screening worth? Estimating the value of active case finding for tuberculosis in South Africa, China, and India. *BMC Med, 12*, 216. doi:10.1186/s12916-014-0216-0

Banu Rekha, V. V., Jagarajamma, K., Wares, F., Chandrasekaran, V., & Swaminathan, S. (2009). Contact screening and chemoprophylaxis in India's Revised Tuberculosis Control Programme: a situational analysis. *Int J Tuberc Lung Dis, 13*(12), 1507-1512.

Becerra, M. C., Pachao-Torreblanca, I. F., Bayona, J., Celi, R., Shin, S. S., Kim, J. Y., . . . Murray, M. (2005). Expanding tuberculosis case detection by screening household contacts. *Public Health Rep, 120*(3), 271-277. doi:10.1177/003335490512000309

Belgaumkar, V., Chandanwale, A., Valvi, C., Pardeshi, G., Lokhande, R., Kadam, D., . . . Bollinger, R. C. (2018). Barriers to screening and isoniazid preventive therapy for child contacts of tuberculosis patients. *Int J Tuberc Lung Dis, 22*(10), 1179-1187. doi:10.5588/ijtld.17.0848

Bell BA, One M, Smiley W, & Schoeneberger JA. (April 28-May 2013). *A Multilevel Model Primer using SAS PROC MIXED.* Paper presented at the SAS Global Forum, Moscone West San Franscisco.

Bell, B. A., One, M., Smiley, W., & Schoeneberger, J. A. (2013). *A Multilevel Model Primer using SAS PROC MIXED.* Paper presented at the SAS Global Forum, Moscone West San Franscisco.

Bengtsson, M. (2016). How to plan and perform a qualitative study using content analysis. *NursingPlus Open, 2*, 8-14. doi:https://doi.org/10.1016/j.npls.2016.01.001

Benjamin, I. J., Griggs, R. C., Wing, E. J., & Fitz, J. G. (2016). *Andreoli and Carpenter's Cecil essentials of medicine* (9th edition. ed.). Philadelphia, PA: Elsevier/Saunders.

Birungi, F. M., Graham, S., Uwimana, J., & van Wyk, B. (2018). Assessment of the Isoniazid Preventive Therapy Uptake and Associated Characteristics: A Cross-Sectional Study. *Tuberculosis research and treatment, 2018*, 8690714-8690714. doi:10.1155/2018/8690714

Black, F., Amien, F., & Shea, J. (2018). An assessment of the isoniazid preventive therapy programme for children in a busy primary healthcare clinic in Nelson Mandela Bay

Health District, Eastern Cape Province, South Africa. *S Afr Med J, 108*(3), 217-223. doi:10.7196/SAMJ.2018.v108i3.12639

Black, W., Haggstrom, D., & Gilbert Welch, H. (2002). All-Cause Mortality in Randomized Trials of Cancer Screening. *JNCI: Journal of the National Cancer Institute, 94*(3), 167-173. doi:10.1093/jnci/94.3.167

Blower, S. M., McLean, A. R., Porco, T. C., Small, P. M., Hopewell, P. C., Sanchez, M. A., & Moss, A. R. (1995). The intrinsic transmission dynamics of tuberculosis epidemics. *Nat Med, 1*(8), 815-821.

Borgdorff, M. W. (2004). New measurable indicator for tuberculosis case detection. *Emerg Infect Dis, 10*(9), 1523-1528. doi:10.3201/eid1009.040349

Borgdorff, M. W., Nagelkerke, N. J., de Haas, P. E., & van Soolingen, D. (2001). Transmission of Mycobacterium tuberculosis depending on the age and sex of source cases. *Am J Epidemiol, 154*(10), 934-943.

Borgen, K., Koster, B., Meijer, H., Kuyvenhoven, V., van der Sande, M., & Cobelens, F. (2008). Evaluation of a large-scale tuberculosis contact investigation in the Netherlands. *Eur Respir J, 32*(2), 419-425. doi:10.1183/09031936.00136607

Bos, J. C., Smalbraak, L., Macome, A. C., Gomes, E., van Leth, F., & Prins, J. M. (2013). TB diagnostic process management of patients in a referral hospital in Mozambique in comparison with the 2007 WHO recommendations for the diagnosis of smear-negative pulmonary TB and extrapulmonary TB. *Int Health, 5*(4), 302-308. doi:10.1093/inthealth/iht025

Bowen, G. (2009). *Document Analysis as a Qualitative Research Method* (Vol. 9).

Brewer, J., & Hunter, A. (1989). *Multimethod research : a synthesis of styles*. Newbury Park, Calif. ; London: Sage.

Broeck, J. v. d., & Brestoff, J. R. (2013). *Epidemiology : principles and practical guidelines*. Dordrecht ; London: Springer.

Bruce, N. G. (2008). *Quantitative methods for health research : a practical interactive guide to epidemiology and statistics*. Chichester: John Wiley.

Bruce, N. G., Pope, C., & Stanistreet, D. (2008). *Quantitative methods for health research: A practical interactive guide to epidemiology and statistics*. Chichester: John Wiley.

Burmen, B., Modi, S., Cavanaugh, J., Muttai, H., McCarthy, K., Alexander, H., & Cain, K. (2015). Tuberculosis screening outcomes for newly diagnosed persons living with HIV, Nyanza Province, Kenya, 2009. *Int J Tuberc Lung Dis, 20*(1), 79-84. doi:10.5588/ijtld.15.0053

Burmen, B., Mogunde, J., & Kwaro, D. (2017). Ethically providing routine HIV testing services to bereaved populations. *Nursing Ethics*. doi:10.1177/0969733017693442

Bursac, Z., Gauss, C. H., Williams, D. K., & Hosmer, D. W. (2008). Purposeful selection of variables in logistic regression. *Source Code Biol Med, 3*, 17. doi:10.1186/1751-0473-3-17

Cabana, M. D., Rand, C. S., Powe, N. R., Wu, A. W., Wilson, M. H., Abboud, P. A., & Rubin, H. R. (1999). Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA, 282*(15), 1458-1465.

Cain, K. P., McCarthy, K. D., Heilig, C. M., Monkongdee, P., Tasaneeyapan, T., Kanara, N., . . . Varma, J. K. (2010). An algorithm for tuberculosis screening and diagnosis in people with HIV. *N Engl J Med, 362*(8), 707-716. doi:10.1056/NEJMoa0907488

Capanu, M., Orlow, I., Berwick, M., Hummer, A. J., Thomas, D. C., & Begg, C. B. (2008). The use of hierarchical models for estimating relative risks of individual genetic variants: an application to a study of melanoma. *Stat Med, 27*(11), 1973-1992. doi:10.1002/sim.3196

Cavanaugh, J. S., Modi, S., Musau, S., McCarthy, K., Alexander, H., Burmen, B., . . . Cain, K. (2016). Comparative Yield of Different Diagnostic Tests for Tuberculosis among People Living with HIV in Western Kenya. *PLOS ONE, 11*(3), e0152364. doi:10.1371/journal.pone.0152364

Centers for Disease Control and Prevention. (2016). Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. Retrieved from https://www.cdc.gov/tb/publications/ltbi/treatment.htm

Chafe, R. (2017). The Value of Qualitative Description in Health Services and Policy ResearchValeur de la description qualitative dans la recherche sur les politiques et services de santé. *Healthcare policy = Politiques de sante, 12*(3), 12-18.

Chakhaia, T., Magee, M. J., Kempker, R. R., Gegia, M., Goginashvili, L., Nanava, U., & Blumberg, H. M. (2014). High Utility of Contact Investigation for Latent and Active Tuberculosis Case Detection among the Contacts: A Retrospective Cohort Study in

Tbilisi, Georgia,2010–2011.*PLOS ONE*, *9*(11), e111773. doi:10.1371/journal.pone.0111773

Chan, P.-C., Shinn-Forng Peng, S., Chiou, M.-Y., Ling, D.-L., Chang, L.-Y., Wang, K.-F., . . . Huang, L.-M. (2013). Risk for Tuberculosis in Child Contacts. Development and Validation of a Predictive Score. *Am J Respir Crit Care Med, 189*(2), 203-213. doi:10.1164/rccm.201305-0863OC

Chheng, P., Nsereko, M., Malone, L. L., Okware, B., Zalwango, S., Joloba, M., . . . Stein, C. M. (2015). Tuberculosis case finding in first-degree relative contacts not living with index tuberculosis cases in Kampala, Uganda. *Clin Epidemiol, 7*, 411-419. doi:10.2147/CLEP.S82389

Clark, M., Riben, P., & Nowgesic, E. (2002). The association of housing density, isolation and tuberculosis in Canadian First Nations communities. *Int J Epidemiol, 31*(5), 940-945.

Coetzee, D., Hilderbrand, K., Goemaere, E., Matthys, F., & Boelaert, M. (2004). Integrating tuberculosis and HIV care in the primary care setting in South Africa. *Trop Med Int Health, 9*(6), A11-15. doi:10.1111/j.1365-3156.2004.01259.x

Corbett, E. L., Bandason, T., Duong, T., Dauya, E., Makamure, B., Churchyard, G. J., . . . Hayes, R. J. (2010). Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. *Lancet, 376*(9748), 1244-1253. doi:10.1016/s0140-6736(10)61425-0

County Government of Kisumu. (2013). Kisumu County: First County Integrated Development Plan 2013-2017. Retrieved from file:///C:/Users/Burmen/Downloads/Kisumu%20County%20Integrated%20Development%20Plan.pdf

Dai, J., Li, Z., & Rocke, D. (2006). *Hierarchical logistic regression modeling with SAS GLIMMIX*.

Datiko, D. G., Yassin, M. A., Theobald, S. J., & Cuevas, L. E. (2017). A community-based isoniazid preventive therapy for the prevention of childhood tuberculosis in Ethiopia. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 21*(9), 1002-1007. doi:10.5588/ijtld.16.0471

Department of Health Republic of South Africa. (2014). National Tuberculosis Management Guidelines. Retrieved from http://www.tbonline.info/media/uploads/documents/ntcp_adult_tb-guidelines-27.5.2014.pdf

Dias, S. S., Andreozzi, V., Martins, M. O., & Torgal, J. (2009). Predictors of mortality in HIV-associated hospitalizations in Portugal: a hierarchical survival model. *BMC Health Serv Res, 9*, 125. doi:10.1186/1472-6963-9-125

Division of Leprosy Tuberculosis and Lung Diseases Program. (2011a). *Annual Report 2010*. Retrieved from https://www.nltp.co.ke/annual-reports/.

Division of Leprosy Tuberculosis and Lung Diseases Program. (2011b). *National Paediatric Tuberculosis Care Guidelines*. Nairobi Kenya: Division of Leprosy, Tuberculosis and Lung Diseases.

Division of Leprosy Tuberculosis and Lung Diseases Program. (2012). *Annual Report 2011*. Retrieved from https://www.nltp.co.ke/annual-reports/.

Division of Leprosy Tuberculosis and Lung Diseases Program. (2013a). *Annual Report 2012*. Retrieved from https://www.nltp.co.ke/annual-reports/#.

Division of Leprosy Tuberculosis and Lung Diseases Program. (2013b). *Guidelines for Management of Tuberculosis and Leprosy in Kenya*. Retrieved from http://guidelines.health.go.ke:8000/media/TB_Treatment_GUIDELINES_2013.pdf.

Dowdle, W. R. (1998). The principles of disease elimination and eradication. *Bulletin of the World Health Organization, 76 Suppl 2*(Suppl 2), 22-25.

Dowdy, D. W., Basu, S., & Andrews, J. R. (2012). Is passive diagnosis enough? The impact of subclinical disease on diagnostic strategies for tuberculosis. *Am J Respir Crit Care Med, 187*(5), 543-551. doi:10.1164/rccm.201207-1217OC

Dye, C., Hosseini, M., & Watt, C. (2007). Did we reach the 2005 targets for tuberculosis control? *Bull World Health Organ, 85*(5), 364-369.

Egere, U., Togun, T., Sillah, A., Mendy, F., Otu, J., Hoelscher, M., . . . Kampmann, B. (2017). Identifying children with tuberculosis among household contacts in The Gambia. *Int J Tuberc Lung Dis, 21*(1), 46-52. doi:10.5588/ijtld.16.0289

Eisenberg, R. L., & Pollock, N. R. (2010). Low Yield of Chest Radiography in a Large Tuberculosis Screening Program. *Radiology, 256*(3), 998-1004. doi:10.1148/radiol.10100485

Elliott, A. M., Hayes, R. J., Halwiindi, B., Luo, N., Tembo, G., Pobee, J. O., . . . McAdam, K. P. (1993). The impact of HIV on infectiousness of pulmonary tuberculosis: a community study in Zambia. *AIDS, 7*(7), 981-987.

Ene, M., Leighton, E. A., Blue, G. L., & Bell, B. A. (2014). *Multilevel Models for Categorical Data using SAS PROC GLIMMIX: The basics*. Paper presented at the The SouthEast SAS Users Group (SESUG) Conference 2014, Embassy Suites Myrtle Beach SC. https://pdfs.semanticscholar.org/a216/864a2a2de19eb194c6523fb8566e601ffa32.pdf

Erkens, C. G., Kamphorst, M., Abubakar, I., Bothamley, G. H., Chemtob, D., Haas, W., . . . Lange, C. (2010). Tuberculosis contact investigation in low prevalence countries: a European consensus. *Eur Respir J, 36*(4), 925-949. doi:10.1183/09031936.00201609

Esmail, H., Barry, C. E., 3rd, Young, D. B., & Wilkinson, R. J. (2014). The ongoing challenge of latent tuberculosis. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 369*(1645), 20130437-20130437. doi:10.1098/rstb.2013.0437

Esmail, H., Dodd, P. J., & Houben, R. (2018). Tuberculosis transmission during the subclinical period: could unrelated cough play a part? *Lancet Respir Med, 6*(4), 244-246. doi:10.1016/s2213-2600(18)30105-x

Espinal, M. A., Peréz, E. N., Baéz, J., Hénriquez, L., Fernández, K., Lopez, M., . . . Reingold, A. L. (2000). Infectiousness of Mycobacterium tuberculosis in HIV-1-infected patients with tuberculosis: a prospective study. *Lancet, 355*(9200), 275-280. doi:10.1016/S0140-6736(99)04402-5

Fatima, R., Qadeer, E., Yaqoob, A., Haq, M. U., Majumdar, S. S., Shewade, H. D., . . . Kumar, A. M. (2016). Extending 'Contact Tracing' into the Community within a 50-Metre Radius of an Index Tuberculosis Patient Using Xpert MTB/RIF in Urban, Pakistan: Did It Increase Case Detection? *PLOS ONE, 11*(11), e0165813. doi:10.1371/journal.pone.0165813

Fennelly, K. P., Martyny, J. W., Fulton, K. E., Orme, I. M., Cave, D. M., & Heifets, L. B. (2003). Cough-generated aerosols of Mycobacterium tuberculosis: a new method to study infectiousness. *Am J Respir Crit Care Med, 169*(5), 604-609. doi:10.1164/rccm.200308-1101OC

Festic, E., Rawal, B., & Gajic, O. (2016). How to improve assessment of balance in baseline characteristics of clinical trial participants-example from PROSEVA trial data? *Annals of translational medicine, 4*(4), 79-79. doi:10.3978/j.issn.2305-5839.2016.01.30

Fetters, M. D., & Freshwater, D. (2015). Publishing a Methodological Mixed Methods Research Article. *Journal of Mixed Methods Research, 9*(3), 203-213. doi:10.1177/1558689815594687

Floyd, S., Sismanidis, C., Yamada, N., Daniel, R., Lagahid, J., Mecatti, F., . . . Floyd, K. (2013). Analysis of tuberculosis prevalence surveys: new guidance on best-practice methods. *Emerging Themes in Epidemiology, 10*, 10-10. doi:10.1186/1742-7622-10-10

Fox, G. J., Barry, S. E., Britton, W. J., & Marks, G. B. (2013). Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J, 41*(1), 140-156. doi:10.1183/09031936.00070812

Fox, G. J., Loan, l. P., Nhung, N. V., Loi, N. T., Sy, D. N., Britton, W. J., & Marks, G. B. (2015). Barriers to adherence with tuberculosis contact investigation in six provinces of Vietnam: a nested case-control study. *BMC Infect Dis, 15*, 103. doi:10.1186/s12879-015-0816-0

Ganmaa, D., Khudyakov, P., Buyanjargal, U., Jargalsaikhan, B., Baigal, D., Munkhjargal, O., . . . Martineau, A. R. (2018). Prevalence and determinants of QuantiFERON-diagnosed tuberculosis infection in 9,810 Mongolian schoolchildren. *Clin Infect Dis*. doi:10.1093/cid/ciy975

Garg, R. (2016). Methodology for research I. *Indian journal of anaesthesia, 60*(9), 640-645. doi:10.4103/0019-5049.190619

Gebregergs, G. B., & Alemu, W. G. (2015). Household Contact Screening Adherence among Tuberculosis Patients in Northern Ethiopia. *PLOS ONE, 10*(5), e0125767-e0125767. doi:10.1371/journal.pone.0125767

Getahun, H., Kittikraisak, W., Heilig, C. M., Corbett, E. L., Ayles, H., Cain, K. P., . . . Varma, J. K. (2011). Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med, 8*(1), e1000391. doi:10.1371/journal.pmed.1000391

Glaziou, P., Sismanidis, C., Floyd, K., & Raviglione, M. (2015). Global epidemiology of tuberculosis. *Cold Spring Harbor perspectives in medicine, 5*(2), a017798-a017798. doi:10.1101/cshperspect.a017798

Golub, J. E., Cohn, S., Saraceni, V., Cavalcante, S. C., Pacheco, A. G., Moulton, L. H., . . . Chaisson, R. E. (2015). Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. *Clin Infect Dis, 60*(4), 639-645. doi:10.1093/cid/ciu849

Gomes, V. F., Andersen, A., Lemvik, G., Wejse, C., Oliveira, I., Vieira, F. J., . . . Gustafson, P. (2013). Impact of isoniazid preventive therapy on mortality among children less than 5 years old following exposure to tuberculosis at home in Guinea-Bissau: a prospective cohort study. *BMJ Open, 3*(3). doi:10.1136/bmjopen-2012-001545

Gorzoni, M. L., Aguado, M. R. V., Pires, S. L., & Faria, L. F. C. (2017). Compulsory notification at skilled nursing facilities. *Rev Assoc Med Bras (1992), 63*(5), 447-451. doi:10.1590/1806-9282.63.05.447

Graham, S. M., Ahmed, T., Amanullah, F., Browning, R., Cardenas, V., & Casenghi, M. (2012). Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. *J Infect Dis, 205*. doi:10.1093/infdis/jis008

Graham, S. M., Gie, R. P., Schaaf, H. S., Coulter, J. B., Espinal, M. A., & Beyers, N. (2004). Childhood tuberculosis: clinical research needs. *Int J Tuberc Lung Dis, 8*(5), 648-657.

Guetterman, T. C., Fetters, M. D., & Creswell, J. W. (2015). Integrating Quantitative and Qualitative Results in Health Science Mixed Methods Research Through Joint Displays. *Ann Fam Med, 13*(6), 554-561. doi:10.1370/afm.1865

Guwatudde, D., Nakakeeto, M., Jones-Lopez, E. C., Maganda, A., Chiunda, A., Mugerwa, R. D., . . . Whalen, C. C. (2003). Tuberculosis in household contacts of infectious cases in Kampala, Uganda. *Am J Epidemiol, 158*(9), 887-898.

Hall, C., Sukijthamapan, P., dos Santos, R., Nourse, C., Murphy, D., Gibbons, M., & Francis, J. R. (2015). Challenges to delivery of isoniazid preventive therapy in a cohort of children exposed to tuberculosis in Timor-Leste. *Trop Med Int Health, 20*(6), 730-736. doi:10.1111/tmi.12479

Heale, R., & Forbes, D. (2013). Understanding triangulation in research. *Evid Based Nurs, 16*(4), 98. doi:10.1136/eb-2013-101494

Herchline, T. E., & Amorosa, J. K. (2017). Tuberculosis. Retrieved from https://emedicine.medscape.com/article/230802-overview

Houben, R. M. G. J., & Dodd, P. J. (2016). The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLOS Medicine, 13*(10), e1002152. doi:10.1371/journal.pmed.1002152

Hughes, R. (2008). *Patient Safety and Quality: An Evidence-Based Handbook for Nurses*.

Issel, L. M. (2004). *Health program planning and evaluation : a practical, systematic approach for community health*. Sudbury, Mass. ; London: Jones and Bartlett Publishers.

Jasmer, R. M., Nahid, P., & Hopewell, P. C. (2002). Clinical practice. Latent tuberculosis infection. *N Engl J Med, 347*(23), 1860-1866. doi:10.1056/NEJMcp021045

Katoch, V. M. (2004). Infections due to non-tuberculous mycobacteria (NTM). *Indian J Med Res, 120*(4), 290-304.

Kay, A. W., Islam, S. M., Wendorf, K., Westenhouse, J., & Barry, P. M. (2018). Interferon-gamma Release Assay Performance for Tuberculosis in Childhood. *Pediatrics, 141*(6). doi:10.1542/peds.2017-3918

Kenya Law. (2010). *Constitution of Kenya*. Retrieved from www.kenyalaw/org/lex/actview.xql?actid=Const2010.

Kenya National Bureau of Statistics. (2010). 2009 Population and Housing Census. Retrieved from https://www.knbs.or.ke/publications/

Kenya National Bureau of Statistics. (2015). *Kenya Demographic and Health Survey 2014*. Nairobi Kenya: Kenya National Bureau of Statistics Retrieved from https://dhsprogram.com/pubs/pdf/fr308/fr308.pdf.

Khan, P. Y., Glynn, J. R., Mzembe, T., Mulawa, D., Chiumya, R., Crampin, A. C., . . . Fielding, K. L. (2017). Challenges in the Estimation of the Annual Risk of Mycobacterium tuberculosis Infection in Children Aged Less Than 5 Years. *Am J Epidemiol, 186*(8), 1015-1022. doi:10.1093/aje/kwx153

Kumar, S., Quinn, S. C., Kim, K. H., Musa, D., Hilyard, K. M., & Freimuth, V. S. (2011). The social ecological model as a framework for determinants of 2009 H1N1 influenza vaccine uptake in the United States. *Health education & behavior : the official publication of the Society for Public Health Education, 39*(2), 229-243. doi:10.1177/1090198111415105

Last, J. M., & Adelaide, D. P. (2013). The iceberg: 'completing the clinical picture' in general practice. 1963. *Int J Epidemiol, 42*(6), 1608-1613. doi:10.1093/ije/dyt113

Lienhardt, C. (2001). From exposure to disease: the role of environmental factors in susceptibility to and development of tuberculosis. *Epidemiol Rev, 23*(2), 288-301.

Lienhardt, C., Bennett, S., Del Prete, G., Bah-Sow, O., Newport, M., Gustafson, P., . . . McAdam, K. (2002). Investigation of Environmental and Host-related Risk Factors for Tuberculosis in Africa. I. Methodological Aspects of a Combined Design. *American Journal of Epidemiology, 155*(11), 1066-1073. doi:10.1093/aje/155.11.1066

Linas, B. P., Wong, A. Y., Freedberg, K. A., & Horsburgh, C. R. (2011). Priorities for screening and treatment of latent tuberculosis infection in the United States. *Am J Respir Crit Care Med, 184*(5), 590-601. doi:10.1164/rccm.201101-0181OC

Liu, E., Cheng, S., Wang, X., Hu, D., Zhang, T., & Chu, C. (2010). A systematic review of the investigation and management of close contacts of tuberculosis in China. *J Public Health (Oxf), 32*(4), 461-466. doi:10.1093/pubmed/fdq032

Lwanga, S. K., & Lemeshow, S. (1991). *Sample size determination in health studies : a practical manual*: World Health Organization.

MacIntyre, C. R., & Plant, A. J. (1998). Impact of policy and practice on the effectiveness of contact screening for tuberculosis. *Prev Med, 27*(6), 830-837. doi:10.1006/pmed.1998.0366

Mancuso, J. D., Tribble, D., Mazurek, G. H., Li, Y., Olsen, C., Aronson, N. E., . . . Keep, L. W. (2011). Impact of targeted testing for latent tuberculosis infection using commercially available diagnostics. *Clin Infect Dis, 53*(3), 234-244. doi:10.1093/cid/cir321

Marais, B. (2016). Childhood tuberculosis-out of the shadows. *Pneumonia (Nathan Qld.), 8*, 22-22. doi:10.1186/s41479-016-0022-x

Marais, B. (2017). Improving access to tuberculosis preventive therapy and treatment for children. *Int J Infect Dis, 56*, 122-125. doi:10.1016/j.ijid.2016.12.015

Marais, B., Gie, R., Schaaf, H., Hesseling, A., Obihara, C., & Starke, J. (2004). The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis, 8*.

Martínez-Mesa, J., González-Chica, D. A., Bastos, J. L., Bonamigo, R. R., & Duquia, R. P. (2014). Sample size: how many participants do I need in my research? *An Bras Dermatol, 89*(4), 609-615.

Martinez, L., Shen, Y., Mupere, E., Kizza, A., Hill, P. C., & Whalen, C. C. (2017). Transmission of Mycobacterium Tuberculosis in Households and the Community: A Systematic Review and Meta-Analysis. *Am J Epidemiol, 185*(12), 1327-1339. doi:10.1093/aje/kwx025

Masini, E. O., Sitienei, J., & Weyeinga, H. (2013). Outcomes of isoniazid prophylaxis among HIV-infected children attending routine HIV care in Kenya. *Public Health Action, 3*(3), 204-208. doi:10.5588/pha.13.0013

Mays, N., & Pope, C. (1995). Qualitative research: Observational methods in health care settings. *BMJ, 311*(6998), 182-184.

Medecins Sans Frontieres. (2014). *Tuberculosis Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries*. Retrieved from http://refbooks.msf.org/msf_docs/en/tuberculosis/tuberculosis_en.pdf.

Melsew, Y. A., Doan, T. N., Gambhir, M., Cheng, A. C., McBryde, E., & Trauer, J. M. (2018). Risk factors for infectiousness of patients with tuberculosis: a systematic review and meta-analysis. *Epidemiol Infect, 146*(3), 345-353. doi:10.1017/s0950268817003041

Miller, A. C., Golub, J. E., Cavalcante, S. C., Durovni, B., Moulton, L. H., Fonseca, Z., . . . Soares, E. C. (2010). Controlled trial of active tuberculosis case finding in a Brazilian favela. *Int J Tuberc Lung Dis, 14*(6), 720-726.

Ministry of Health. (2017). Kenya Master Facility List. http://kmhfl.health.go.ke/

Ministry of Public Health and Sanitation. (n.d.). *Division of Vaccines and Immunization Comprehensive Multi year plan 2013-2017*. Retrieved from http://www.nationalplanningcycles.org/sites/default/files/country_docs/Kenya/cmyp_kenya_2013-2017_1.pdf.

Moore, D. A. (2016). What can we offer to 3 million MDRTB household contacts in 2016? *BMC Med, 14*, 64. doi:10.1186/s12916-016-0610-x

Morgan, D. L. (1998). Practical strategies for combining qualitative and quantitative methods: applications to health research. *Qual Health Res, 8*(3), 362-376. doi:10.1177/104973239800800307

Munthali, L., Khan, P. Y., Mwaungulu, N. J., Chilongo, F., Floyd, S., Kayange, M., . . . Crampin, A. C. (2014). The effect of HIV and antiretroviral therapy on characteristics of pulmonary tuberculosis in northern Malawi: a cross-sectional study. *BMC Infect Dis, 14*, 107. doi:10.1186/1471-2334-14-107

Murray, C. J. L., & Salomon, J. A. (1998). Expanding the WHO tuberculosis control strategy: rethinking the role of active case-finding [The Pittsfield Lecture]. *Int J Tuberc Lung Dis, 2*(9), 9-15.

Nair, D., Rajshekhar, N., Klinton, J. S., Watson, B., Velayutham, B., Tripathy, J. P., . . . Swaminathan, S. (2016). Household Contact Screening and Yield of Tuberculosis Cases-A Clinic Based Study in Chennai, South India. *PLOS ONE, 11*(9), e0162090-e0162090. doi:10.1371/journal.pone.0162090

National AIDS and STI Control Program NASCOP. (2014). *Kenya AIDS Indicator Survey 2012: Final Report*. NASCOP Retrieved from http://nacc.or.ke/wp-content/uploads/2015/10/KAIS-2012.pdf.

National Institutes of Health. (2016). Protection of Human Research Participants. Retrieved from https://humansubjects.nih.gov/hs/phrp

National Tuberculosis Leprosy and Lung Disease Program. (2017a). *Annual Report 2016*. Ministry of Health Retrieved from https://www.nltp.co.ke/annual-reports/.

National Tuberculosis Leprosy and Lung Disease Program. (2017b). Kenya Tuberculosis Prevalence Survey 2016. Retrieved from https://www.chskenya.org/wp-content/uploads/2018/04/Final-TB-Prevalence-Survey-Report.pdf.

Nayak, S., & Acharjya, B. (2012). Mantoux test and its interpretation. *Indian Dermatol Online J, 3*(1), 2-6. doi:10.4103/2229-5178.93479

Nelson, L. J., & Wells, C. D. (2004). Global epidemiology of childhood tuberculosis. *Int J Tuberc Lung Dis, 8*(5), 636-647.

Nezlek, J. B. (2008). An Introduction to Multilevel Modeling for Social and Personality Psychology. *Social and Personality Psychology Compass, 2*(2), 842-860. doi:10.1111/j.1751-9004.2007.00059.x

Nyirenda, M., Sinfield, R., Haves, S., Molyneux, E. M., & Graham, S. M. (2006). Poor attendance at a child TB contact clinic in Malawi. *Int J Tuberc Lung Dis, 10*(5), 585-587.

Odhiambo, F. O., Laserson, K. F., Sewe, M., Hamel, M. J., Feikin, D. R., Adazu, K., . . . Vulule, J. M. (2012). Profile: the KEMRI/CDC Health and Demographic Surveillance System-- Western Kenya. *Int J Epidemiol, 41*(4), 977-987. doi:10.1093/ije/dys108

Oliveira, S. P. d., Carvalho, M. D. d. B., Pelloso, S. M., Caleffi-Ferracioli, K. R., Siqueira, V. L. D., Scodro, R. B. d. L., & Cardoso, R. F. (2017). Influence of the identification of contacts on the adherence of index tuberculosis cases to treatment in a high incidence country. *International Journal of Infectious Diseases, 65*, 57-62. doi:https://doi.org/10.1016/j.ijid.2017.09.005

Oluoch, T., Katana, A., Kwaro, D., Santas, X., Langat, P., Mwalili, S., . . . de Keizer, N. (2015). Effect of a clinical decision support system on early action on immunological treatment failure in patients with HIV in Kenya: a cluster randomised controlled trial. *Lancet HIV, 3*(2), e76-84. doi:10.1016/S2352-3018(15)00242-8

Osman, M., Hesseling, A. C., Beyers, N., Enarson, D. A., Rusen, I. D., Lombard, C., & van Wyk, S. S. (2013). Routine programmatic delivery of isoniazid preventive therapy to children in Cape Town, South Africa. *Public Health Action, 3*(3), 199-203. doi:10.5588/pha.13.0034

Parab, S., & Bhalerao, S. (2010). Choosing statistical test. *International journal of Ayurveda research, 1*(3), 187-191. doi:10.4103/0974-7788.72494

Porskrog, A., Bjerregaard-Andersen, M., Oliveira, I., Joaquím, L. C., Camara, C., Andersen, P. L., . . . Wejse, C. (2011). Enhanced tuberculosis identification through 1-month follow-up of smear-negative tuberculosis suspects. *Int J Tuberc Lung Dis, 15*(4), 459-464. doi:10.5588/ijtld.10.0353

Porter, M. E. (2010). What Is Value in Health Care? *New England Journal of Medicine, 363*(26), 2477-2481. doi:10.1056/NEJMp1011024

Pothukuchi, M., Nagaraja, S. B., Kelamane, S., Satyanarayana, S., Shashidhar, Babu, S., . . . Wares, F. (2011). Tuberculosis contact screening and isoniazid preventive therapy in a South Indian district: operational issues for programmatic consideration. *PLOS ONE, 6*(7), e22500. doi:10.1371/journal.pone.0022500

Pourhoseingholi, M. A., Vahedi, M., & Rahimzadeh, M. (2013). Sample size calculation in medical studies. *Gastroenterol Hepatol Bed Bench, 6*(1), 14-17.

Raj, S. B. (2016). *Concepts of EpidemiologyIntegrating the ideas, theories, principles, and methods of epidemiology*. Oxford, UK.

Ramos, J. M., Biru, D., Tesfamariam, A., Reyes, F., & Górgolas, M. (2013). Screening for tuberculosis in family and household contacts in a rural area in Ethiopia over a 20-month period. *Int J Mycobacteriol, 2*(4), 240-243. doi:10.1016/j.ijmyco.2013.10.001

Reichler, M. R., Reves, R., Bur, S., Thompson, V., Mangura, B. T., Ford, J., . . . Group, C. I. S. (2002). Evaluation of investigations conducted to detect and prevent transmission of tuberculosis. *JAMA, 287*(8), 991-995.

Rieder, H. L., Chadha, V. K., Nagelkerke, N. J., van Leth, F., & van der Werf, M. J. (2011). Guidelines for conducting tuberculin skin test surveys in high-prevalence countries. *Int J Tuberc Lung Dis, 15 Suppl 1*, S1-25.

Roderick, J. A. L. (1988). A Test of Missing Completely at Random for Multivariate Data with Missing Values. *Journal of the American Statistical Association, 83*(404), 1198-1202. doi:10.2307/2290157

Roya-Pabon, C. L., & Perez-Velez, C. M. (2016). Tuberculosis exposure, infection and disease in children: a systematic diagnostic approach. *Pneumonia, 8*(1), 23. doi:10.1186/s41479-016-0023-9

Rubio-Tapia, A., & Murray, J. A. (2010). Celiac disease. *Current opinion in gastroenterology, 26*(2), 116-122. doi:10.1097/MOG.0b013e3283365263

Sadaphal S, K. N. H. S. S.-A. A. M. R. (2013). *Quality Improvement Handbook for TB and MDR-TB programs*. Retrieved from http://tbcare2.org/sites/default/files/TBCAREII%20ImprovementHandbook_July%2030.pdf.

Salgame, P., Geadas, C., Collins, L., Jones-López, E., & Ellner, J. J. (2015). Latent tuberculosis infection--revisiting and revising concepts. *Tuberculosis (Edinb), 95*. doi:10.1016/j.tube.2015.04.003

Sandelowski, M., Voils, C. I., & Barroso, J. (2006). Defining and Designing Mixed Research Synthesis Studies. *Research in the schools : a nationally refereed journal sponsored by the Mid-South Educational Research Association and the University of Alabama, 13*(1), 29-29.

SAS Institute Inc. (2012). Statistical Analyses System SAS 9.2.

Schaible, U. E., & Kaufmann, S. H. (2007). Malnutrition and infection: complex mechanisms and global impacts. *PLoS Med, 4*(5), e115. doi:10.1371/journal.pmed.0040115

Schulz, K. F., Altman, D. G., Moher, D., & Group, C. (2011). CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Int J Surg, 9*(8), 672-677. doi:10.1016/j.ijsu.2011.09.004

Shashidhar, H. R., & Grigsby, D. G. (2017). Malnutrition. Retrieved from https://emedicine.medscape.com/article/985140-overview

Shayo, G. A., Moshiro, C., Aboud, S., Bakari, M., & Mugusi, F. M. (2015). Acceptability and adherence to Isoniazid preventive therapy in HIV-infected patients clinically screened for latent tuberculosis in Dar es Salaam, Tanzania. *BMC Infect Dis, 15*, 368. doi:10.1186/s12879-015-1085-7

Shivaramakrishna, H. R., Frederick, A., Shazia, A., Murali, L., Satyanarayana, S., Nair, S. A., . . . Moonan, P. K. (2014). Isoniazid preventive treatment in children in two districts of South India: does practice follow policy? *Int J Tuberc Lung Dis, 18*(8), 919-924. doi:10.5588/ijtld.14.0072

Sifuna, P., Oyugi, M., Ogutu, B., Andagalu, B., Otieno, A., Owira, V., . . . Otieno, W. (2014). Health & demographic surveillance system profile: The Kombewa health and demographic surveillance system (Kombewa HDSS). *Int J Epidemiol, 43*(4), 1097-1104. doi:10.1093/ije/dyu139

Singh, A., Kharate, A., Bhat, P., Kokane, A., Bali, S., Sahu, S., . . . Kumar, A. (2017). Isoniazid Preventive Therapy among Children Living with Tuberculosis Patients: Is It Working? A Mixed-Method Study from Bhopal, India. *J Trop Pediatr, 63*(4), 274-285. doi:10.1093/tropej/fmw086

Singh, M., Mynak, M., Kumar, L., Mathew, J., & Jindal, S. (2005). Prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. *Arch Dis Child, 90*(6), 624-628. doi:10.1136/adc.2003.044255

Skinner, D., & Claassens, M. (2016). It's complicated: why do tuberculosis patients not initiate or stay adherent to treatment? A qualitative study from South Africa. *BMC Infect Dis, 16*(1), 712. doi:10.1186/s12879-016-2054-5

Sloot, R., Schim van der Loeff, M. F., Kouw, P. M., & Borgdorff, M. W. (2014). Risk of Tuberculosis after Recent Exposure. A 10-Year Follow-up Study of Contacts in Amsterdam. *Am J Respir Crit Care Med, 190*(9), 1044-1052. doi:10.1164/rccm.201406-1159OC

Social Science Statistics. (n.d.). p value from chi-square calculator. Retrieved from http://www.socscistatistics.com/pvalues/chidistribution.aspx

Sommet, N., & Morselli, D. (2017). Keep calm and learn Multilevel Logistic Modelling: A simplified Three-stem procedure using Stata, R, Mplus and SPSS. *International Review of Social Pyschology, 30*(1). Retrieved from

Speak, A., Escobedo, F. J., Russo, A., & Zerbe, S. (2018). Comparing convenience and probability sampling for urban ecology applications. *Journal of Applied Ecology, 55*(5), 2332-2342. doi:10.1111/1365-2664.13167

Sperandei, S. (2014). Understanding logistic regression analysis. *Biochemia medica, 24*(1), 12-18. doi:10.11613/BM.2014.003

Statistics, S. (2016a). Data analysis plan: Binary Logistic Regression. Retrieved from http://www.statisticssolutions.com/membership-resources/member-profile/data-analysis-plan-templates/binary-logistic-regression/

Statistics, S. (2016b). Hierarchical Linear Modelling. Retrieved from https://www.statisticssolutions.com/hierarchical-linear-modeling/

Surkis, A., & Read, K. (2015). Research data management. *Journal of the Medical Library Association : JMLA, 103*(3), 154-156. doi:10.3163/1536-5050.103.3.011

Szkwarko, D., Ogaro, F., Owiti, P., & Carter, E. J. (2013). Implementing a tuberculosis child contact register to quantify children at risk for tuberculosis and HIV in Eldoret, Kenya. *Public Health Action, 3*(3), 209-213. doi:10.5588/pha.13.0018

Tadesse, Y., Gebre, N., Daba, S., Gashu, Z., Habte, D., Hiruy, N., . . . G Suarez, P. (2016). Uptake of Isoniazid Preventive Therapy among Under-Five Children: TB Contact Investigation as an Entry Point. *PLOS ONE, 11*(5), e0155525. doi:10.1371/journal.pone.0155525

Taushanova, B., Pavlovska, I., & Arsevska, E. (2011). Cut-off value of mantoux induration in tuberculous children in R. Macedonia and their nutritional status. *Prilozi, 32*(1), 257-268.

Teklay, G., Teklu, T., Legesse, B., Tedla, K., & Klinkenberg, E. (2016). Barriers in the implementation of isoniazid preventive therapy for people living with HIV in Northern Ethiopia: a mixed quantitative and qualitative study. *BMC Public Health, 16*(1), 840-840. doi:10.1186/s12889-016-3525-8

The Project Definition. (n.d.). Lessons Learned. Retrieved from https://www.theprojectdefinition.com/lessons-learned-ll/

The Project Management Institute. (n.d.). Lessons Learned.

The Royal Melbourne Hospital. (n.d.). Tuberculosis in Children and Adults. Retrieved from https://www.thermh.org.au/sites/default/files/media/documents/Tuberculosis%20in%20Children%20and%20Adolescents.pdf

Thomas, B. E., Subbaraman, R., Sellappan, S., Suresh, C., Lavanya, J., Lincy, S., . . . Mayer, K. H. (2018). Pretreatment loss to follow-up of tuberculosis patients in Chennai, India: a cohort study with implications for health systems strengthening. *BMC Infectious Diseases, 18*(1), 142-142. doi:10.1186/s12879-018-3039-3

Tiemersma, E. W., van der Werf, M. J., Borgdorff, M. W., Williams, B. G., & Nagelkerke, N. J. (2011). Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PLOS ONE, 6*(4), e17601. doi:10.1371/journal.pone.0017601

Tornee, S., Kaewkungwal, J., Fungladda, W., Silachamroon, U., Akarasewi, P., & Sunakorn, P. (2005). Risk factors for tuberculosis infection among household contacts in Bangkok, Thailand. *Southeast Asian J Trop Med Public Health, 35*(2), 375-383.

Turner, R. D., & Bothamley, G. H. (2014). Cough and the transmission of tuberculosis. *J Infect Dis, 211*(9), 1367-1372. doi:10.1093/infdis/jiu625

United States Department of Health and Human Services. (2013). Latent Tuberculosis Infection: A practical guide for Primary Health Care Providers. Retrieved from https://www.cdc.gov/tb/publications/ltbi/pdf/targetedltbi.pdf

van der Hoeven, M., Kruger, A., & Greeff, M. (2012). Differences in health care seeking behaviour between rural and urban communities in South Africa. *Int J Equity Health, 11*, 31. doi:10.1186/1475-9276-11-31

Van Dyke, T. E., & Sheilesh, D. (2005). Risk factors for periodontitis. *Journal of the International Academy of Periodontology, 7*(1), 3-7.

Van Wyk, S. S., Mandalakas, A. M., Enarson, D. A., Gie, R. P., Beyers, N., & Hesseling, A. C. (2012). Tuberculosis contact investigation in a high-burden setting: house or household? *Int J Tuberc Lung Dis, 16*(2), 157-162. doi:10.5588/ijtld.11.0393

Verdier, J., de Vlas, S., Kidgell-Koppelaar, I., & Richardus, J. (2012). Risk factors for tuberculosis contact investigations in Rotterdam, the Netherlands. *Inf Dis Resp, 4*(2), e26. doi:10.4081/idr.2012.e26

Vijayakumar, M., Bhaskaram, P., & Hemalatha, P. (1990). Malnutrition and childhood tuberculosis. *J Trop Pediatr, 36*(6), 294-298.

Volpp, K. G., Loewenstein, G., & Asch, D. A. (2012). Assessing value in health care programs. *JAMA, 307*(20), 2153-2154. doi:10.1001/jama.2012.3619

Vynnycky, E., & Fine, P. E. (1997). The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiol Infect, 119*(2), 183-201.

Wheeldon, J., & Mauri, A. (2012). Visualizing Social Science Research: Maps, Methods, & Meaning. Thousand Oaks, California: SAGE Publications, Inc. Retrieved from http://methods.sagepub.com/book/visualizing-social-science-research. doi:10.4135/9781483384528

Whitley, E., & Ball, J. (2002). Statistics review 4: sample size calculations. *Crit Care, 6*(4), 335-341.

Wood, R., Johnstone-Robertson, S., Uys, P., Hargrove, J., Middelkoop, K., Lawn, S. D., & Bekker, L. G. (2010). Tuberculosis transmission to young children in a South African community: modeling household and community infection risks. *Clin Infect Dis, 51*(4), 401-408. doi:10.1086/655129

World Health Organization. (2006). The Stop TB Strategy. Retrieved from https://www.who.int/tb/strategy/stop_tb_strategy/en/

World Health Organization. (2008). A brief history of Tuberculosis in Kenya. Retrieved from https://www.who.int/tb/publications/tb-kenya-report/en/

World Health Organization. (2011). Guidelines for Intensified Tuberculosis Case Finding and Isoniazid preventative Therapy for people living with HIV in resource constrained settings. Retrieved from http://www.who.int/tb/publications/ICF_IPTguidelines/en/

World Health Organization. (2012). *Recommendations for investigating contacts of persons with infectious Tuberculosis in low and middle income countries*. Retrieved from http://apps.who.int/iris/bitstream/10665/77741/1/9789241504492_eng.pdf?ua=1.

World Health Organization. (2013a). *Road Map for Childhood Tuberculosis*. Retrieved from http://apps.who.int/iris/bitstream/10665/89506/1/9789241506137_eng.pdf?ua=1&ua=1.

World Health Organization. (2013b). Systematic Screening for Active Tuberculosis: Principles and Recommendations Definitions. Geneva.

World Health Organization. (2014). Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis.15, Management of contacts of MDR-TB patients.

World Health Organization. (2016). Implementing the End TB Strategy: The essentials. Retrieved from https://www.who.int/tb/publications/2015/The_Essentials_to_End_TB/en/

World Health Organization. (2017). Global Tuberculosis Report 2017. Retrieved from http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1

World Health Organization. (2018). *Tuberculosis Fact Sheet*. Retrieved from http://www.who.int/mediacentre/factsheets/fs104/en/.

World Health Organization. (n.d.). Health Topics: Risk factors. Retrieved from https://www.who.int/topics/risk_factors/en/

Wurie, F. B., Lawn, S. D., Booth, H., Sonnenberg, P., & Hayward, A. C. (2016). Bioaerosol production by patients with tuberculosis during normal tidal breathing: implications for transmission risk. *Thorax, 71*(6), 549-554. doi:10.1136/thoraxjnl-2015-207295

Yang, J., Zhao, Z., Li, Y., Krewski, D., & Wen, S. W. (2009). A multi-level analysis of risk factors for Schistosoma japonicum infection in China. *International Journal of Infectious Diseases, 13*(6), e407-e412. doi:https://doi.org/10.1016/j.ijid.2009.02.005

Yassin, M. A., Datiko, D. G., Tulloch, O., Markos, P., Aschalew, M., Shargie, E. B., . . . Theobald, S. (2013). Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia. *PLOS ONE, 8*(5), e63174. doi:10.1371/journal.pone.0063174

Yau, K. K., Lee, A. H., & Gracey, M. (2005). Multilevel modelling of hospitalisations for recurrent diarrhoeal disease in Aboriginal and non-Aboriginal infants and young children in Western Australia. *Paediatr Perinat Epidemiol, 19*(2), 165-172. doi:10.1111/j.1365-3016.2005.00638.x

Younge, J. O., Kouwenhoven-Pasmooij, T. A., Freak-Poli, R., Roos-Hesselink, J. W., & Hunink, M. G. M. (2015). Randomized study designs for lifestyle interventions: a tutorial. *International Journal of Epidemiology, 44*(6), 2006-2019. doi:10.1093/ije/dyv183

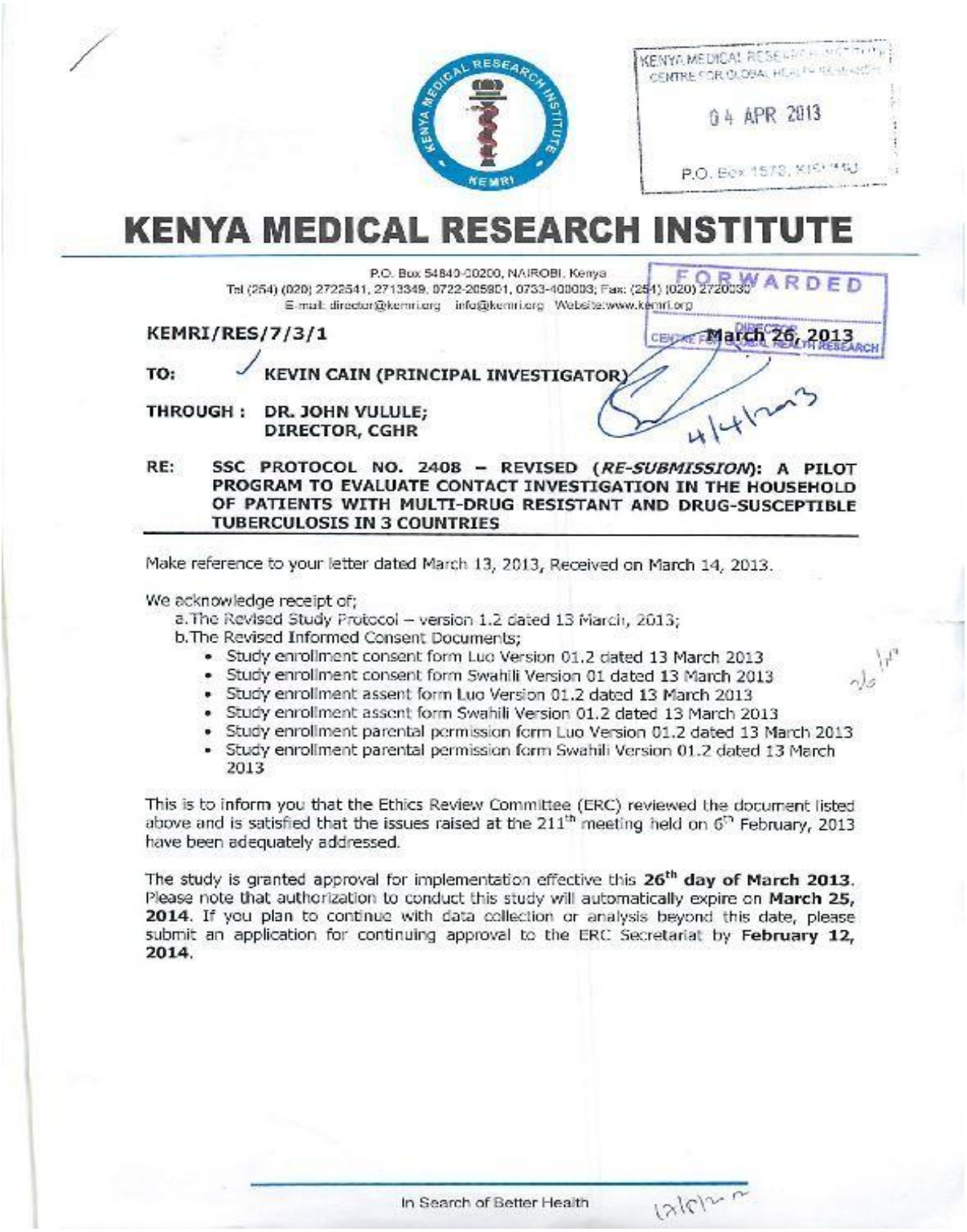
Yun, K. W., Kim, Y. K., Kim, H. R., Lee, M. K., & Lim, I. S. (2016). Usefulness of interferon-γ release assay for the diagnosis of latent tuberculosis infection in young children. *Korean Journal of Pediatrics, 59*(6), 256-261. doi:10.3345/kjp.2016.59.6.256

Zelner, J. L., Murray, M. B., Becerra, M. C., Galea, J., Lecca, L., Calderon, R., . . . Cohen, T. (2014). Age-specific risks of tuberculosis infection from household and community exposures and opportunities for interventions in a high-burden setting. *Am J Epidemiol, 180*(8), 853-861. doi:10.1093/aje/kwu192

Zhang, D., Wang, L., Lv, F., Su, W., Liu, Y., Shen, R., & Bi, P. (2007). Advantages and challenges of using census and multiplier methods to estimate the number of female sex workers in a Chinese city. *AIDS Care, 19*(1), 17-19. doi:10.1080/09540120600966158

APPENDICES

Appendix 1: IRB Approval for KEMRI SSC # 2408



KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel (254) (020) 2722541, 2713349, 0722-205901, 0733-400003; Fax: (254) (020) 2720030
E-mail: director@kemri.org info@kemri.org Website:www.kemri.org

KENYA MEDICAL RESEARCH INSTITUTE
CENTRE FOR GLOBAL HEALTH RESEARCH
04 APR 2013
P.O. Box 1578, KISUMU

FORWARDED
DIRECTOR
CENTRE FOR GLOBAL HEALTH RESEARCH

KEMRI/RES/7/3/1 March 26, 2013

TO: KEVIN CAIN (PRINCIPAL INVESTIGATOR)

THROUGH : DR. JOHN VULULE;
DIRECTOR, CGHR

RE: SSC PROTOCOL NO. 2408 – REVISED (*RE-SUBMISSION*): A PILOT PROGRAM TO EVALUATE CONTACT INVESTIGATION IN THE HOUSEHOLD OF PATIENTS WITH MULTI-DRUG RESISTANT AND DRUG-SUSCEPTIBLE TUBERCULOSIS IN 3 COUNTRIES

Make reference to your letter dated March 13, 2013, Received on March 14, 2013.

We acknowledge receipt of;

a. The Revised Study Protocol – version 1.2 dated 13 March, 2013;
b. The Revised Informed Consent Documents;
- Study enrollment consent form Luo Version 01.2 dated 13 March 2013
- Study enrollment consent form Swahili Version 01 dated 13 March 2013
- Study enrollment assent form Luo Version 01.2 dated 13 March 2013
- Study enrollment assent form Swahili Version 01.2 dated 13 March 2013
- Study enrollment parental permission form Luo Version 01.2 dated 13 March 2013
- Study enrollment parental permission form Swahili Version 01.2 dated 13 March 2013

This is to inform you that the Ethics Review Committee (ERC) reviewed the document listed above and is satisfied that the issues raised at the 211th meeting held on 6th February, 2013 have been adequately addressed.

The study is granted approval for implementation effective this **26th day of March 2013**. Please note that authorization to conduct this study will automatically expire on **March 25, 2014**. If you plan to continue with data collection or analysis beyond this date, please submit an application for continuing approval to the ERC Secretariat by **February 12, 2014**.

In Search of Better Health

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel (254) (020) 2722541, 2713349, 0722-205901, 0733-400003; Fax: (254) (020) 2720033
E-mail: director@kemri.org info@kemri.org Website:www.kemri.org

KEMRI/RES/7/3/1 **February 18, 2014**

TO: **DR. KEVIN CAIN (PRINCIPAL INVESTIGATOR)**

THROUGH : **DR. STEPHEN MUNGA,**
ACTING DIRECTOR, CGHR
KISUMU

Dear Sir,

RE: **SSC PROTOCOL NO. 2408 – (*REQUEST FOR ANNUAL RENEWAL*): A PILOT PROGRAM TO EVALUATE CONTACT INVESTIGATION IN THE HOUSEHOLD OF PATIENTS WITH MULTI-DRUG RESISTANT AND DRUG-SUSCEPTIBLE TUBERCULOSIS IN 3 COUNTRIES**

Thank you for the continuing review report for the period **26th March 2013** to **21st January 2014.**

This is to inform you that during the 224th meeting of the KEMRI/ERC held on **18th of February, 2014,** the Committee **conducted the annual review and approved** the above referenced application for another year.

This approval is valid from today **18th February 2014** through to **17th February 2015.** Please note that authorization to conduct this study will automatically expire **February 17, 2015.** If you plan to continue with data collection or analysis beyond this date please submit an application for continuing approval to the ERC secretarial by **6th January 2015.**

You are required to submit any amendments to this protocol and any other information pertinent to human participation in this study to the ERC for review prior to initiation.

Yours faithfully,

DR. ELIZABETH BUKUSI,
ACTING SECRETARY,
KEMRI ETHICS REVIEW COMMITTEE

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel: (254) (020) 2722541, 2713349, 2722-205801, 2733-100003, Fax: (254) (020) 2720030
E-mail: director@kemri.org info@kemri.org Website:www.kemri.org

KEMRI/RES/7/3/1 **February 12, 2015**

TO: **DR. KEVIN CAIN**
PRINCIPAL INVESTIGATOR

THROUGH: **DR. STEPHEN MUNGA,**
THE DIRECTOR, CGHR,
KISUMU

Dear Sir,

RE: **SSC PROTOCOL NO. 2408 *(RESUBMISSION-REQUEST FOR ANNUAL RENEWAL):* A PILOT PROGRAM TO EVALUATE CONTACT INVESTIGATION IN THE HOUSEHOLD OF PATIENTS WITH MULTI-DRUG RESISTANT AND DRUG-SUSCEPTIBLE TUBERCULOSIS IN 3 COUNTRIES**

Reference is made to your letter dated 3rd February 2015. The KEMRI/Scientific and Ethics Review Unit (SERU) acknowledges receipt of the revised document on 6th February 2015.

This is to inform you that the Committee reviewed the document submitted, and determined that the issue raised at the 235th SERU meeting of the KEMRI/SERU held on the 21st January, 2015, has been adequately addressed.

This study is granted approval for implementation effective this **February 12, 2015.** Please note that authorization to conduct this study will automatically expire on **February 11, 2016**. If you plan to continue with data collection or analysis beyond this date please submit an application for continuing approval to SERU by **January 5, 2016.**

You are required to submit any amendments to this protocol and other information pertinent to human participation in this study to SERU for review prior to initiation.

Yours faithfully,

PROF. ELIZABETH BUKUSI,
ACTING SECRETARY,
KEMRI/ETHICS REVIEW COMMITTEE

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840 - 00200 NAIROBI - Kenya
Tel: (254) (020) 2722541, 254 (020) 2713349, 0722-205901, 0733-400003 Fax (254) (020) 2720030
Email: director@kemri.org info@kemri.org Website:www.kemri.org

KEMRI/RES/7/3/1 **January 22, 2016**

TO: **DR. KEVIN CAIN**
PRINCIPAL INVESTIGATOR

THROUGH: **DR. STEPHEN MUNGA,**
THE DIRECTOR, CGHR,
KISUMU

FORWARDED
DIRECTOR
CENTRE FOR GLOBAL HEALTH RESEARCH

Dear Sir,

RE: **SSC PROTOCOL NO. 2408 *(REQUEST FOR ANNUAL RENEWAL):* A PILOT PROGRAM TO EVALUATE CONTACT INVESTIGATION IN THE HOUSEHOLD OF PATIENTS WITH MULTI-DRUG RESISTANT AND DRUG-SUSCEPTIBLE TUBERCULOSIS IN 3 COUNTRIES**

Thank you for the continuing review report for the period **February 12, 2015** to **December 2, 2015**

This is to inform that during the 247th Committee B meeting of the KEMRI Scientific and Ethics Review Unit (SERU) meeting held on **20th January 2016**, the Committee **conducted the annual review and approved** the above referenced application for another year.

This approval is valid from **February 12, 2016** through to **February 11, 2017**. Please note that authorization to conduct this study will automatically expire on **January 20, 2017** If you plan to continue with data collection or analysis beyond this date please submit an application for continuing approval to the SERU by **December 31, 2016.**

You are required to submit any amendments to this protocol and other information pertinent to human participation in this study to the SERU for review prior to initiation.

Yours faithfully,

PROF. ELIZABETH BUKUSI,
ACTING HEAD,
KEMRI SCIENTIFIC AND ETHICS REVIEW UNIT

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel: (254) (020) 2722541, 2713349, 0722-205901, 0733-400003, Fax: (254) (020) 2720030
E-mail: director@kemri.org, info@kemri.org, Website. www.kemri.org

KEMRI/RES/7/3/1 **January 31, 2017**

TO: **DR. KEVIN CAIN,**
PRINCIPAL INVESTIGATOR

THROUGH: **DR. STEPHEN MUNGA,**
THE DIRECTOR, CGHR,
KISUMU

14/2/2017

Dear Sir,

RE: **SSC PROTOCOL NO. 2408 *(RESUBMITTED- REQUEST FOR ANNUAL RENEWAL):* A PILOT PROGRAM TO EVALUATE CONTACT INVESTIGATION IN THE HOUSEHOLD OF PATIENTS WITH MULTI-DRUG RESISTANT AND DRUG-SUSCEPTIBLE TUBERCULOSIS IN 3 COUNTRIES**

Reference is made to your letter dated 24th January, 2017. The KEMRI/Scientific and Ethics Review Unit (SERU) acknowledges receipt of the revised study documents on 31st January, 2017.

The Committee notes that the issue raised during the 259th Joint Committee A, B and ERC meeting of the KEMRI/SERU held on 17th January, 2017, have been adequately addressed.

Consequently, the study is granted approval for continuation effective **January 31, 2017** through to **January 30, 2018.** Please note that authorization to conduct this study will automatically expire on **January 30, 2018.** If you plan to continue with data collection or analysis beyond this date, please submit an application for continuing approval to SERU by **December 19, 2017.**

You are required to submit any proposed changes to this study to the SERU for review and the changes should not be initiated until written approval from the SERU is received. Please note that any unanticipated problems resulting from the implementation of this study should be brought to the attention of the SERU and you should advise them when the study is completed or discontinued.

You may continue with the study.

Yours faithfully,

for **DR. EVANS AMUKOYE,**
ACTING HEAD,
KEMRI/SCIENTIFIC AND ETHICS REVIEW UNIT

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel: (254) (020) 2722541, 2713349, 0722-205901, 0733-400003, Fax: (254) (020) 2720030
E-mail: director@kemri.org, info@kemri.org, Website. www.kemri.org

KEMRI/RES/7/3/1 **January 15,2018**

TO: **DR. JANET AGAYA,**
PRINCIPAL INVESTIGATOR

THROUGH: **THE DIRECTOR, CGHR,**
KISUMU.

Dear Madam,

FORWARDED
DIRECTOR - CGHR

RE: **SSC PROTOCOL No. 2408 (*REQUEST FOR ANNUAL RENEWAL*): A PILOT PROGRAM TO EVALUATE CONTACT INVESTIGATION IN THE HOUSEHOLD OF PATIENTS WITH MULTI-DRUG RESISTANT AND DRUG-SUSCEPTIBILITY TUBERCULOSIS IN 3 COUNTRIES.**

Thank you for the continuing review report for the period **January 31, 2017 and November 27, 2017.**

This is to inform you that the expedited review team of the KEMRI Scientific and Ethics Review Unit (SERU) was of the informed opinion that the progress made during the reported period is satisfactory. The study has therefore been granted **approval**.

This approval is valid from **January 31, 2018** through to **January 30, 2019**. Please note that authorization to conduct this study will automatically expire on **January 30, 2019.** If you plan to continue with data collection or analysis beyond this date please submit an application for continuing approval to the SERU by **December 19, 2018.**

You are required to submit any amendments to this protocol and any other information pertinent to human participation in this study to the SERU for review prior to initiation.

You may continue with the study.

Yours faithfully,

FOR: **THE HEAD,**
KEMRI/SCIENTIFIC AND ETHICS REVIEW UNIT.

Appendix 2: Memorandum of Understanding between participating facilities and KEMRI

This agreement is made on this___ day of_____in the year**….**between**….**health facility whose postal address for the purpose of this agreement is_____(hereinafter called the **Health facility**), **and the KEMRI/CDC Research and Public Health Collaboration**, whose postal address for the purpose of this agreement is Post Office Box 1578-40100, Kisumu, (hereinafter referred to as the **KEMRI/CDC**).

Time period: The period of this agreement will be from **January 2014** till **December 2016**

This agreement is on an annual basis and takes effect from the date both parties sign it and may be renewed subject to such terms and conditions that will be agreed upon by both parties.

Objectives: This Memorandum of Understanding serves to demarcate the points of agreement between**…** Health facility and the KEMRI/CDC Research and Public Health Collaboration with regards to reimbursement/facilitation of patient care, rent/space, electricity, provision of water and staff support, as applicable. It delineates general guidelines for both participating parties and outlines their roles in the various patient centered activities. Both parties have agreed it is of mutual interest to develop the capacity for operation of successful collaborative studies.

Now therefore: for the purposes hereof, the two parties agree as follows.

Terms of Agreement

1. **Staff:** The KEMRI/CDC Research and Public Health Collaboration agree to supply the necessary staff whose primary responsibility is to conduct KEMRI/CDC study activities at the health facility. Study activities that involve simple additions to routine clinical care, such as using new health screening algorithms, will be conducted by health facility clinical staff, and supported by study staff. For this study, a site supervisor will be assigned to the health facility to assist with study enrollment and other procedures. A KEMRI/CDC Principal Investigator may agree to allow study staff to assist in patient care when study procedures allow for such an agreement, after study duties are completed and as approved by the said Principal Investigator. However, the KEMRI/CDC staff can never be given the sole responsibility for a health facility clinic, department or health facility since at any time the KEMRI/CDC staff may be required for study procedures in

which situation health facility staffs has to be immediately available to take over all regular health facility duties.

2. **Medical Care for Patients:** KEMRI/CDC will facilitate medical care at the health facility for enrolled participants as long as the particular study agrees to pay for the medical care. Study-related medical procedures that are not part of routine care will be coordinated and reimbursed through KEMRI/CDC study staff.
3. **Data:** Medical data needed for medical management of the patient will be shared with appropriate medical staff at the clinic; other data will be shared in aggregate form, without identifiers, for the MOH/clinic information/use.
4. **Space:** The health facility agrees to provide a room for the project for consultation with study participants which will be returned to the health facility at the end of the project.
5. **Equipment:** KEMRI/CDC will utilize existing radiological facilities for the conduct of the study at pre-arranged costs for study participants.
6. **Monitoring:** Monitoring of the KEMRI/CDC studies is done on a regular basis. One or more team members of a particular study or external monitors in the case of clinical trials will monitor the quality of the studies and visit this health facility on a regular basis. This will be to ensure that the conduct of the study is within the acceptable standards, medical records, samples and clinical records are being kept according to the right regulations. The facility in-charge agrees to allow these monitors to review the study records and all related documents kept in the facility, as needed.
7. **Relationship between the parties:** Nothing contained herein shall be construed as establishing a relationship of agent and principal or master and servant between the parties. Each party shall have full control of its operations and undertakings and shall have full responsibility for activities and duties carried by it and on its behalf. This MOU is not intended to, and does not, and may not be relied upon to create a right or benefit, substantive or procedural, enforceable by law by either party against the United States.
8. **Good faith and Fairness:** The parties undertake to act in good faith with respect to each other‟s rights under the terms of agreement and objectives of this MoU.
9. **Confidentiality: The** parties recognize the impracticality of providing for every contingency, which may arise during or after the life of the MoU and hereby agree t

operate fairly. The parties shall exchange all necessary documents of incorporation at the start of co-operation and keep each other informed of any changes thereafter.

1. **Notices:** This agreement may be terminated by either party upon 30 days written notice.
2. **Meetings:** There will be meetings held every three months between both parties throughout the course of the year, however, during initial stages of this agreement, it may be necessary to have more frequent meetings. Additionally, reports will be provided by both parties to discuss the agreement and any changes needed.

This agreement may be modified upon agreement by both parties.

The Principal KEMRI/CDC contact is Center Director &The principal contact for the health facility is the officer in charge.Both Parties hereby agree to the terms laid out by this Memorandum of Understanding, and agree that it is in the best interest of the community and all members involved that operation of this collaborative effort is a success.

1) For KEMRI/CDC Research and Public Health Collaboration

Signature_____Date……

Collaborative Agreement Principal Investigator

2) For the health facilities,

Signed……Date……

……

Health facility in charge

Cc: Dr._____Medical officer of Health

Appendix 3: Informed Consent Documents

Appendix F. Enrollment Informed consent

Consent: A pilot program to evaluate contact investigation in the household of patients with multi-drug resistant and drug-susceptible tuberculosis in 3 countries

Flesch-Kincaid Grade Level 6.1

Investigators	Affiliation
Dr. Kevin Cain,	CDC-Kenya
Dr. Kayla Laserson,	CDC-Kenya
Dr. Vincent Otieno,	KEMRI/CDC-Kenya.
Dr. Barbara Burmen	KEMRI/CDC-Kenya.
Janet Agaya,	KEMRI/CDC-Kenya
Peter Nyamthimba ,	KEMRI/CDC-Kenya
Dr. Mary Reichler,	DTBE, CDC-USA
Dr. Heather Menzies,	DTBE, CDC-USA

INTRODUCTION

You are being asked to participate in a pilot program that seeks to test people who live in the same places a patient with TB to see if they also have TB. The decision to agree or not agree to participate in this program is completely yours.

In this program, we will investigate people who live in the same places the person with TB, to determine the spread of TB within the same house/home or compound.

WHY IS THIS RESEARCH STUDY BEING DONE?

This program seeks to collect health information by investigating those living in the same place as the patients diagnosed with TB. We will see if the program does a good job of finding more patients who need treatment for TB or HIV earlier. Here in Kenya, the Ministry of Health, Division of Leprosy, TB, and Lung Disease has encouraged that those in the same house as the patients with TB should be investigated for TB to increase the early detection of patients with TB in Kenya, thereby reducing spread and finally decreasing the burden of TB in Kenya. However, this type of program is not implemented in very many places in Kenya, and no data exist about the result of such a program.

VOLUNTARY PARTICIPATION

You are free to choose not to participate in this pilot program. Even if you choose not to participate in this pilot program, you will not loose any of your rights

PROCEDURE

Who will be in this Pilot Program: Patients who have been newly diagnosed TB and people living in the same place as those patients may be eligible for the pilot program.

The TB patient will be requested to inform the household members that he/she has been identified with TB and that they are to report to a specified clinic within the study area for screening within 7 days. A follow-up visit to the place where the patient lives will be made 14-30 days after the patient was diagnosed with TB to identify and screen for TB other members of the house/home who did not manage to present to the clinic for screening or were not named by the TB patient.

Contact screening. All household members of selected TB patients, along with the patients, will be interviewed to collect symptom, exposure, and risk information. A TB skin test will be done for the people living in the same place as the TB patient: The TB skin test is done by injecting a substance under the skin of the forearm with a needle. It will form a bump right after the injection and which will last for about 10 minutes. Within 8 to 72 hours after the injection, a bump can be expected if you have a positive reaction. The test will be read and its meaning explained to the participant.

If the first TB skin test is negative, another test will be performed 8-10 weeks later. A chest x-ray will be performed for all patients with a positive TB skin test or symptoms of TB. HIV testing will be offered to all TB patients and all people who live with them.

Follow up Visits: Follow-up visits or telephone calls will be made to the household of each selected TB patient at 6, 12, 18, and 24 months after the study entry. At each follow-up visit or telephone encounter, you and the head of the household will be asked whether you or any member of the household has been diagnosed with active TB, or has developed symptoms of TB. If you or any household member has been diagnosed with active TB, it will be confirmed at the health facility where the diagnosis was made (if the facility is reachable), and clinical data obtained from the medical records. Any household member with symptoms of TB at the time of the follow-up visit will be referred for clinical evaluation at the nearby hospital. If clinical evaluation suggests the possibility of TB, a chest radiograph will be performed and specimens for TB culture will be obtained.

All new cases of TB detected during the TB investigations on those living in the same place will be referred to the local TB control program for further evaluation and treatment. Those contacts who are HIV positive and all child contacts who are less that 5 years of age will be referred to the local TB control program for further evaluation for TB disease and TB infection and for treatment. During follow-up, sputum specimens may be collected for patients diagnosed with TB to ensure appropriate response to treatment.

All those contacts who are HIV positive and all children of less than 5 years of age will be referred to the local TB control program for further evaluation and consideration for treatment

according to national policies and guidelines. Treatment for TB will be carried out by the TB program according to national policies and guidelines, and is not a part of this pilot project.

HOW MANY PEOPLE WILL BE IN THE STUDY?

There will be up a minimum of 1950 patients with TB included in the study

Where Will The Study Be Done?

This pilot study will be conducted in 3 countries, Kenya, South Africa and India. In Kenya the study will be conducted in Nyanza province in Kisumu and Siaya Counties.

ARE THERE ANY ALTERNATIVES TO BEING IN THIS STUDY?
Your alternative is to not to participate in the pilot program

IS THERE ANY REIMBURSEMENT?
There will be reimbursement to the participant for procedures such as x ray done at the facility. However, there will be no reimbursement for procedures done in the home.

WHAT IS THE DURATION OF THE PILOT STUDY

It is expected that the study will take a period of 2 years

RIGHT TO REFUSE AND REASONS FOR WITHDRAWAL

Accepting to participate in this pilot program is your choice. You do not have to accept to participate in this pilot project if you do not want to. If you choose to participate in this pilot project, you may change your mind and choose not to continue with participation at any time. If you decide to change your mind at any time, you are requested to inform the study staff as soon as you can. You will not be required to provide the reason for changing your mind.

BENEFITS AND RISKS

Some of the benefits that you are likely to see when you accept to participate in this study is that the there will be early diagnosis and treatment of the TB cases which could result to lower risk of harm or death and even decrease the spread of TB to other family members. The information received from this study will also help in providing more information on spread of TB within households. This will help to improve TB control in Kenya.

The only risk to patient is the loss of confidentiality; however, multiple precautions will be instituted to prevent this from happening.

CONFIDENTIALITY
If you agree to participate in this pilot project, study staff will look at and extract information from your health services records. Your study records and specimens will also be assigned a unique study code number but you may also be identified with your name. The sponsor and its

partners will visit the health facilities and review your study and medical records to monitor the proper conduct of the study.

Study investigators may publish reports about this study and present the study findings to scientific groups. Your identity/name will not be revealed.

Your study and medical records may be reviewed by the Ethics Review Committee (ERC). An ERC helps to protect the rights of research subjects.

Your study records will be kept at in private and confidential manner. You will not be able to review your study records until after the study is complete and the data is analysed

PERSONS TO CONTACT

If you have any questions about participation in the pilot study, feel free to ask them. If you have more questions later, if you wish to report a medical problem that may be related to the study, or if you feel that your rights have been affected by this study, you may contact one of the following persons:

Name	Office Number	After-Hours Number
Janet Agaya	057-2022902/59/02	0700553578
Secretary of KEMRI Ethical Review Committee	(020)2722541 or 0722205901, fax (254) (020) 2720030, P. O. Box 54840-00200 Nairobi-Kenya.	

If you have questions about your rights as a research subject, you or your child may contact the KEMRI Ethical Review committee that reviews research being done on humans (Institutional Review Board) by calling (020)2722541 or 0722205901.

We will give you a signed copy of this form to take home.

SENDING OF SPECIMEN FOR FURTHER TESTING:

As part of this study, you may have specimens tested for TB in the laboratory. Specimens are collected to help diagnose TB by growing the bacteria in the laboratory. This will done at the KEMRICDC TB Laboratory in Kisian. For anyone who has a specimen that grows TB, we would like to send some of that TB bacteria to the CDC laboratory in the United States for further testing which will include checking to see if it is the same TB as other people in your home or in your community have. No testing of human genetics will be done as part of this testing, as we will only be doing tests on the TB bacteria. Mark below your preference

_____I do give permission for my samples to be sent to the CDC laboratory in the United States

_____I do not give permission for my samples to be sent to the CDC laboratory in the United States

AGREEMENT AND CONSENT STATEMENT your signature below indicates that:

I have had an opportunity to discuss this study and ask questions and am satisfied with the answers
I hereby agree for to participate in this pilot study
After choosing to participate in this pilot study, I may withdraw this consent at any time
I have been given a chance to ask questions
I feel that my questions have been answered adequately.

_____

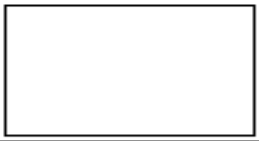
Name of study participant (please print)

_____

Name of participants parent/ guardian (Please print)

_____ _____

Signature of participant's parent/guardian Date



_____ _____

Thumb-print of participant parent/guardian Date

_____

Name of Witness (Please print)

_____ _____

Signature of witness (Please print) Date

_____N

Name of person obtaining consent

_____ _____

Signature of person obtaining consent Date

Appendix G: Enrollment Parental permission

Parental permission form: A pilot program to evaluate contact investigation in the household of patients with multi-drug resistant and drug-susceptible tuberculosis in 3 countries

Flesch-Kincaid Grade Level 6.1

Investigators	Affiliation
Dr. Kevin Cain,	CDC-Kenya
Dr. Kayla Laserson,	CDC-Kenya
Dr. Vincent Otieno,	KEMRI/CDC-Kenya
Janet Agaya,	KEMRI/CDC-Kenya
Dr. Barbara Burmen	KEMRI/CDC-Kenya.
Peter Nyamthimba ,	KEMRI/CDC-Kenya
Dr. Mary Reichler,	DTBE, CDC-USA
Dr. Heather Menzies,	DTBE, CDC-USA

INTRODUCTION

You are being asked to allow your child to participate in a pilot program that seeks to test people who live in the same places a patient with TB to see if they also have TB. The decision to agree or not agree allow your child to participate in this program is completely yours.

In this program, we will investigate people who live in the same places as the person with TB, to determine the spread of TB within the same house/home or compound.

WHY IS THIS RESEARCH STUDY BEING DONE?

This program seeks to collect health information by investigating those living in the same place as the patients diagnosed with TB. We will see if the program does a good job of finding more patients who need treatment for TB or HIV earlier. Here in Kenya, the Ministry of Health, Division of Leprosy, TB, and Lung Disease has encouraged that those who stay in the same place as the patients with TB should be investigated for TB to increase the early detection of patients with TB in Kenya, thereby reducing spread and finally decreasing the burden of TB in Kenya. However, this type of program is not implemented in very many places in Kenya, and no data exist about the result of such a program.

VOLUNTARY PARTICIPATION

You are free to choose not to allow your child to participate in this pilot program. Even if you choose not to allow your child to participate in this pilot program, you or your child will not loose any of your rights

PROCEDURE

Who will be in this Pilot Program: Patients who have been newly diagnosed TB and people living in the same place as those patients may be eligible for the pilot program.

The TB patient will be requested to inform the household members that he/she has been identified with TB and that they are to report to a specified clinic within the study area for screening within 7 days. A follow-up visit to the place where the patient lives will be made 14-30 days after the patient was diagnosed with TB to identify and screen for TB other members of the house/home who did not manage to present to the clinic for screening or were not named by the TB patient.

Contact screening. All household members of selected TB patients, along with the patients, will be interviewed to collect symptom, exposure, and risk information. A TB skin test will be done for the people living in the same place as the TB patient: The TB skin test is done by injecting a substance under the skin of the forearm with a needle. It will form a bump right after the injection and which will last for about 10 minutes. Within 8 to 72 hours after the injection, a bump can be expected if you have a positive reaction. The test will be read and its meaning explained to the participant.

If the first TB skin test for your child is negative, another test will be performed 8-10 weeks later. A chest x-ray will be performed for all patients with a positive TB skin test or symptoms of TB. HIV testing will be offered to all TB patients and all people who live with them.

Follow up Visits: Follow-up visits or telephone calls will be made to the household of each selected TB patient at 6, 12, 18, and 24 months after the study entry. At each follow-up visit or telephone encounter, you, your child and the head of the household will be asked whether you or any member of the household has been diagnosed with active TB, or has developed symptoms of TB. If your child or any household member has been diagnosed with TB, it will be confirmed at the health facility where the diagnosis was made (if the facility is reachable), and clinical data obtained from the medical records. Any household member with symptoms of TB at the time of the follow-up visit will be referred for clinical evaluation at the nearby hospital. If clinical evaluation suggests the possibility of TB, a chest radiograph will be performed and specimens for TB culture will be obtained.

All new cases of TB detected during the TB investigations on those living in the same place will be referred to the local TB control program for further evaluation and treatment. Those contacts who are HIV positive and all child contacts who are less that 5 years of age will be referred to the local TB

control program for further evaluation for TB disease and TB infection and for treatment. During follow-up, sputum specimens may be collected for patients diagnosed with TB to ensure appropriate response to treatment.

All those contacts who are HIV positive and all children of less than 5 years of age will be referred to the local TB control program for further evaluation and consideration for treatment according to national policies and guidelines. Treatment for TB will be carried out by the TB program according to national policies and guidelines, and is not a part of this pilot project.

HOW MANY PEOPLE WILL BE IN THE STUDY?

There will be up a minimum of 1950 patients with TB included in the study

Where Will The Study Be Done?

This pilot study will be conducted in 3 countries, Kenya, South Africa and India. In Kenya the study will be conducted in Nyanza province in Kisumu and Siaya Counties.

ARE THERE ANY ALTERNATIVES TO BEING IN THIS STUDY?

Your alternative is to not allow your child to participate in the pilot program

IS THERE ANY REIMBURSEMENT?

There will be reimbursement to the participant for procedures such as x ray done at the facility. However, there will be no reimbursement for procedures done in the home.

WHAT IS THE DURATION OF THE PILOT STUDY

It is expected that the study will take a period of 2 years

RIGHT TO REFUSE AND REASONS FOR WITHDRAWAL

Agreeing for your child to participate in this pilot program is your choice. You do not have to accept for your child to participate in this pilot project if you do not want to. If you choose to allow your child to participate in this pilot project, you may change your mind and choose not allow him/her to continue with participation at any time. If you decide to change your mind at any time, you are requested to inform your child and the the study staff as soon as you can. You will not be required to provide the reason for changing your mind.

BENEFITS AND RISKS

Some of the benefits that your child is likely to see when you accept to participate in this study is that the there will be early diagnosis and treatment of the TB cases which could result to lower risk of harm or death and even decrease the spread of TB to other family members. The information received from this study will also help in providing more information on spread of TB within households. This will help to improve TB control in Kenya.

The only risk to patient is the loss of confidentiality; however, multiple precautions will be instituted to prevent this from happening.

CONFIDENTIALITY

If you agree for your child to participate in this pilot project, study staff will look at and extract information from his/her health services records. Your childs study records and specimens will also be assigned a unique study code number but your child may also be identified with his/her name. The sponsor and its partners will visit the health facilities and review your childs study and medical records to monitor the proper conduct of the study.

Study investigators may publish reports about this study and present the study findings to scientific groups. Your child's identity/name will not be revealed.

Your child's study and medical records may be reviewed by the Ethics Review Committee (ERC). An ERC helps to protect the rights of research subjects.

Your child's study records will be kept at in private and confidential manner. You or your child will not be able to review the study records until after the study is complete and the data is analysed

PERSONS TO CONTACT

If you have any questions about your child's participation in the pilot study, feel free to ask them. If you have more questions later, if you wish to report your child's medical problem that may be related to the study, or if you feel that your child's rights have been affected by this study, you may contact one of the following persons:

Name	Office Number	After-Hours Number
Janet Agaya	057-2022902/59/02	0700553578
Secretary of KEMRI Ethical Review Committee	(020)2722541 or 0722205901, fax (254) (020) 2720030, P. O. Box 54840-00200 Nairobi-Kenya.	

If you have questions about your child's rights as a research subject, you or your child may contact the KEMRI Ethical Review committee that reviews research being done on humans (Institutional Review Board) by calling (020)2722541 or 0722205901.

We will give you a signed copy of this form to take home.

SENDING OF SPECIMEN FOR FURTHER TESTING:

As part of this study, you may have your child's specimens tested for TB in the laboratory. Specimens are collected to help diagnose TB by growing the bacteria in the laboratory. This will done at the KEMRICDC TB Laboratory in Kisian. For anyone who has a specimen that grows TB, we would like to

send some of that TB bacteria to the CDC laboratory in the United States for further testing which will include checking to see if it is the same TB as other people in your home or in your community have. No testing of human genetics will be done as part of this testing, as we will only be doing tests on the TB bacteria. Mark your preference below

_____I do give permission for my child's samples to be sent to the CDC laboratory in the united states

_____I do not give permission for my child's samples to be sent to the CDC laboratory in the united states

AGREEMENT AND CONSENT STATEMENT your signature below indicates that:

I have had an opportunity to discuss this study and ask questions and am satisfied with the answers
I hereby agree for my child to participate in this pilot study
After allowing my child to participate in this pilot study, I may withdraw this permission at any time
I have been given a chance to ask questions
I feel that my questions have been answered adequately.

_____

Name of study participant (please print)

_____

Name of participants parent/ guardian (Please print)

_____

Signature of participant's parent/guardian Date

_____ _____

Thumb-print of participant parent/guardian Date

_____

Name of Witness (Please print)

_____ _____

Signature of witness (Please print) Date

Name of person obtaining permission	
Signature of person obtaining permission	Date

Appendix 4: Informed Consent Cover Sheet and Checklist

KEMRI/CDC: TB BRANCH

STUDY NAME: CONTACT INVESTIGATION

STUDY FORM TITLE: INFORMED CONSENT

COVERSHEET FORM NO. 0190 Page 1 of 2

Patient ID _____ Participant initials _____

By whom: Consenting staff

Instructions:
1st and 2nd level QC must be completed before any study procedures are conducted

Week Visit/Month:

Version number and date of informed consent used during informed consent discussion

Version Number · Version Date

DD MMM YYYY

Is identification document available for identity verification? YesNo

Date of Informed Consent Discussion**:**

DD MMM YYYY

Time of Informed Consent Discussion: Time (24hr) Time (24 hr**)**

Start time	End Time

No (*If No, an impartial and literate witness should be present during the entire informed consent discussion*) staff

Is the participant/participant‟s

parent/guardian literate?

Language of informed consent discussion? English Kiswahili Luo

Was this a re-consenting? Yes No

Were all participant‟s/participant‟s parent/guardian questions answered**?** Yes No N/A

Was the assessment of comprehension completed? Yes No

Did the participant/participant‟s parent/ guardian comprehend all information required to make an informed decision? Yes No

Was participant/participant‟s parent given ample time to consider all options before making an informed decision? Yes No

For illiterate participant/participant‟s parent/ guardian oral consent and thumbprint obtained before witness signs and dates the ICF? Yes No N/A

Has participant/participant‟s parent/ guardian provided consent/assent**?** Yes No

Has a copy of signed and dated informed consent form been given to the participant/participant‟s parent/ guardian? Yes No *If no, explain reason below:*

Notes on the Informed consent process:

Form completed by:_____

Date Form Completed :

DD MMM YYYY

KEMRI/CDC: TB BRANCH
STUDY NAME: CONTACT

INVESTIGATION STUDY FORM TITLE:

INFORMED CONSENT QC CHECKLIST

FORM NO. 0119 Page 1 of 1

Patient ID _____ Date of Consent____/ __ __/ _____

Description of activity	**1st level self-checks (TICK/N/A)**	**2nd level QC checks (TICK/N/ A)**	**3rd level QC checks**
Confirm identity of participant			
Verify literacy level of the participant.			
Preferred language			
Consent: Right version date, number and number of pages.			
Correct names are written on the correct fields.			
Check for signature consistency on forms.			
Confirm documentation of dates			
Check for errors in documentation			
Legibility of data checked			
Appropriate documentation if witness is used			
Explanation provided for discrepancies, errors in spelling, overwriting among others if any			
A signed copy of the consent form given to the participant			
Staff Initials, Signature and Date			

Comments_____

_____

Staff Initials (Self-QC Check)_____ Date__ Staff Initials (2nd QC

Check)_____Date_____

QC Officers Initials_____Date_____

Appendix 5: Appointment schedules

Timeline	Steps	Activities	Location
Day 0			Health Facility
Day 0-4	Smear(+) TB patient identified		Health Facility
Day 0-7	Molecular MDR-TB testing of sputum*	Sputum culture HIV Test Medical History Contact identified	Health Facility
Day 5-30	TB patient evaluati and interview on	TST Exposure history Medical History CXR if required	Health Facility/Household
Day 40-60	Contact evaluation	Identify contacts	Household
Day 40-60	TB patient 2nd interview	Identify Contacts Home visit	Health Facility/Household
Day 90 – 105	Household visit	TST for initial TST-ve Symptom Screen CXR if required	Health Facility/Household
6 months	Contact 2nd evaluation	History of TB in contacts Where treated/dates/type TB symptoms in contacts	Health Facility/Household
12 months	Household visit or telephone call	History of TB in contacts Where treated/dates/type TB symptoms in contacts	Health Facility/Household
18 months	Household visit or telephone	History of TB in	Health

	call	contacts Where treated/dates/type TB symptoms in contacts	Facility/Household
24 months	Household visit or telephone call	History of TB in contacts Where treated/dates/type TB symptoms in contacts	Health Facility/Household

Appendix 6: Activity Checklist

Checklist: Contact Investigation Study

PID:_____Date_____Completed By_____

(dd/mmm/yyy)

CRF/Activity Title	Outcome (Tick N/A)	1st QC Level Initials	Date	2nd QC Level Initials	Date
Screening form completed					
Eligible					
Ineligible					
Consent Form					
Consented					
Declined					
Assent Form					
Assented					
Declined					
Index interview Completed					
Index Medical Record Review					
Index Laboratory Record Review					
Household contacts identified					
Household site visit conducted					
Contacts traced					
Contact screened for eligibility					
Contacts transported to facility for screening					
Contacts completed Screening					
Follow up interview done					

QC_____(dd/mmm/yyy) By :_

Appendix 7: Data Collection Tools

Tables
Index Case
CC001: Patient Eligibility
CC002: CaseClinicRecordReview
CC004: CaseInterview
CC004B: HouseholdContactsIdentification
CC005A: IndexHIVTestResults
CC005B: IndexCXR
CC006: IndexLabCultureDSTResults
CC009: HouseholdSiteVisit
Contacts
CC007: ContactInitialTracingAttemp
CC008: ContactEligibility
CC010:ContactInterview
CC011A:ContactHIVTestResults
CC011B:ContactTST
CC011A:ContactCXR
CC012:CONTACTLabResults
CC013:ContactFollowupTracingAttempts
CC014:ContactFollowUpInterview

Appendix 8: Columns of the IPT Register

Serial Number	
District Registration Number	
Province	
County	
District	
Zone	
Health Facility	
Year	
Quarter	
Sex M/F	
Age on registration	
Weight (Kgs)	
Physical Address	
Mobile	
Comprehensive Care Clinic No	
Indication For IPT	
Dose	
Date Started IPT	
Treatment Outcome	
Treatment Outcome Date	
Reason For TNC	
Month 6 Follow up TB Status	
Month 12 follow-up TB Status	
Month 18 follow up TB Status	
Month 24 follow-up TB Status	
HIV Status	
Remarks	

Appendix 9: IRB Approval KEMRI SSC # 2494

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel (254) (020) 2722541, 2713349, 0722-339801, 0733-400805, Fax: (254) (020) 2720051
E-mail: director@kemri.org info@kemri.org Website: www.kemri.org

KEMRI/RES/7/3/1 February 26, 2013

TO: KEVIN CAIN,
PRINCIPAL INVESTIGATOR

THRO': DR. JOHN VULULE,
THE DIRECTOR, CGHR,
KISUMU

FORWARDED
DIRECTOR
CENTRE FOR GLOBAL HEALTH RESEARCH

RE: SSC PROTOCOL NO. 2494 (*INITIAL SUBMISSION*): IMPROVING TUBERCULOSIS CASE DETECTION IN WESTERN KENYA (VERSION 1.2 DATED 13 NOVEMBER 2012)

This is to inform you that during the 212th meeting of the KEMRI/ERC meeting held on 26th February 2013, the above study was reviewed.

The Committee notes that the above referenced study is a cluster randomized study that will determine the increase in TB case detection achieved through 4 different strategies as shown below:

Strategy	Study participant	Diagnostic method
Standard practice	Patient	Daily Observed Therapy (DOTS)
Facility based case finding	Patient and person accompanying patient household members	Acid Fast Bacillus (AFB) sputum smears Xpert MTB/Rif assay
Household contact investigation	Patient and household members	Tuberculin testing AFB sputum smears Xpert MTB/Rif assay Culture and drug susceptibility (if indicated) Smear negative and extra-pulmonary assessment will be done according to the MoH guidelines
Community based	Community members who will be mobilized by CHW.	Tuberculin testing AFB sputum smears

	Mobile field sites will remain in an area for 2 weeks at a time	Xpert MTB/Rif assay Culture and drug susceptibility (if indicated) Smear negative and extra-pulmonary assessment will be done according to the MoH guidelines
Combination	All the interventions will be implemented simultaneously within communities to this strategy	Tuberculin testing AFB sputum smears Xpert MTB/Rif assay Culture and drug susceptibility (if indicated) Smear negative and extra-pulmonary assessment will be done according to the MoH guidelines

The request for waiver of consent is justified and approved. Due consideration has been given to ethical issues and the study is hereby **granted approval** for implementation effective this **28th day of February 2013**, for a period of twelve (12) months.

Please note that authorization to conduct this study will automatically expire on **25th February 2014**. If you plan to continue with data collection or analysis beyond this date, please submit an application for continuing approval to the ERC Secretariat by **13th January 2014**.

You are required to submit any amendments to this protocol and other information pertinent to human participation in this study to the ERC prior to initiation. You may embark on the study.

Yours sincerely,

DR. ELIZABETH BUKUSI,
ACTING SECRETARY,
KEMRI/ETHICS REVIEW COMMITTEE

Appendix 10: Randomization strategy and Health Facility assignment

Unit	Strategy	Location	Sublocation	Facilities
W1	HC	N Central Seme	Kadero	Nduru Kadero Dispensary
		S Central Seme	E Kanyadwera	Kolenyo Dispensary
		S Central Seme	W Kanyadwera	OriangKanyadwera dispensary
		West Seme	East Reru	Shalom Medical Clinic
		West Seme	Ngere East	
		West Seme	West Ngere	Oswere Dispensary
		West Seme	West Reru	Arito Langi Dispensary, Opapla Dispensary,
W2	HC	S Central Seme	Lower Kombewa	Melkasons Clinic
		S Central Seme	W Othany	Bodi Health Center , Asat Beach Dispensary
		S West Seme	Alwala	OriangAlwala Dispensary
		S West Seme	Ang'oga	
		S West Seme	E Kadinga	Manyuanda Sub County Hospital
		S West Seme	N Alungo	
		S West Seme	S Alunga	Dago Jonyo dispensary
		S West Seme	W Kadinga	
W3	H	N Central Seme	Katieno East	Bar Korwa Dispensary
		N Central Seme	Katieno West	Korwenje Dispensary
		N Central Seme	Kowe North	
		N Central Seme	Kowe South	Otieno Owala Dispensary
		S Central Seme	Upper Kombewa	Kombewa Sub county referral hospital
		Otwenya	N Ratta	Ratta Dispensary
		Otwenya	S Ratta	Onyinjo Dispensary
W4	HCM	East Seme	Kaila	Kuoyo dispensary
		East Seme	Kit Mikaye	Langi Kawino Dispensary
		East Seme	KokerKajulu	Rodi dispensary
		Otwenya	E Kolunje	Miranga Sub County Hospital
		Otwenya	W Kolunje	
		S Central Seme	E Othany	Lolwe Dispensary
W5	H	Kisumu NW	Marera	Chulaimbo sub district hospital
		Kisumu NW	Sunga	Sunga Dispensary
		West Kisumu	Lower Kadongo	
		West Kisumu	Newa	
		West Kisumu	Upper Kadongo	Lwala Kadawa Dispensary

W6	HCM	Kisumu NW	E Karateng	Siriba Dispensary, Mbaka Oromo dispensary
		Kisumu NW	W Karateng	Maseno Medical Clinic, Universit Maseno Mission y Masabo Hospital, Hospital
		West Kisumu	N Kapuonja	Riat Dispensary
		West Kisumu	S Kapuonja	Mainga Dago Jonyo Dispensar y, Dispensary
L1	HCM	Kisumu East	Kogony	SOS Children Medical Clinic
		Town	Bandari	Port florence hospital, Usoma Dispensary
L2	HC	Kisumu East	Kanyakwar	LBDA dispensary
L3	H	Kolwa Central	Kasule	Geva Family Health Services, K Met clinic, Olps Clinic
L4	HCM	Town	Northern	Victoria Sub District Hospital, Liverpool VCT (Kisumu East), Kisumu District Hospital, St Lukes Hospital , Railways Dispensary,
		Town	Southern	Administration Police Dispensary, Star Maternity and Nursing Home, ST Vincents Clinic (Kisumu East), Mosque Dispensary, Central Clinic (Kisumu East), St Judes Clinic, Jalaram Nursing Home, Tuungane Youth Transition center, Tuungane youth center, Aga Khan Hospital, Avenue Health Care clinic, MV patel Clinic, Sayyid Asha Dispensary, Guru Nanak dispensary, Al Nur Medical Clinic and Laboratory , Kisumu Diagnostic Center
L5	H	Kolwa West	Nyalenda 'A'	Hope for Widows and Children foundation nursing home, Abundant Life Clinic, Interfelk Medical Center, kowino dispensary
L6	HC	Kolwa West	Nyalenda 'B'	Milimani Hospital, Nyalenda Health Center, PandPieri Community Dispensary, St Johes and Ring Road Health Clinic, Dunga Nursing Home
M1	C	Kajulu East	Kadero	Gita Sub–county hospital, Got Nyabondo dispensary
		Kajulu East	Okok	

M2	M	Kajulu West	konya	St Monica hospital, Mt Sinai Hospital, Disciples of Mercy Clinic, Careplus Medical Services, Mamboleo Medical Clinic
		Kajulu West	WathOrego	Simba Opepo Dispensary
M3	S	Kondele	Migosi	
M4	M	Kondele	Nyawita	K Met Cockran
M5	C	Kondele	Manyatta 'A'	Helsamy Medical Clinic, Nightingale Medical Clinic
M6	S	Kolwa West	Manyatta 'B'	Kuoyo Health Center, JOOTRH, Marie Stopes Nursing Home (Kisumu), KASH DICE, Tuungane Youth Transition Center, Avenue Hospital, Nyaweri Deaf VCT, FPOHK Dispensary, Kisumu police Lines dispensary, Tumaini DICE

Appendix 11: Columns of TB registers

Serial Number
Date of Registration
District Registration Number
Province
County
District
Zone
Health Facility
Year
Quarter
Sector
Sex M/F
Age on registration
Weight (Kgs)
Height (Mtrs)
BMI
MUAC
Physical address (Neighbor,Primary School) Cell Phone
DOT by
Type of TB P/EP
EPTB Sub Type
EPTB Others
Type of patient
CD4 First Date
CD4 Last Date
Culture S
Culture R

Culture E
Culture H
X-ray Y/N
Sputum Smear Examination 0th Month Result
0th Month Serial No and Quantification
Sputum Smear Examination 2by3 Month Result
2by3 Month Serial No and Quantification
Sputum Smear Examination 5th Month Result
5th Month Serial No and Quantification
Sputum Smear Examination 6by8 Month Result
6by8 Month Serial No and Quantification
Regimen
Date of treatment started
Gen expert
Lipa Hain Rifampicin
Lipa Hain Isoniazid
HIV Test Date
HIV Status
Partner HIV Test Date
Partner HIV Status
Referred BY: VCT/HCC/STI/HBC/PS/ANC/SR/CI
Referred TO VCT/HCC/STI/HBC/PS/ANC
Cotrimoxazole Preventive Therapy Y/N
Cotrimoxazole Preventive Therapy (Date Started)
ART Y/N
ART (Date Started)
Nutrition Support

Treatment Outcome
Treatment Outcome Date
Remarks

Appendix 12: Number of TB cases in children by health facilities in Kisumu County

Health Facility	**2013**	**2014**	**2015**
Arito Langi Dispensary	1	0	6
Aga Khan Hospital (Kisumu)	0	17	0
Avenue Health Care Clinic	0	0	6
Bodi Health Centre	4	0	3
Got Nyabondo Dispensary	3	1	0
Kajulu/Gita Dispensary	0	0	3
Kisumu District Hospital	13	12	11
Liverpool VCT (Kisumu East)	0	1	0
Manyuanda Health Centre	1	0	0
Maseno Mission Hospital	4	1	1
Maseno University Medical Clinic	1	0	0
Miranga Sub District Hospital	0	0	1
Nyalenda Health Centre	1	9	4
Nyanza Provincial General Hospital (PGH)	18	20	7
OriangAlwala Dispensary	2	0	1
PandPieri Community Health Centre	2	0	0
Railways Dispensary (Kisumu)	1	0	0
Rodi Dispensary	3	0	0
St Jones &Ring Road Health Clinic	1	0	0
Tuungane Youth Centre (Kisumu East)	0	0	1
Total	**55**	**61**	**44**

Appendix 13: Number of children put on IPT in facilities in Kisumu County

Health Facility	**2014**	**2015**
Administration Police Dispensary (Kisumu East)	0	4
Arito Langi Dispensary	0	1
Bodi Health Centre	2	5
Kisumu District Hospital	0	23
Manyuanda Health Centre	0	1
Maseno Mission Hospital	0	2
Miranga Sub District Hospital	0	1
Nduru Kadero Dispensary	0	1
Nyanza Provincial General Hospital (PGH)	0	12
PandPieri Community Health Centre	0	6
Railways Dispensary (Kisumu)	0	5
Rodi Dispensary	0	2
Total	**2**	**63**