EFFECTIVENESS OF ISONIAZID PROPHYLAXIS IN PREVENTION OF TUBERCULOSIS IN CHILD HOUSEHOLD CONTACTS OF ADULTS WITH PULMONARY TUBERCULOSIS IN NAIROBI COUNTY, KENYA

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P97/13283/2009

A THESIS SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF DOCTOR OF PHILOSOPHY IN PUBLIC HEALTH (EPIDEMIOLOGY AND DISEASE CONTROL) IN THE SCHOOL OF PUBLIC HEALTH, KENYATTA UNIVERSITY

APRIL 2015

DECLARATION

This thesis is my original work and has not been presented for a degree in any other University or for any other award.

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DEDICATION

I dedicate this thesis to the almighty God, giver of life and the source of all wisdom. I also dedicate it to all the children and their parents/ guardians, who participated in this noble course, so as to allow future generations of children in similar circumstances to benefit.

ACKNOWLEDGEMENT

Special thanks to my supervisors Dr. John Paul Oyore and Prof. Fred Were, for their guidance, constructive criticism and encouragement throughout the study. I greatly appreciate staff working at the study sites; specifically Lilian Muiruri, Celina Sungu, and Mary Mutheu of Kayole II sub-district hospital. I appreciate Josephine Karani, Sarah Koine and Martin Chwowe of Dandora II Health Center. Many thanks to staff at Medical Missionary of Mary, Mukuru Health Center, specifically Sister Bright, Sister Colleta, Rose Kithii and David Obara. All other staffs that indirectly supported the project through referrals and information sharing, your input was indeed appreciated. Thanks to all laboratory technicians at all study sites, including Clara Maigachio of Kenyatta University, Mulama and Felix both of Kayole II Health center, Paul of Mukuru center, and Beatrice of Dandora II Health center.

Thanks to the Division of TB and lung disease, Director Dr. Joseph Sitenei, for allowing me to use program facilities, and the District TB coordinators, Dorothy Mibei, Elizabeth Mweni, and Mr. Wambugu, for assisting in logistical issues and patient referrals. Thanks to KEMRI staff Dr. Evans Amukoye and Dr. On'gang'o for advice at proposal development stage. I appreciate faculty at Kenyatta University, namely Dr. Peterson Warutere, Dr. George Ochieng', and Dr. Samson Gwer for assisting in data analysis.

I am most grateful to the 'National Council of Science, Technology and Innovation' for and the Kenyatta University Management for financial support accorded to this project. I am indebted to my family for moral support. Last but not least, I appreciate every parent/guardian and child that agreed to participate. To all who contributed in one way or the other to this study, may God bless you mightily.

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OPERATIONAL DEFINITIONS OF TERMS

Definitions used in contact screening

Source case: Adult case of pulmonary tuberculosis (PTB) which results in infection or disease among contacts

Contacts: All children aged below 5 years who are in close contact with a source case

Close contact: Living in the same household as or in frequent contact with a source case for the preceding 3 months.

Definition of a positive tuberculin skin-test

Diameter of induration of $\geq$5 mm in HIV-infected or severely malnourished children.

Diameter of induration of $\geq$10 mm in all other children (whether or not they have received BCG vaccination).

A suggestive chest radiograph of tuberculosis

A chest radiograph with any of the following; primary complex, hilar adenopathy, milliary pattern, cavitation, pleural effusion, or any opacity or infiltration not explained by other disease. For those with a history of contact with tuberculosis or a significantly reactive tuberculin test, any lung infiltrate was considered indicative of tuberculosis.

Contact tracing

Screening of close household contacts to a source case with infectious pulmonary tuberculosis to identify infected contacts in the communities, and/or offer some preventive measures to susceptible individuals.

Isoniazid prophylaxis therapy

The administration of the drug isoniazid to vulnerable or susceptible individuals, who are at risk of tuberculosis infection, for purposes of preventing development or progression of infection.

ABBREVIATIONS AND ACRONYMS

AAFB Acid Alcohol fast bacilli

AAP American Academy of Paediatrics

AIDS Acquired immune deficiency

ARV Antiretroviral therapy

ATS American thoracic society

BCG Bacille Calmette - Guérin

BTS British Thoracic Society

CDC Center for disease control

CI Confidence Interval

CHW Community Health Worker

CNR Case Notification Rate

CSF Cerebrospinal fluid

CXR Chest X-ray

DOI Diffusion of innovation theory

DLTLD Division of Leprosy, Tuberculosis and Lung disease

DOTS Directly observed therapy

EPTB Extra pulmonary Tuberculosis

FGD Focused group discussions

FNA Fine needle aspirate

HIV Human immunodeficiency virus

HR Hazard ratio

IAP Indian Academy of Pediatrics

IDI In-depth interviews

INH Isoniazid

IPT Isoniazid prophylaxis therapy

IUAT International Union Against Tuberculosis

KNDH Kenya National Demographic Health Survey

KII Key informant Interview

KDHS Kenya demographic health survey

LFT Liver function Tests

MDG Millennium Development Goal

MDR Multidrug-resistant

MOH Ministry of Health

NASCOP National AIDS and STI Control Program

NTP National Tuberculosis program

OR Odds ratio

PCR Polymerase chain reaction

PTB Pulmonary tuberculosis

PPD Purified protein derivative

RCT Randomized controlled trial

RR Relative risk

RNA Ribonucleic acid

STI Sexually transmitted diseases

SPSS Statistical Package for Social Sciences

TB Tuberculosis

TST Tuberculin skin test

TU Tuberculin unit

UK United Kingdom

US United States of America

WHO World Health Organization

ABSTRACT

Sub-Saharan Africa continues to document high burden of pediatric TB, driven by the HIV epidemic. The urban poor are at highest risk of infection. Infected children experience rapid disease progression and severer disease. Contacts' tracing and isoniazid prophylaxis is an effective prevention strategy, but has been administered inconsistently in most resource poor countries. Perceived obstacles have been sub-optimal effectiveness in view of continuous transmission and re-infections, as well as adherence and safety concerns. The objectives of this study was to evaluate the effectiveness of IPT in preventing TB related morbidity in children in household contact with adults with TB from informal settlements in Nairobi. A prospective longitudinal cohort study was done. Child contacts of recently diagnosed PTB smear-positive adults were enrolled. Recruitment started in December 2011 to July 2013. Consent was sought. A structured questionnaire was used to get information on source case TB treatment, socio-demographic characteristics and TB knowledge. Contacts underwent baseline clinical evaluations to exclude TB disease using clinical algorithms. TST, microscopy and histology were done whenever indicated. Contacts with chronic illnesses were excluded. A blood sample was obtained at baseline for liver enzymes assays and for PCR for HIV DNA. Contacts were then put on isoniazid for 6 months and followed up monthly for 1 year for new TB infection, and compliance and adverse events monitored. Qualitative data was provided by 2FGD and KIIs. Data was analyzed using SPSS. IPT acceptability was 320 out of 366(87.3%) of eligible source cases. Most (96%) were from poor social backgrounds, and 83.4% had below tertiary level of education. All source cases were on first line anti-TB treatment. Of 428 contacts screened, 6.3% were HIV positive. The baseline prevalence of latent TB was 92 (22.2%), while 14 (3.2%) had TB disease. IPT completion rate was 368 of 414 (88.8%). Overall compliance rate was 89%. IPT failure was documented in 6 (1.6%) cases, the relative risk of new TB disease in contacts on IPT was 0.49 (95% CI 0.21 -0.86). IPT effectiveness in preventing TB in exposed contacts was 50%. On multivariate logistic regression of factors influencing IPT failure, only weight faltering of contact was significant (p= 0.005). The leading programmatic challenges reported were too many hospital visits (65.2%) and difficulties in administering tablets to children (44.3%). Side effects were documented in 22.2%, mainly skin rash (12.5%), but significant hepatotoxicity occurred in only 3(0.08%). In conclusion, child TB is prevalent in exposed contacts in informal settlings. Contact screening and IPT is an effective, acceptable and safe child TB prevention strategy for exposed child contacts in these settings, however its implementation is fraught by various social and programmatic challenges minimizing overall benefits realized. Therefore, there is need to prioritize these children in informal settlements in TB screening programs. Furthermore, linkage of IPT strategy to nutrition interventions programs, and the provision of minimal adherence support to households could greatly optimize overall effectiveness attained.

CHAPTER ONE: INTRODUCTION

1.1 Background to the study

TB is a major global public health problem, responsible for more than 4500 deaths each day. About 90% of TB cases and 98% of deaths occur in the developing world (WHO, 2012). A decade of intensified efforts at TB control has reduced global incidence except in Africa, where the disease continues to rise, due to the HIV pandemic and poverty. Children are often infected through household contact with a close relative (Marais *et al*., 2004). Childhood TB therefore reflects increasing adult TB cases. In 2011, there were an estimated 490 000 episodes of childhood TB worldwide, accounting for 6% of the total incident cases and 64 000 deaths (WHO 2012). Childhood TB remains a neglected area of research despite the severe risk of morbidity and mortality in this population.

Recent years have seen an increase in susceptible child hosts in most Sub- Saharan Africa. This has resulted from large numbers of at risk contacts aged less than 5 years, increase in HIV infected contacts, as well as the malnourished, preterm children and those with viral co-morbidities such as measles. In addition, worsening poverty and increasing conflict regions have left many children homeless or living in poor and crowded shelters, including informal settlements and camps. These environments predispose children to TB (Miller *et al*., 1973). Prevention remains the best strategy to reduction of the burden of childhood TB. The recommended preventive approaches by WHO include prompt identification and treatment of infectious adult TB cases, BCG vaccination and contact tracing and treatment of non-infectious disease and latent

infection (WHO, 1994). Despite widespread administration of neonatal BCG immunization in high burden countries, childhood TB is still on the rise. This is especially so in HIV endemic areas (von Reyn *et al*., 1987). Contact tracing and management offers the best earliest opportunity to identify infected children in the communities, and/or offer some preventive measures to susceptible individuals (Beyers *et al*., 1997, Rieder *et al*., 2002, Zachariah *et al*., 2003, CDC, 2006, WHO, 1994). WHO and IUAT both recommend treatment of latent TB in high risk patients (WHO, 1994, WHO breastfeeding update, WHO, 2006, IUAT trial 1982). IPT is the most studied chemoprophylaxis. It has also been widely used to prevent TB in household contacts with TB infected adults (IUAT trial, 1982, Whalen *et al*., 1997).

However, in resource poor settings, where majority of childhood TB occurs, use of IPT for household child contacts has been administered inconsistently. Reasons for this include fears of sub-optimal effectiveness in view of constant TB exposures and transmissions, and varied population susceptibility profiles. IPT is likely to be ineffective in preventing infection from contacts of multiple drug resistant (MDR) TB cases (Schaaf *et al*., 1999, WHO, 2006). It is also anticipated that the different social dynamics in informal settlements may influence its acceptability, adherence and feasibility. Safety concerns may also have effect on the overall effectiveness of IPT in these settings.

The National pediatric TB treatment guidelines in Kenya were launched in 2012. It recommends use of IPT in children under 5 years in household contact with TB infected adults. However, contacts tracking and IPT administration remain erratic. There are currently no published local studies to assess the effectiveness of IPT in preventing

childhood TB in informal settlings and/or to evaluate factors that influence IPT effectiveness in these informal settlings. This study sought to explore these gaps.

1.2 Problem statement

There continues to be a high prevalence of both subclinical and active disease among adults in many disadvantaged communities in Sub-Saharan Africa. TB has become endemic. Increasingly, children in such settings find themselves in households with adults with TB, hence at high risk of TB infection. Seventy percent of exposed child contacts get infected. Although universal neonatal BCG vaccination has been adopted in most Sub-Saharan Africa, Kenya included, many immunized children still contract TB from their contacts. Furthermore, passive case finding as is often the case, leads to delayed diagnosis, with significant morbidity and mortality.

According to NASCOP report 2008, Childhood TB constitutes one third of the TB case burden in Kenya (DLTLD, report 2008). From the same report, 17% of all adult TB cases came from Nairobi province. The province also recorded the second highest TB CNR of 612/ 100,000 in the country. Most of the cases reported come from the informal settlements. With a population of about 5 million Nairobians, the adult population at risk of TB is estimated at 1 million, while the child population at risk is over 330,000 children. This state therefore posses a significant public health problem. This is in a background of a HIV prevalence of 7% in Nairobi, the second highest after Nyanza province (NASCOP/MOH: 2008). Furthermore, the under 5 mortality rates for Nairobi remains high, at 64/100,000 live births. This is so despite an overall vaccine coverage of about 73% and BCG coverage of 89% (KDHS 2008-2009).

Although contact screening/IPT is an effective child TB prevention strategy, its uptake in most high burden settings and especially within the informal settlings has been inconsistent. Obstacles to its uptake have ranged from perceived questionable effectiveness, as well as acceptability and feasibility challenges. Hence, the strategy benefits have not been optimized.

1.3 Justification of study

Urban populations continue to document high TB prevalence due to overcrowding, poor ventilation and illumination of residences, poverty, and high numbers of HIV infected adults, among others. The spatial proximity of a child to an adult with infectious TB in the household posses the biggest risk of disease transmission to the child. Pediatric TB is therefore rapidly becoming a major public health concern among the urban poor, as more children are getting exposed at a very young age. Moreover, Sub-Saharan Africa, Kenya included, continues to document large numbers of susceptible hosts.

Nairobi is one of the African cities with mushrooming informal settlements. Close to 70% of urban dwellers in Nairobi now reside in informal settlements. Three informal settlements sites within Nairobi were selected for this study. These were sites that had reported an average case notification rate (CNR) of at least 15 smear positive and 30 smear negative TB patients per month, in the preceding year (anecdotal clinic TB records).

Studies from low burden countries have found IPT to be an effective child TB control strategy for household contacts to TB infected adults. Indeed, contact screening/IPT has been recommended by WHO guidelines (2010) and IUAT, and also by the local

National TB control program guidelines, for child TB contacts to infectious adults (NASCOP, 2012). Unfortunately, maximum benefit has not been realized from this strategy for contacts living in informal settlings in Nairobi. The study will inform the local TB control program and other policy makers on IPT scale up course. The findings will contribute towards helping Kenya achieve the MDG target for tuberculosis, which aims to halt and begin to reverse the incidence of TB by 2015 and MDG 5 that aims to reduce childhood mortality by two thirds by 2015.

1.4 Research Questions

1. What is the prevalence of TB infection and disease among children aged below 5 years in household contact with adults with smear positive PTB from informal settlements?
2. What is the effectiveness of 'contact screening and IPT' on reducing incidence of TB disease in children under 5 years in household contact with PTB infected adults from informal settlements.
3. What are the factors that influence the effectiveness of 'contact screening and IPT' as a TB preventive strategy for child contacts aged below 5 years in close contact with PTB smear positive adults from informal settlements?
4. What is the level of adherence to 'contact tracing and IPT' for child contacts of PTB smear positive adults from informal settlements?

1.5 Hypothesis

H_0: There is no difference in the prevalence of TB disease in child household contacts to smear positive PTB infected adults who receive IPT as compared to those who do not.

1.6 General Objective

To establish the effectiveness of 'contact tracing and IPT' in preventing TB related morbidity and mortality among children aged under 5 years, in household contact with adults with smear positive PTB.

1.7 Specific objectives

1. To determine the prevalence of TB infection and disease among children aged under 5 years in household contact with adults with smear positive PTB.
2. To determine the effectiveness of 'contact screening and IPT' on reducing incidence of TB disease in children in household contact with smear positive PTB infected adults from informal settlements.
3. To establish the factors that influences the effectiveness of 'contact screening and IPT' as a TB preventive strategy for child household contacts with PTB smears positive adults in informal settlements.
4. To establish the level of adherence to 'contact screening and IPT' use for child household contacts to PTB smears positive adults in informal settlements.

1.8 Limitations

Only adult source cases seeking treatment in the selected public TB centers were enrolled. Hence, those that may have been attending private facilities within these

communities may have been missed out. Any inherent vulnerability of contacts to TB infection was not altered, and neither did the study exhaustively evaluate all confounders to risk of TB, such as individual cough etiquette practices. The types and magnitude of exposures to external TB source cases were not determined. TST was used to identify TB infection, while the modified Kenneth Jones clinical TB score chart was used to diagnose TB disease, despite their limitations as confirmatory screening tools. Mycobacterial cultures and drug sensitivity testing were not done. All the study sites were level 2 facilities that did not have capacity to undertake detailed TB diagnostic tests, such as the histology, body fluid analysis, or radiologic tests. Hence contacts that required further evaluations were referred to the Mbagathi Hospital, a level 5 health facility, with TB diagnostic and treatment facilities. All cases referred were requested to bring back their results to the health center. The final data analysis excluded those contacts that were lost to follow- up. Although attrition from study was expected in a longitudinal study, this group comprised those with extreme form of non-adherence, hence may have led to an overestimate of adherence in this cohort.

1.9 Delimitations

The CHWs tracked all exposed contacts residing in their regions, and requested them to be brought to the ‘contacts clinics’. Regular scheduling of clinic visits ensured that any contacts with new TB suggestive symptoms were promptly evaluated. These review clinics were also used to monitor adherence and provide support to those with minor challenges, whenever needed. In order to minimize missing reports, the regional referral Hospital, the Mbagathi Hospital, was advised to send feedback reports directly to the referring center whenever they received our clients.

1.10 Assumptions

This study assumed that most TB exposures in young children occurred at household level; hence household contacts' tracing captured most childhood TB cases. It was assumed that majority of the TB source cases in the communities were diagnosed through the public TB clinics and hence enabled tracing of most of the exposed child contacts in these communities. It was presumed that all contacts completing IPT follow-up achieved optimal adherence to prevent TB disease in these children. For those contacts referred for further evaluations to Mbagathi District Hospital, it was assumed that the investigations were done by competent personnel and hence reports given were accurate and conclusive.

1.11 Conceptual framework

The main concepts used in this study originated from review of various literatures. The findings from the various studies were considered in the selection and definition of various concepts forming the conceptual framework of this research. Three theories used to construct the conceptual frame work for this study, were the diffusion of innovation (DOI) theory (White *et al*, 2003), the social cognitive theory (Glanz *et al*., 2002), and the Health believe model (Glanz *et al*, 2001).

According to DOI theory, decision to adopt a program is influenced by 3 types of knowledge; awareness knowledge that the innovation exists, procedural knowledge about how to use the innovation, and principles knowledge or understanding of how the innovation works. Diffusion is the process by which an innovation is communicated through certain channels over time among members of a social system. According to Rogers *et al.*, 2003, 5 elements determine rate of adoption of an innovation,

1. Relative advantage- is the innovation perceived to be a better than the idea it supersedes?
2. Compatibility- is the innovation consistent with existing values, past experiences, and needs of potential adopters.
3. Complexity- is the idea perceived to be difficult to understand of use?
4. Trialability- can the innovation be experimented with on a limited basis?
5. Observability- are the results of the innovation visible?

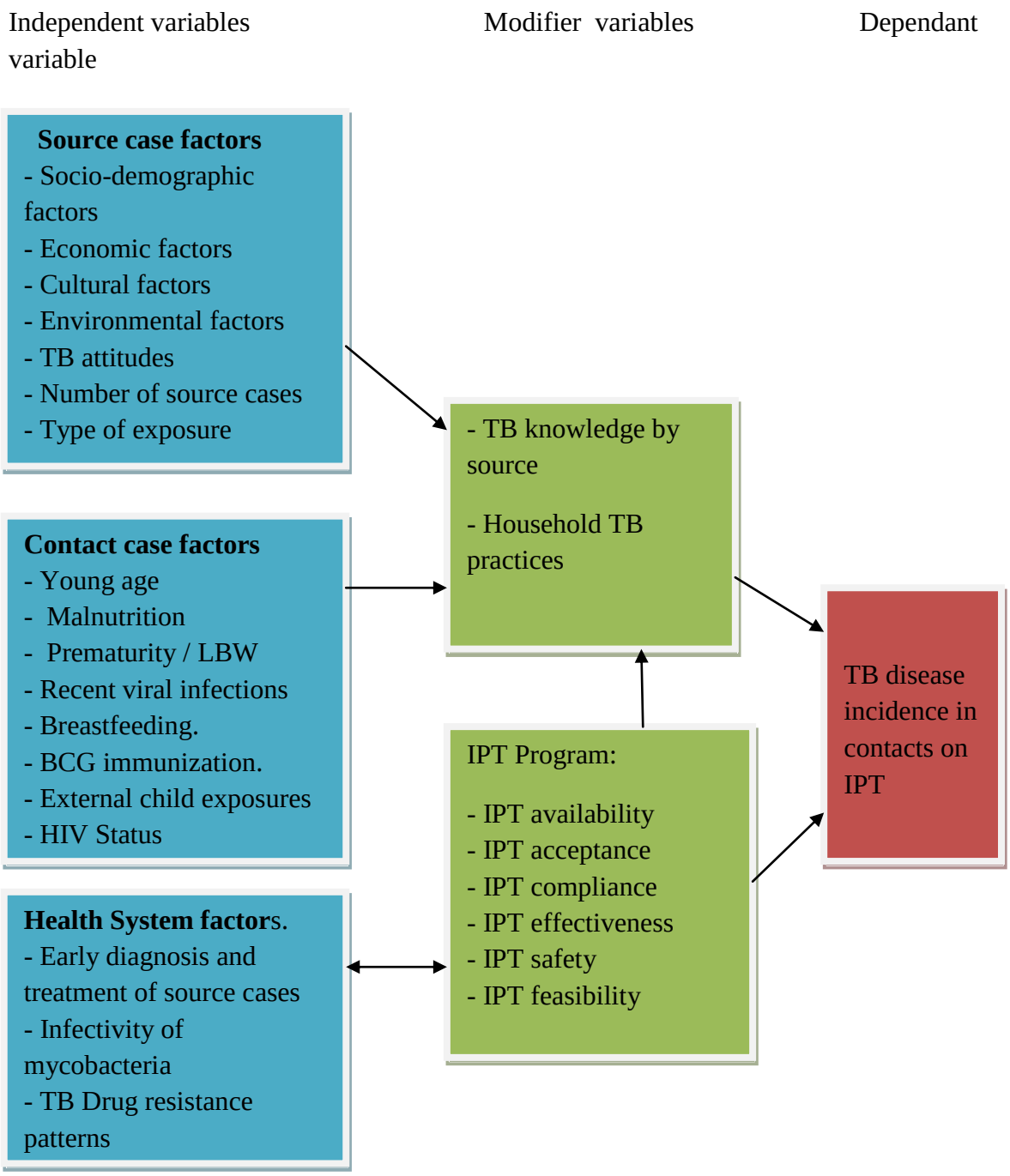
From the social cognitive theory, the concepts of environment and situation were adopted and adapted. This theory refers to the objective factors that affect a person's behavior, but are physically external to that person, and are external to the cognitive

representation of the environment by that person (Glanz *et al*., 2002). This was used to conceptualize health system and programmatic factors in this study.

The health belief model (Glanz *et al*., 2001) looks at determinants of adoption health care practices, which include the knowledge of its existence, perceived benefits and easiness of access. In this study, key determinants were existence of the service, easiness of accessing the service as determined by program factors and staff attitudes.

Source case factors and health system factors directly determined IPT uptake. Contact factors on the other hand directly determined effectiveness. TB knowledge and household practices were modifier factors that influenced IPT uptake and the observed effectiveness, respectively. Similarly, perceived program organization, efficiency and safety further determined IPT uptake. These in turn determined the effectiveness of the strategy in reducing incidence of new TB disease, hence preventing child TB or having no impact on IPT incidence. The overall conceptual framework adopted is diagrammatically presented in figure 1.

Figure 1: Conceptual and theoretical framework



Developed from literature review

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology of pediatric tuberculosis

Child TB eradication has been on the global agenda since the 70s, with very little progress reported to date. Tuberculosis remains one of the major diseases afflicting children worldwide. It is estimated that children younger than 15 years contribute 15%–20% of the global tuberculosis burden (Marais *et al,* 2010). In developing countries, the annual risk of tuberculosis infection in children is 2.5%. Nearly 8-20% of the deaths caused by tuberculosis occur in children (Kabra *et al*., 2002). WHO has estimated approximately 1 million new cases and 400,000 deaths per year in children due to TB (WHO, 2009). According to WHO TB report of 2012, the highest burden of pediatric TB occurs in Sub-Saharan Africa, where it constitutes approximately 20% and up to 40% of the case-load in certain communities. Data available is from low-burden countries and suggests that incidence rates of childhood TB constitutes approximately between < 1 to 10/100 000, however, higher rates of > 50/100 000 occurs in some cities, among subgroups within the socially disadvantaged and immigrant communities. From the few published data from high-burden countries, the proportion of TB that occurs in children vary from 2.7% in Thailand to > 20% in Afghanistan, Brazil and Pakistan. According to Nelson *et al*., 2004 analysis of the global epidemiology of childhood tuberculosis, child TB represented 10.7% of all TB cases; 75% of childhood cases were in 22 high burden countries, where case rates for childhood TB varied from 15/100 000 in Thailand to 237/100 000 in South Africa (Donald *et al*., 2007). A national facility-based survey in Malawi in 1998 showed that childhood tuberculosis accounted for 12% of all the cases notified and for 37% of the overall smear-negative and extra-pulmonary

TB burden (Harries *et al.*, 2002). The National incidence of TB in South Africa in 1993, was 224/100 000 and children constituted 20% of the TB case-load (Department of Health, 1995). In one community near Cape Town with a particularly high TB incidence of 1149/100, 000, children constituted 39% of the case-load (Van Rie *et al*., 1999). These figures suggest that as the TB incidence rises under the influence of deteriorating socioeconomic circumstances, and there is a disproportionate increase in the percentage of the TB case-load comprised of children.

As is the case with adults, epidemiological shifts have been observed in the HIV era. Children with HIV/AIDS are exceptionally susceptible to *M. tuberculosis* infection and disease (Chintu *et al*., 1995, Oud-Alblas *et al*., 2002). At the Queen Elizabeth Hospital, Blantyre (Malawi), the number of children admitted with a diagnosis of TB increased from 64 in 1986 to 525 in 1993. Of these, 105 children were tested for HIV and 64% were positive (Harries *et al*., 1997). TB is a major cause of morbidity in HIV-infected children: HIV infected children have a 6-8 fold higher risk TB disease; HIV positive infants had a 20-25 fold higher incidence of TB. According to the Kenya DLTLD 2008 annual report, the distribution of TB cases in Kenya follows a particular pattern that is in line with poverty and HIV indices. In 2008, Nyanza province contributed to 20% of the TB load, Rift Valley province 19% and Nairobi (17%), pediatric cases comprised of about one third of all TB cases reported (DTLC report, 2009).

2.2 Factors that influence risk of TB infection and disease transmission

2.2.1 Risk factors for TB infection

An individual's risk of infection depends on the extent and duration of exposure to droplet nuclei coughed out from a case with TB, his or her susceptibility to infection and the infectivity of the mycobacteria. Factors that predict likely transmission of TB from an index case to a contact include anatomical site of disease; only patients with pulmonary or laryngeal TB can transmit their infection (Braden *et al.*, 1995), but pleural disease sputum cultures can yield *M. tuberculosis* even when no lung abnormalities are apparent on a radiograph (Conde *et al*., 2003). The risk of transmission from sputum smear-negative PTB is low, and even lower from someone with EPTB. Relative infectiousness is associated with positive sputum culture results and is highest when the smear is also positive (Bailey *et al*., 2002, Liippo *et al.*, 1993, Marks *et al*., 2000). Patients with lung cavities on a CXR are more infectious than patients with non-cavitatory pulmonary disease (Bailey *et al*., 2002, Marks *et al.*, 2000, Madhi *et al.*, 2002). Rarely, endobronchial TB in severely immune compromised patients with normal CXRs have contributed to TB outbreaks in the US. In one group of HIV-infected TB patients, 3% of those who were smear positive had normal CXRs at the time of diagnosis (Perlman *et al*., 1997, CDC, 2004). TB patients who are HIV-infected with low CD4 T-cell counts frequently have atypical CXR findings. They tend to have more mediastinal adenopathy and less likely to have upper-lobe infiltrates and cavities (Garay *et al*., 1996). Atypical CXR findings increase the potential for delayed diagnosis, which increases transmission. However, HIV-infected patients who have pulmonary or laryngeal TB are as contagious as non HIV infected TB patients (Carvalho *et al*., 2001, Cruciani *et al.*, 2001).

Degree of exposure based on air volume, exhaust rate and circulation predict the likelihood of transmission in an enclosed space. In large indoor settings, because of diffusion and local circulation patterns, the degree of proximity between contacts and the index patient can influence the likelihood of transmission. Other subtle environmental factors such as humidity and light may have a bearing. The volume of air shared between an infectious TB patient and contacts dilute the infectious particles (Catanzaro *et al*., 1982, Gammaitoni *et al*., 1997, Nardell *et al*., 1991). Local circulation and overall room ventilation dilute infectious particles, but both factors can redirect exposure into spaces not visited by the source case.

Behaviors that increase aerosolization of respiratory secretions may also increase infectiousness. However, cough frequency and severity are not predictive of contagiousness (Loudon *et al*., 1969). Singing is associated with TB transmission (Bates *et al*., 1965, Mangura *et al*., 1998). Sociability of the index patient contributes to contagiousness because of the increased number of contacts and the intensity of exposure. Transmission from children aged less than 10 years is rare, but may occur in pulmonary forms (Curtis *et al*., 1969, Lawrence *et al*., 1996,). Following administration of effective treatment, a TB patient rapidly become less contagious. This has been corroborated by measuring the number of viable bacilli in sputa and by observing infection rates in household contacts (Dietze *et al*., 2001, Gunnel *et al*., 1997, Riley *et al.*, 1994). Drug resistance can delay effective bactericidal activity and prolong contagiousness.

Almost 60% of exposures of young children often occur at household level. The duration of infectiousness, infectivity of the bacteria and proximity to infectious case may be used as measure of likelihood of infection (Cotton *et al*., 2009, Hesseling *et al*., 2008, Schaaf *et al*., 2006). Increases with urbanization, migration, poor housing, poverty and malnutrition, recent viral infections all contribute to the spread of TB in children (Van Rie *et al*., 1999). The urban poor populations living in informal settlements within large cities have been shown to have proportionately higher incidences of childhood TB, compared to adult TB cases (Van Rie *et al*., 1999). In a prospective study done in Madrid, India to asses risk of infection of child household contacts of TB infected adults, 73.1% tested TST positive, whereas 33.1% of these developed TB disease (Castan *et al*., 1991). In another study done in Karachi, Pakistan to assess the risk factors to TST positivity among household contacts, the prevalence of TST positivity among household contacts of smear positive index patients was 49.4%; age, sleeping site relative to index case, intensity of index case AAFB sputum smear positivity and contact's BCG status were found to be independent predictors of TST positivity. Poor housing conditions seemed to contribute to the spread of TB infection (Rathi *et al*., 2002).

Children with HIV are more likely to be in contact with adults who are having TB. In a study done in South Africa, 77 of 766 (10.1%; 95% CI 8.0–12.4) HIV-exposed South African infants had TB contact at 3months. HIV-exposed infants have 2 fold higher risk of TB exposure and TB infection in HIV positive children often led to "relevant disease"(Cotton *et al*., 2009, Hesseling *et al*., 2008, Schaaf, *et al*., 2006).

2.2.2 Risk of progression to disease following infection

Once infected, majority (90%) of people without HIV infection who are infected, do not develop TB disease. Infected persons can develop TB at any time, the risk being greatest during the first two years following exposure. In the absence of any preventive measures 5 -15% will develop reactivation of TB during their lifetime. Infected infants and young children are at greater risk of developing disease than older people because they have a qualitative and quantitative immaturity of the immune system (Smith *et al*., 1997). Reduced chemotaxis, activation and antigen presentation by macrophages and reduced specificity of T-cell maturation and specific response have been documented in young infants, all factors which would predispose to spread of TB within the body in this age group. In young child contacts, disease usually develops within 2 years of infection, but in infants the time-lag can be as short as a few weeks (Gaisford, 1946).

Various physical or emotional stresses may trigger progression of infection to disease. From observational studies done in adults, certain groups have been identified to be at an increased risk of reactivation. The most important trigger is weakening of immune resistance, especially by HIV infection, or malnutrition. Persons infected with HIV are now recognized to be at the highest risk of reactivation with rates reported at 8-9% per year in recent studies. HIV infection results in the progression of infection to TB disease more frequently and more rapidly than any other known factor, with disease rates estimated at 35 - 162 per 1,000 person-years of observation and a greater likelihood of disseminated and extrapulmonary disease (CDC, 1991, Cohn *et al*., 2000, Daley *et al.*, 1992, Fischl *et al.*, 1992). In patients with silicosis, head and neck cancer, jejunoileal bypass or gastrectomy, or in those with end-stage renal disease who require

hemodialysis, the relative risk is reported to be increased 10-30 times over that of the baseline population. The relative risk for patients with low body weight or nutritional deficiency, diabetes mellitus, or gastrectomy is reported to be increased 2-5 times. Others at risk are those with haematologic malignancies, patients on immunosuppressants or on high doses of steroids for prolonged periods, hematological and reticuloendothelial diseases, chronic malabsorption syndrome, or low body weight, the urban poor, persons living in shelters, intravenous drug users and alcoholics. Native resistance to TB has been seen in males and persons aged between 5- 10years and 18 - 45years.

2.3 Child tuberculosis prevention Strategies

Child TB preventive strategies remains largely a neglected aspect of National TB control program, mainly due to difficulty in establishing a definitive diagnosis and a lower public health priority, as most are smear negative. The WHO and CDC TB prevention strategies of 2009 identified 3 key prevention strategies, which individually or in combination reduce the risk to TB infection. These are discussed henceforth. In addition, improving contact's nutrition, good hydration and regular exercising have been shown to reduce TB spread.

2.3.1 Treatment of sputum positive adult TB cases

Early diagnosis and successful treatment of an infectious adult patient is the best way to protect children from becoming infected with TB. Therefore a good TB control program, which ensures early diagnosis and treatment of adult cases with infectious forms of TB, is the best way to prevent TB in children (WHO, 2009).

2.3.2 BCG vaccination

BCG has been recommended in some settings for high-risk contacts, but may not protect against infection or subsequent disease later in life (Lotte *et al*., 1988). There has been ongoing debate about the effectiveness of BCG vaccination for a number of years. The ability of neonates to mount adequate immune response following BCG vaccination is questionable. Effectiveness in different studies varies between zero and 80% (Ryder *et al*., 1993). Partly because of this, BCG policies in different countries vary between no immunization (US), high risk immunization at birth with universal immunization at 13 years (UK), universal neonatal immunization (Indian subcontinent and much of Africa), and multiple immunization (much of Eastern Europe). BCG seems more effective in trials in temperate rather than tropical areas. A theory to explain the variability of BCG has been proposed based on the immunity generated by naturally occurring soil mycobacteria, more prevalent in the tropics, which may be enough to nullify any additional effect of BCG (Springett *et al*., 1994).

2.3.3 Contact screening and management

Numerous studies have found contact investigations a valuable means of identifying symptomatic new TB cases (Schaaf *et al.*, 1999, Schaaf *et al*., 2002, Singh *et al*., 2005, Topley *et al*., 1996). It also allows finding and treating persons with LTB and opportunity for preventive therapy for susceptible individuals. Active contact tracing is recommended by WHO and the IUAT as part of infection control (WHO, 2006b, WHO, 1998). TST is the recommend screening for TB infection, while CXR for TB disease, but where these are not available as is often the case in low resource settings, it should not preclude contact screening and management, as this can be conducted on the basis

of simple clinical assessment (Mandalakas *et al.*, 2013, Rieder *et al*., 2002). According to American Academy of Pediatrics (AAP), contact screening investigation should be considered if the index patient has confirmed or suspected pulmonary, laryngeal, or pleural TB or if the sputum positive for AAFB. The infectious period starts 3 months before a TB diagnosis and is closed following effective treatment for at least 2 weeks, diminished symptoms and mycobacteriologic response. MDR TB can extend infectiousness if the treatment regimen is ineffective (AAP, 2002). In view of limited resources, contact priority should be directed to selecting contacts who have secondary cases of TB disease, have recent infection, especially sputum positive and so are most likely to benefit from treatment and are most likely to become ill with TB disease if they are infected (i.e. susceptible contacts) or who could suffer severe morbidity if they have TB disease (i.e. vulnerable contacts) such as children aged below 5 years (AAP, 2003). Currently, contact screening and management is recommended by most NTPs, but rarely happens in low resource settings, where the majority of childhood TB occurs. Most studies have clearly showed benefit of chemoprophylaxis (Ferebee *et al*., 1970).

2.3.4 Role of IPT in child TB prevention

Isoniazid is the drug that has been studied extensively for chemoprophylaxis. There are more than 20 clinical trials evaluating the role of IPT in preventing TB reported in the literature. It has been used for chemoprophylaxis in diverse at-risk patients. There is good evidence to support INH prophylaxis in skin test converters regardless of age (Comstock *et al*., 1962, Curry *et al*., 1967, Veening *et al*., 1968). In one study in the US, IPT was evaluated in a cohort of nursing home patients with TST conversion, TB developed in 1 of 605 converters receiving INH (1.6 per 1,000) and in 45 of 757 (59 per

1,000) receiving no treatment (Stead *et al*., 1985). This was statistically significant. A similar study done in the Netherlands among Navy recruits whose skin tests converted to positive following exposure to an active case of PTB, of those randomized to receive INH, 7.5/1,000 (n =133) developed TB compared to 70/ 1,000 (n =128), not on IPT, a significant difference (Veening *et al*., 1968). In a non-randomized comparative study evaluating IPT in public school students with a large immigrant population from San Francisco, 1 of 2,910 children in the INH-treated group (0.34 /1,000) and 25 of 1,192 in no treatment (20.9/1,000) developed active TB (Curry *et al*., 1967). Although demonstrating a highly statistical and clinical benefit of IPT, there were concerns about the comparability of the two groups, as racial differences were noted between the treatment and control groups that may have influenced IPT uptake. Akolo *et al*, 2009 also found IPT to have protective benefit among TST positive adults in South Africa, RR = 0.38. In the UK, treatment is recommended for asymptomatic children under the age of 16 years with a positive TST (BTS joint report, 2000). In the US, the age cut off is 35 years (CDC report, 2000).

There is good evidence to support the use of IPT in patients with HIV infection, where it has played a major role by reducing TB incidence and death (Churchyard *et al*, Lugada *et al*., 2002, Mohammed *et al*., 2007, Woldehanna *et al*., 2004). In a study done in Haiti in 1989, 118 asymptomatic HIV positive persons were randomized to receive INH prophylaxis with vitamin B6 or B6 alone for 12 months. Eleven of 60 (18%) patients in the B6 group developed active TB over the study period, in contrast to 4 of 62 (6.5%) who received INH and B6, p = 0.03. This is consistent with a reduction from 7.5 to 2.2 cases per 100-person years (Pape *et al*., 1993). IPT has been shown to reduce

TB incidence and death in HIV infected children (Gray *et al*., 2009). IPT was associated with a 54% reduction in all-cause mortality and a 72% reduction in the incidence of tuberculosis among children living with HIV (Zar *et al.*, 2007). In a randomized controlled trial done in South Africa to investigate the impact of IPT on mortality and incidence of TB in children with HIV aged above 8 weeks, showed that mortality was lower in the INH group than in the placebo group, 11 (8%) versus 21 (16%), (HR 0.46, 95% CI 0.22 to 0.95, p = 0.015). The benefit applied across CDC clinical categories and in all ages. The incidence of TB was lower in the INH group (5 cases, 3.8%) than in the placebo group (13 cases, 9.9%) (HR 0.28, CI 0.10 to 0.78, p = 0.005). All cases of TB confirmed by culture were in children in the placebo group. They concluded that IPT has an early survival benefit and reduces incidence of TB in children with HIV (Zar *et al*., 2007). IPT also reduces progression of HIV (Pape *et al*., 1993).

Several studies assessed evidence to support the role of IPT in household contacts of active TB in low burden areas (Ferebee *et al*., 1962, Mount *et al*., 1962). Most of these were non-HIV infected children. In a study done in 1960 by 'The TB Program of the US Public Health Service', household contacts of new active PTB case in the U.S.A and Puerto Rico were randomized to receive IPT or placebo for one year. Two thirds of all participants were aged below 20 years. TB developed in 6.5/1,000 placebo recipients, versus 1.5/ 1,000 INH recipients (USA advisory committee 1990). A similar household-based study in Japan failed to show a benefit of INH prophylaxis, although there was a trend toward decreased TB in the INH treated group (8 per 1,142), compared to the control group (11 per 1,096). Poor compliance and the small sample size were the most likely reasons for the lack of significant effect (Bush *et al*., 1965). In a meta-analysis of

11 randomized controlled trials (RCT) of IPT benefit among non HIV infected contacts, treatment with INH resulted in a relative risk (RR) of developing active TB of 0.40, (95% CI 0.31 to 0.52), over two years or longer (Smieja *et al.*, 2000). Another metanalysis of 8 RCTs on efficacy of IPT in children, found IPT to be efficacious in preventing development of TB, with a pooled RR of 0.65 (95% CI 0.47, 0.89) $p = 0.004$ (Ayieko *et al.*, 2014). However, in a study from South Africa, no benefit of IPT was observed among HIV-infected and uninfected infants without prior exposure to TB (Madhi *et al*, 2011).

2.4 Programmatic factors influencing IPT effectiveness

2.4.1 IPT treatment duration

Different durations of IPT have been used with varying efficacy. Most studies evaluating IPT have utilized a 1 year course of therapy. In studies done in the US, although a 9 months and 12 month regimes of IPT were found to be effective (Comstock *et al*., 1999, WHO 2006), there has been a search for shorter regimens to improve compliance. Six months of isoniazid has a higher relapse rate. In a meta-analysis of RCTs, there was no significant difference between 6 and 12 month courses (RR of 0.44, 95% CI 0.27 to 0.73 for six months, and 0.38, 95% CI 0.28 to 0.50 for 12 months) (Smieja *et al*, 2000). A cost analysis study has suggested that a 24 week regime was more cost effective (IUAT trial, 1986). The WHO and 'The IUAT' paediatric TB management guidelines (2010), suggest a 6 month course of IPT. Different NTPs have adopted different approaches of use of IPT. The US recommends duration of 9 months of IPT (CDC report, 2000). India's Revised NTB control program in 2003 adopted a 6 month regime. Kenyan childhood TB guidelines (2011) also adopted a 6 month regime.

However, dual therapy may be preferable because it allows shorter duration of treatment hence better compliance (Marais, 2006). Two months of pyrazinamide and rifampicin is effective but there have been reports of liver toxicity (CDC, 2001, Gordin *et al*., 2000). A 3- or 4-month regimen of isoniazid plus rifampicin is at least as effective as a 9-month course of isoniazid monotherapy in treating latent TB in children, according to results of a prospective, randomized trial (Whalen *et al.*, 1997). In the UK, isoniazid and rifampicin for 3 months is recommended and is safe, (Ormerod *et al*., 1998). The regime could be extended to 12 months for immune compromised hosts (AAP, 2003).

2.4.2 Safety of isoniazid

Though relatively safe, IPT has been associated with adverse events in adults, including hypersensitivity reactions, INH-induced lupus-like syndrome, peripheral neuropathy, gastrointestinal distress, and central nervous system abnormalities ranging from memory loss to psychosis or seizures. Fifteen percent of patients will experience a transient asymptomatic increase in their liver transaminases on treatment (Kopanoff, 1978). Clinical hepatitis is much less common and is rarely fatal, particularly when recommendations for surveillance are followed. It is most significant and potentially dose-limiting side effect (CDC 2001). In the IUAT trial, 1982, the risk of INH-related hepatitis was 0.5%, with a mortality rate of 14 per 100,000, but significant liver toxicity is more likely in those who are malnourished or severely unwell at diagnosis. The best prospective study to determine the incidence of INH hepatitis documented 236 suspected cases among 13,838 receiving prophylaxis. The case rates appeared to increase with age, with rates lowest for cases aged below 20 years (0 / 1,000) and

highest rate in age 50-64 years (23/1,000). Racial distribution was orientals (18/ 1,000), whites 11.4/ 1,000 and 7.1 /1,000 for blacks (Kopanoff, 1978). In a meta-analysis of 11 RTCs evaluating IPT in non-HIV infected persons, hepatotoxicity was observed in 0.36% of people on 6 months treatment and in 0.52% of people treated for 12 months (Smieja *et al.*, 2000). Children on concurrent medications such as anticonvulsants are also at risk. Pyridoxine to counteract the peripheral neuropathy of isoniazid is not necessary unless the child is malnourished, preterm, or a breastfed infant.

2.4.3 Adherence to IPT

Compliance remains an important barrier to effective chemoprophylaxis. IPT delivery to children remains an operational challenge in both high and low HIV prevalence settings, due to a wide range of health system barriers (Getahun *et al*, 2010), with only 16% – 66% of eligible contacts receiving the drug (Banu *et al*., 2009, Marais *et al*., 2006, Pothukuchi *et al*., 2011, Zachariah *et al*, 2003). Common barriers to adherence include complex dosing schedules, toxicity, pill burden and financial cost to the patient.

There is no gold standard for adherence (Osterberg *et al.*, 2005). As with adherence to HAART, comparing estimates of adherence to IPT between studies is complicated by varying definitions of adherence and the use of different adherence tools (Mills *et al.*, 2006, Vreeman *et al.*, 2008,). Traditionally, completion rates (based on taking more than 80% of the prescribed doses) have been used to describe adherence to TB prophylaxis (Ferebee *et al*., 1970). In various clinical trials, compliance ranged from 50-75% through one year of preventive therapy, (Marais *et al*., 2006, Nabukeera-Barungi, 2007, Szakacs *et al*., 2006, van Zyl *et al*., 2006). In a South African RCT comparing 2 dose scheduling of IPT in HIV infected children, the mean adherence was 93.8% in

those on daily dosing, compared to 95.5% in 3 times a week dosing. Most (78.6%) children achieved a mean adherence above 90% (Stanzi *et al.*, 2009). In this study, 88% of children prescribed INH completed a minimum of 6 months of prophylaxis. This was attributed to substantial adherence support accorded to the caregivers. On the contrast, in one prospective and one retrospective study evaluating adherence to INH prophylaxis in operational settings in Cape Town, South Africa, only 15% and 27% respectively of the children completed 5-6 months of isoniazid (Marais *et al.*, 2006, van Zyl *et al*., 2006). In HIV exposed children, common barriers to adherence include complex dosing schedules, toxicity, pill burden and financial costs to the patient (Mills *et al*., 2006, Vreeman *et al*., 2008).

Compliance can be determined based on urine strips that detect isoniazid metabolites in urine, pill counts, prescription records, caregiver self reports, as well as attendance at all clinic follow-up visits (Starr *et al*., 1999, Stanzi *et al.*, 2009) or home visits. Although directly observed therapy (DOT) improves completion rates (Marks *et al*., 2000, Wobeser *et al*., 1989), it is a resource-intensive intervention that might not be feasible for all exposed contacts and may not be sustained after observation is discontinued. Social or behavior impediments (e.g. alcohol addiction, chronic mental illness, injection-drug use, unstable housing, or unemployment) may lead to poor compliance.

IPT program providers in resource poor health care centers outside of a study setting contribute to poor compliance. Patients are more likely to be subjected to long waiting times, interrupted drug supplies and worse interpersonal experiences with care providers (Munro *et al*., 2007). Incentives (such as food coupons or toys for children) and enablers (transportation vouchers to go to the clinic or pharmacy) are recommended

as aids to adherence. Incentives provide simple rewards, whereas enablers increase a patient's opportunities for adherence. Client education on TB treatment duration and anticipated side effects should be part of each patient encounter to enhance compliance.

2.4.4 Role of IPT in multiple drug resistant TB (MDR-TB) cases

Monitoring patients on IPT for development of active disease is also important. There have been case reports of failed INH chemoprophylaxis for patients infected with INH-resistant organisms. The rates of drug resistance among adult TB cases vary from 20% to 80% in different geographic regions (Schaaf *et al*., 2000, WHO guidelines, 2006). Standard IPT is unlikely to be efficacious for either MDR-TB or other isoniazid-resistant forms of TB (Schaaf, 1999, Schaaf *et al*., 2002). The magnitude of such cases in our set-up is not known. No large-scale controlled trials have been conducted to evaluate standard IPT, among contacts of patients with resistant forms of TB. It remains unclear whether IPT would be useful in settings with varied population susceptibility profiles. It is also feared that extensive use of IPT may lead to an increase in isoniazid resistant mycobacteria in the community and hence could promote increased pediatric MDR cases instead.

CHAPTER THREE: MATERIALS AND METHODS

3.1 Study design

This was a prospective longitudinal cohort study of children aged below 5 years, exposed to recently diagnosed PTB smear positive adults from informal settlements in Nairobi. None of the centers chosen had previously offered IPT to child contacts. At baseline, contacts were screened using clinical score charts, to exclude TB disease. Contacts were then put on IPT and followed up for a period of 1 year for development of active TB. Adherence and side effects were also monitored. This design allowed the researcher to explore baseline TB infection and disease rates in exposed contacts not on IPT, to assess the effectiveness of IPT as a preventive strategy and to asses factors influencing IPT effectiveness.

3.2 Variables

3.2.1 The dependant variable

The dependant variable for this study was the incidence of new TB disease in contacts on IPT.

3.2.2 The independent variables

The independent variables for this study included the following; firstly, the source case factors such as socio-demographic, economic, cultural and environmental characteristics, duration and type of TB exposures, and HIV status. The second independent variables were contact factors including their demographic data, breastfeeding status, nutrition status, BCG status, and HIV status. Lastly, the study also

assessed social, health facility and programmatic factors including compliance and safety of IPT.

3.3 Study site description

Nairobi is the capital city of Kenya with a population of about 5 million. Nairobi has over 15 informal settlements, with an estimate 3 million (70%) of the population living in informal settlements. This was a multicenter study of three TB treatment centers within the informal settlements in Nairobi. The specific centers chosen were Kayole II Sub-district Hospital (Kayole), Dandora II Health Center (Dandora) and The 'Medical Missionary of Mary' Health Center, (Mukuru). In addition, other TB treatment and diagnostic facilities within 5km radius to these centers were requested to refer eligible adults to the study sites. The catchment facilities for Kayole site were Kayole I Health Center, that for Dandora site was Dandora 1 Health Center and Njiru Health Centers and that for Mukuru site was Kwa-Reuben Health Center. The map of the study site is presented in Appendix 1.

3.4 Study Population

The study population was all children aged below 5 years, who were living in households with smear positive PTB infected adults from these informal settlings.

3.5 Sampling techniques and sample size

3.5.1 Inclusion criteria

Contacts' eligibility criteria was any child aged below 4 years, living in close household contact with an adult source case, recently diagnosed with smear positive PTB, for a

minimum period of at least 1 month and whose parent/caretaker consented to their participation in the study.

3.5.2 Exclusion criteria

Contacts with pre-existing chronic medical conditions such as severe congenital disorders, severe asthmatics, cerebral palsy, cardiac diseases, diabetes mellitus etc, were excluded. Screening was done by a qualified pediatrician who performed a clinical assessment by detailed history and physical examination of all contacts at baseline. Contacts that were non-residents within the informal settlements were also excluded.

3.5.3 Sampling technique

There were 3 levels of sampling done for this study;

1. Health facility sampling: Nairobi was selected purposively due to the high TB incidence reported annually. According to DLTLD, the Nairobi County is divided into 4 districts namely Nairobi West, Nairobi East, and Nairobi North. Nairobi East was purposively selected because it had the highest number of informal settlements within the region. Purposive sampling was done to select three level 2 TB treatment centers within informal settlements, in Nairobi East region. These centers were selected based on link level facilities providing TB diagnostic and treatment services.
2. Source case selection: Purposive sampling was done of consecutive adults with recently diagnosed smear positive PTB, who had contacts aged below 5 years in their households and who consented to participate in the study. Recruitment continued until the desired sample size for child contacts was attained.

3. Contact case sampling: Purposive sampling of any eligible child contact, living in the same household with an eligible smear positive source case was done.

3.5.4 Sample size

A total of 366 consecutive adult source cases were interviewed. For the quantitative part of the study, the sample size for the contacts was determined using Fisher *et al*., 1998 formula:

$$n = \frac{Z^2 \, p \, q \, D}{d^2}$$

n = minimum sample size (for population >10,000) required

Z = the standard normal deviate at the required confidence level (set at 1.96 corresponding to 95%, Confidence level adopted for this study)

p = sample proportion of contacts estimated to require IPT (15%)

q = 1-p (85%)

d = the degree of accuracy required (0.05).

D = the design effect (1).

Therefore, $n = \frac{1.96^2 \times 0.15 \times 0.85 \times 1}{0.05^2} = 392$ contacts

But, n_f needed since the N <10,000, our N= 6,000

$$n_f = \frac{n}{1 + \frac{n}{N}} = 387$$

In order to cover for attrition from a longitudinal study, extra 10% (39) children were added, to make 426 as the minimum sample size. A final sample size of 428 children was recruited since some households had 2 or more contacts.

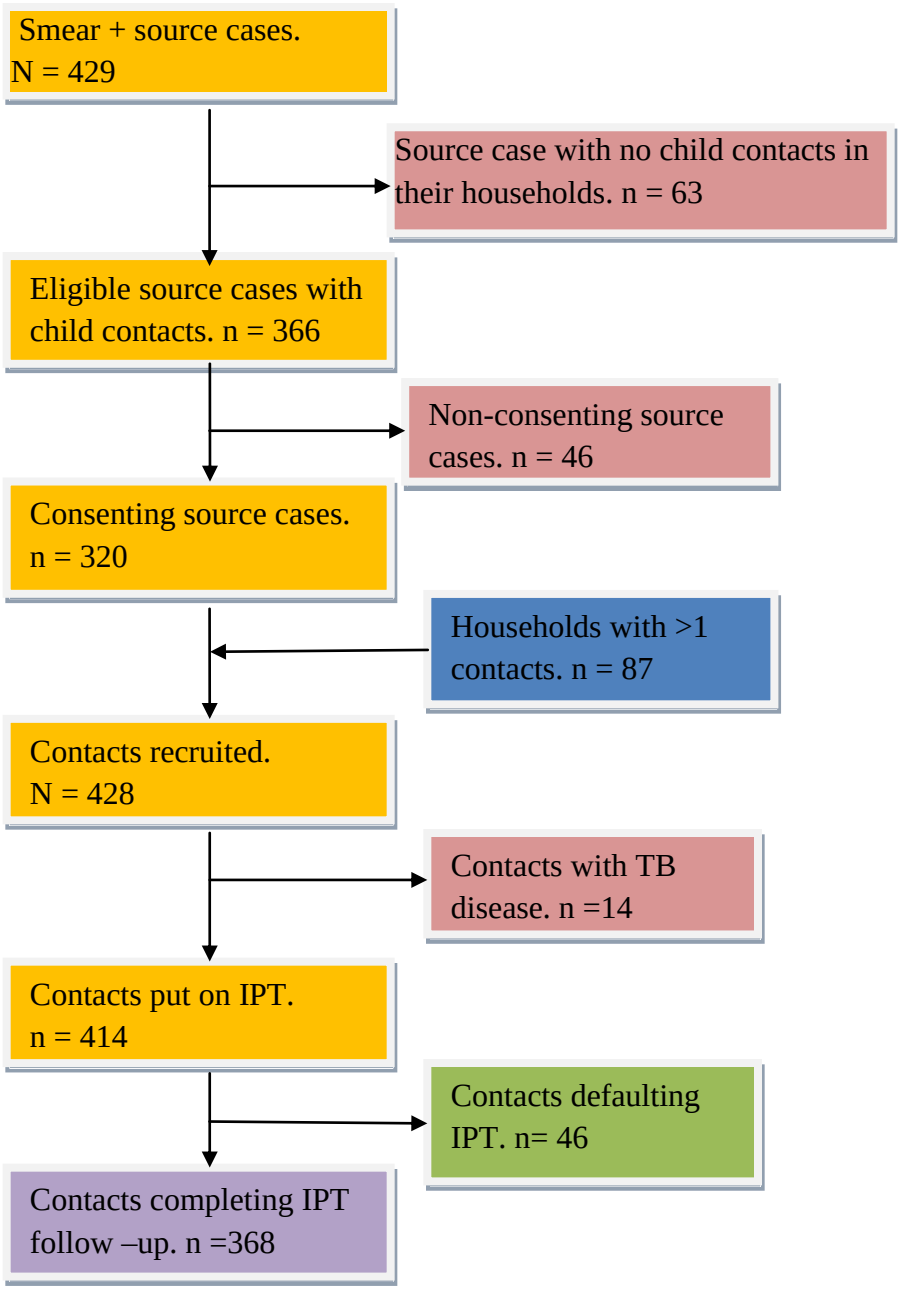
3.5.5 The subject enrollment procedures and participants

A total of 429 PTB smear positive adults were diagnosed from all the 3 sites during the study period. Of these, 366 cases had child contacts in their households, hence eligible for recruitment. However, only 320 (88.8%) consented to participate in the study; 108 from Kayole, 118 from Dandora, and 94 from Mukuru. At least 87 (27.1%) households had more than one eligible contact, hence a total of 428 contacts were enrolled and underwent baseline screenings. None had previously used IPT. Fourteen (3.2%) contacts had TB disease at baseline, 2 were already on TB treatment at the point of recruitment. The summary of subjects' enrollment and participants is presented in figure 2.

3.6 Construction of the research instruments

Four research tools were developed and used in the study. They included a detailed structured baseline source case questionnaire, a contact clinical assessment, follow-up and investigations record chart, compliance and toxicity monitoring chart, and the FDG and KII guides.

Figure 2: Subjects' enrollment and participants



3.7 Data collection tools

3.7.1 Quantitative Data

A structured questionnaire was administered to the adult source case at baseline. The child contacts assessment form was used to document contact information during clinic visits. Approved standardized anthropometric measurement instruments were used to collect contacts data. A pediatric pan weighing scale used to take weights for infants, while a 'stand on scale' was used for older children. An infantometer was used to measure length for children aged < 1 year, while height measuring board was used to measure heights for children >1 year. The Mid upper arm circumference (MUAC) tape used to measure the MUAC. Standard WHO growth charts were used to classify the child's nutrition status.

3.7.2 Qualitative data

3.7.2.1 Focus group discussions

These comprised of 2 groups of 8 people each, who comprised of persons who were residents from the respective communities, health workers and CHWs. Members were consented individually and requested to converge in a private room to discuss child TB issues, based on key themes, by using the FDG guides (Appendix 5.6).

3.7.2.2 In depth interviews

These were conducted by the researcher on a one to one basis with 2 key health workers per site, the nursing officer in-charge of facility and the TB clinic nurse. Information on child TB prevalence and IPT challenges was sought using the Key informant Interview (KII) guides.

3.8 Pretesting of instruments

This was carried out at Soweto Primary Health Center, to test questionnaires for completeness and clarity to the respondents. The tools were subsequently refined.

3.9 Validity

Three research assistants were engaged for each of the study sites; a nurse, a laboratory technologist and a community health worker (CHW). These were staffs already working with the TB program. They were trained on standardized data collection procedures. The nurse was trained on performance of nutrition assessments, TST procedures, collection of sputum samples, and maintenance of patient records. The laboratory technician was trained on how to process blood and sputum samples. The CHWs were trained how to conduct the interviews using questionnaires and when to make follow up visits for those that did not honor their appointments.

3.10 Reliability

Measurements taken by the research assistants were compared with random measurements taken by the researcher. The modified Jones clinical TB diagnosis tool was reviewed by a team of pediatricians and my supervisors to ensure is was reliable. All clinical examinations were performed by the researcher.

3.11 Data collection techniques.

Enrollment started in December 2011 to December 2012, but contacts' follow-up continued until July 2013. Each facility had a staff briefing done at onset, to seek their cooperation on identification and referral of eligible adults to the TB clinic. A total of 429 TB smear positive adult cases were diagnosed at the 3 centers during the enrollment

period; 148 from Kayole, 166 from the Dandora and 115 from Mukuru. Following explanation of study, written consent was sought from the parent or legal guardians, to have their children participate (Appendices 2.1, 2.2). Those not sure were given time to make the decision and return the signed form on a subsequent visit, a week later. A "contacts' clinic" was established at each of the study sites, on a specific day and time per week. Consenting source cases were requested to bring their eligible contacts to the contacts clinic'. The promptness of response to this invitation was assessed based on how soon the contacts were brought in. Those that did not come on the scheduled date were contacted by a telephone reminder. Those that failed to respond after this were tracked down to their home by the CHWs. A child contacts register was maintained for each site. Minor support including bus-fare, or home delivery of drugs, was offered to those that had challenges in honoring their clinic follow up visits.

3.11.1 Source case information

A structured questionnaire was administered at enrollment (Appendix 3). This was translated to Swahili. Further information was obtained from the client's TB clinic record card and by interview. This included when diagnosis of TB was made, duration of symptoms prior to diagnosis, treatment regimens, levels of adherence, residence, socio-demographic, environmental factors, TB knowledge and HIV status. If the HIV test had not been done previously, pre-test counseling was done and consent obtained, before the sample was drawn for a rapid HIV test and subsequently a post- test counseling session done by the nurse.

3.11.2 Contact case information

Clinical history was obtained using a structured contact form (Appendix 4) that collected information on symptoms, past medical history, immunization status including BCG scar, nutrition history, social and family history and history of ARV use. Baseline clinical assessments were done including anthropometric measurements that consisted of height (centimeters) and weight (kilograms), and height-for-age, weight-for-age, body mass index (BMI)–for-age and weight-for-height *z* scores were calculated according to WHO and Centers for Disease Control and Prevention growth standards (WHO, 2006). Stunting, underweight, low BMI, and wasting were defined as a *z* score $\leq$ 2 for height-for-age, weight-for-age, BMI-for-age, and weight-for-height, respectively. A blood sample was taken; a dried blood spot for HIV DNA PCR (from 6 weeks) and 1ml for ALT and AST assays. Contacts with cough for more than 2 weeks had a spot sputum sample obtained either by direct expectoration or sputum induction and sent for smear microscopy for AAFBs (Annex 9). Contacts aged over 2 months had a TST done at baseline, using 2 TU of tuberculin PPD RT23 administered to the proximal lateral aspect of the right fore-arm and read after 72 hours (Annex 8). TB was diagnosed by a modified Kenneth Jone's clinical scoring algorithm (Annex 9). Those with scores of $\geq$ 6 were considered to have TB disease and therefore excluded from IPT, but put on full TB treatment.

Contacts were then put on isoniazid tablets daily, at a dose of 10 mg/kg, with range of 8-12 mg/kg depending on whether half or quarter tablets were required, for 6 months. Drugs were collected weekly in the first 2 months and monthly thereafter for 4 months. Scheduled pediatrician's reviews were done after 1 month, then every 2 monthly; where

detailed history was taken enlisting any new TB suggestive symptoms (fevers, weight loss, night sweats) and clinical examination with specific attention to TB suggestive signs (lymphadenopathy, hepatospleenomegally, spinal deformity, cold abscesses, breathing problems). Sputum samples was obtained from symptomatic contacts and sent for microscopy for AAFB. A second ALT and AST assays were repeated after 1 month of IPT. Monthly monitoring was done for drug related adverse events by caregiver self reports. The level of compliance was monitored using the compliance monitoring form (appendix 5), that looked into attendance of scheduled follow-up visits, pill counts and level of parental supervision of drug administration. Compliance rate of $\geq$ 90% was considered optimal. Contacts requiring further investigations such as radiologic tests, histology for FNA or tissue biopsies, and body fluid analysis were referred to the Mbagathi District Hospital.

3.12 Logistical and Ethical considerations

Approvals were sought from Kenyatta University Graduate School, the Ministry of Health officials and/or facility in–charges in the respective health facilities and from the National Division of leprosy, TB, and Lung disease (DLTLD) program officials at headquarters. A research permit was obtained from the National Council for Science, Technology, and Innovation (NACOSTI). Ethical approval was obtained from the Kenyatta University Ethical Review Committee – Research permit number NCT/RRI/12/1/MED 011/175 (see attachment). Written consent was obtained from the parents/ legal guardians of all participating children (Appendices 2.1, 2.2). Voluntary pre- and post- HIV test counseling was done for the source cases and their contacts. HIV exposed or infected children were subsequently linked with the local

'comprehensive care clinics' for follow up. Contacts that were confirmed to have TB disease were subsequently started on anti-TB treatment and monitored till completion.

3.13 Data quality control measures

3.13.1 Quality control at data collection stage

Cross checking and inspection of the information on the questionnaires was done in order to ensure data quality. Research instruments were scrutinized to ensure the data collected was accurate and unambiguous. This was undertaken concurrently with data collection in order to attain high levels of completeness, consistency and uniformity of the collected data. Verification for completeness and accuracy of questionnaires were done once every month. Accuracy was realized by ensuring that all study instruments with contradictory information were discarded and repeat interview done to replace it.

3.13.2 Quality control during data entry and processing

All questionnaire data was double entered and verified before being analyzed. Further, statistical tools used for data entry and analysis contained interval checks to alert the researcher on any missing variables. This was confirmed with the source case and child clinic record and corrected immediately.

Cross checking and verification of information presented in the figures and tables was done by the researcher to ensure consistency. Multiple comparisons of the various independent variables and the dependant variables helped to ensure validity of the data.

3.14 Data management and analysis

Data collected was coded, entered and analyzed using statistical software; the Epi Info™ version 3.5.3 and SPSS version 19.1. Data on children whose guardians declined

further study follow-up and those who did not continue follow up to end point at 1 year were censored at the date of the last follow-up visit, and excluded from the analysis. Descriptive statistics were used to analyze quantitative data (frequencies, percentages, means, and ratios). This was done for both contact's and source case characteristics. All variables were collapsed into 2 x 2 tables due to the small number of TB disease cases. Proportions were established for dependant variables, and comparisons made in those with and without IPT failure, the independent variable. Cross tabulations were done and associations determined by inferential statistics (P-value, Odds ratio, confidence intervals) by comparing case characteristics (the dependant variables) of those with TB disease (IPT failure), and those without TB (the independent variable). Statistical significance level was fixed at $P < 0.005$. Correlations were established by the odds ratio and relative risk. For advance statistics, factors showing associations with IPT failure were entered into the multivariate logistic regression model to establish any relationship with IPT failure.

For quantitative data, all questionnaires were analyzed by content analysis based on key themes. The themes included social, programmatic and drug related challenges experienced. Summary was presented as percentages and median events.

CHAPTER FOUR: RESULTS

4.1 Subjects characteristics

4.1.2 Contacts' characteristics at enrollment

A total of 428 contacts were enrolled. The male to female ratio was 1:1. Their ages ranged from 1 to 48 months. Majority 233 (54.4%) were aged below 2 years, but out of these, 107(25%) were aged below 1 year. The growth assessment for this group were as follows; 361(85.4%) had normal weight for age, 52 (12.2%) were underweight, 10 (2.3%) were severely wasted, and 133 (31.4%) were stunted. Majority (96.7%) were reported to have received BCG vaccination at birth, but only 321(77.1%) had a visible BCG scar on their left forearms. Most attended their regular scheduled child welfare clinics and were up to date on their childhood immunizations schedules, but 2.2% had missed at least one vaccine.

As regards their birth order, majority 179 (41.8%) were first born. Some 22 (5.1%) contacts had been born with low birth weights (below 2500g). While 266 (62.1%) were still breast feeding, only 51 (12.0%) were on exclusive breastfeeding, and 54 (12.6%) had been weaned before the recommended age of 4 -6 months. On existence of possible external TB exposures, 90 (21.0%) were reported to have attended social places, such as daycare centers or kindergartens, or accompanied their parents/ guardians to social places like churches, mosques, or market places.

Regarding their morbidity status, majority 357 (83.4%) had attended the general out-patient clinic for varied issues in the preceding 3 months, but only 53 (11.1%) reported

a previous admission since birth. Although most children were asymptomatic at enrollment, at least 96 (22.4%) reported some symptoms such as cough, fever, poor weight gain, irritability or reduced playfulness. Out of these, at least 63 (14.7%) had positive clinical signs. Their general examination revealed cervical adenitis in 56 (13.1%), skin rashes in 34 (7.9%) and 26 (6.3%) had fever of 38 ^{0}C. On chest examination, 24 (5.6%) had ronchi, while 37 (8.6%) had crackles. At least 27 (6.3%) tested HIV PCR RNA positive. Further evaluation was only done for symptomatic contacts. Forty three (10.1%) had a baseline CXR done, but 28(6.5%) showed none - specific opacities that resolved after antibiotics dose. Only 9 (2.1%) had TB suggestive X-ray findings. Sputum samples were obtained from 22 cases, of which 4 (0.01%) were smear positive. Nine children required further diagnostic tests including 6 for FNA histology, and 3 for pleural aspirates. The summary of the clinical presentations of contacts at baseline are presented in Table 4.1.

Table 4.1: Summary of clinical presentations of contacts at baseline

Contact factor	**Category**	**N = 428 (%)**
Contact age	≤ 2 years	54.4
	>2 years	45.6
BCG scar	Absent	22.9
	Present	77.1
HIV RNA PCR	Positive	6.3
	Negative	93.7
TB suggestive symptoms	Anorexia	10.7
	Cough > 2 weeks	22.0
	Fever > 2 weeks	3.6
	Malaise, reduced play	9.3
	Night sweats	8.1
	Weight loss/faltering	17.8
TB suggestive signs	Temp >38^0C	6.3
	Lymphadenitis	13.1
	Respiratory signs	12.3
	Hepatomegally	2.6
	Abdominal distension	2.1
	Cold abscess	0.2
Suggestive laboratory tests	TST positive	22.2
	Biopsy report positive	0.01
	Positive Sputum smear	0.02
	Pleural aspirate report	0.01
Radiologic features	Non-specific CXR	6.5
	Suggestive CXR	1.6

4.1.3 Baseline TB infection and disease among contacts.

TST positivity was used to define baseline infection with tuberculous mycobacteria. Out of the 428 contacts screened, 95 (22.2%) had a positive TST, while 333 (77.8%) were TST negative. Out of those who had TST positive, 4 (4%) children were HIV positive. Of those that had the TST negative, 18(5.4%) were HIV positive. On subsequent TB clinical scoring, 9 (2.1%) of the contacts with a positive TST were

diagnosed with TB disease, and therefore the remaining 86 (90.5%) contacts with a positive TST, had latent TB infection. Moreover, 5 (0.015%) contacts with a negative TST were also found to have TB disease. The odds of contacts with TST positivity developing TB disease was 1.047 < 6.86 < 8.446. The details of TST association with TB outcome are presented in Table 4.2.

Table 4.2 Influence of TST positivity on occurrence of TB disease at baseline.

		TB disease	**No TB disease**	
TST reaction	**TST positive**	9	86	p = 0.001 OR = 6.86 CI (1.047- 8.446)
	TST negative	5	328	
		14 (3.2%)	414 (96.7%)	

4.1.4 Baseline TB disease among contacts.

On clinical scoring, 14 (3.2%) of the contacts were diagnosed to have TB disease because they had a score of 6 and above, and were henceforth excluded from IPT. Two of them were already started on TB treatment. Four of these were from Kayole, 5 from Dandora and 5 from Mukuru. Their ages ranged from 6 -28 months, but 10 (71.4%) were aged below 2 years, and their mean age was 19.6 months. The male to female ratio was 1:2. At least, 11 (78.5%) had weight faltering (7 underweight and 4 wasted). Six (42.8%) of them had been born with low birth weights. Seven (50.0%) of them were first born, while 6 (42.8%) were second born. Nine (64.2%) were still breast feeding. All contacts were reported to have attended some social places. As regards their immunization status, 12 (85.7%) had received BCG at birth, but only 4 (28.6%) had a

visible BCG scar on the left forearm. Two contacts (14.3%) had a missed at least one other routine childhood immunizations.

Regarding their clinical presentations, 6 (42.8%) presented with cough for ≥ 2 weeks, 4 (28.6%) had fevers ≥ 2 weeks and 3 (21.4%) had cervical adenitis. Five (35.7%) were HIV RNA PCR positive. The 12 had TB suggestive chest radiographs, of which 4 radiographs demonstrated apical consolidation, 3 had a widened mediastinum, while showed a non-specific pneumonitis. Sputum smear was positive in only 4 (28.6%) out of the fourteen contacts with confirmed TB disease.

4.1.4.1 Characteristics of Source cases to contacts with TB disease

Their age ranged from 18 - 32 years, with a mean age of 27.3 years. The source case was the mother in 5 (35.7%) cases, the father in 7 (50.0%) cases and a sibling and a grandfather in 1 case (7.1%) each. Four (28.6%) households had more than one TB source case per household in the previous 6 months, and 2 (14.3%) had a child death in same household in the same period. Most were from poor social backgrounds, with average family monthly income of Ksh. 3500/=. While 10 (71.4%) lived in stone houses, 3 (21.4%) lived in houses made of iron sheets and 1 (7.1%) in a mud house. All except 2 lived in single rooms; hence they all shared the sleeping room with the TB source case. The mode size of room was 3-4 m^2, and all the houses had only one window. Mode room density was 3 persons for daytime and 5 persons for the nights. Nine (64.2%) households used smoky fuels as their cooking fuel. This included kerosene in 5 (21.4%) of the households, charcoal in 4 (28.6%) households, firewood in 1 (7.1%), and 3 (21.4%) used mixed fuels. Only 3 (21.4%) used gas as cooking fuel. Six (42.8%) were HIV infected. Half of them reported challenges in their own TB

treatments including side effects or treatment collection challenges. The majority of source cases had very good knowledge of TB causation, and of how TB is spread in adults, but had little knowledge of how TB is diagnosed in children. Details of the source case characteristics are illustrated in Table 4.4.

4.1.5 Risk factors of TB disease at baseline

Contact factors associated with risk of occurrence of TB disease at baseline were nutrition status (p = 0. 000), BCG status (p = 0.000), low birth weight (p = 0.000), HIV status (p = 0.000), and morbidity in previous 3 months (P = 0.000). Details of association of contact factors with risk of TB disease are shown in Table 4.3.

Table 4.3: Contact factors associated with risk of TB disease at baseline.

Characteristics		**TB disease (n= 14)**	**No TB disease (n= 414)**	**Fisher's exact (P- value)**	**Odds ratio (95% CI)**
Age of contact	< 24months	10	223	0.243	**1.792**
	>24months	4	167		0.553- 5.811
Gender of contact	Female	5	196	0.419	**0.578**
	Male	9	204		0.190 – 1.756
Nutrition status of contacts	Normal	3	349	0.000	**0.40**
	Malnutrition	11	51		0.011- 0.148
BGC scar	Positive	4	326	0.000	**0.091**
	Negative	10	74		0.028 – 0.297
Birth weight	LBW	6	16	0.000	**18.000**
	Normal BWT	8	384		5.58 - 58
Breast feeding	No	5	143	0.619	**0.998**
	Yes	9	257		0.328- 3.036
Weaning time	Appropriate	4	254	0.061	**0.230**
	Inappropriate	10	146		0.110 – 0.746
HIV RNA PCR test	Positive	5	22	0.000	**2.141**
	Negative	9	378		1.044 – 3.447
Morbidity in last 3months	yes	14	343	0.000	-
	no	0	57		
Social places attendance	yes	14	76	0.056	-
	no	0	324		

Table 4.4: Source case factors associated with risk of TB disease at baseline

Characteristics		**TB disease (n = 14)**	**No TB disease (n = 414)**	**Fisher's exact (p-value)**	**Odds ratio**
					95% CI
Source age	≤ 30 years	11	308	0.594	**1.095**
	>30 years	3	92		0.299 – 4.000
Source gender	Female	5	199	0.224	**0.561**
	Male	9	201		0.185- 1.704
Marital status	Married	13	304	0.122	**4.105**
	Single	1	96		0.530- 31.789
Relationship with source	Parent	11	299	1.000	**1.239**
	Other	3	109		0.339 – 4.528
Level of education	≤ Secondary	12	304	0.122	**4.105**
	> Secondary	2	96		0.530- 31.789
High risk social habits	Present	5	150	0.566	**0.926**
	Absent	9	250		0.305- 2.815
Crowding index - Nights	≥ 5	0	82	0.043	-
	<5	14	311		
Number of source cases in household	≥2	4	44	0.067	**0.310**
	1	10	355		0.093 -1.030
Share bedroom with child	Sometimes	2	78	0.471	**0.688**
	Always	12	322		0.151-3.137
Residence	Slum	8	293	0.153	**0.487**
	Peri-urban	6	107		0.165 – 1.436
Cooking fuel	Smoky	11	347	0.291	**0.560**
	Non- smoky	3	53		0.151- 2.073
Cough symptom in source	Yes	8	320	0.049	**0.333**
	No	6	80		0.112 - 30.988
Duration of symptoms prior to TB diagnosis	≤4 weeks	11	122	0.000	**8.355**
	> 4 weeks	3	278		2.290 – 30.481
HIV status of source case	Positive	6	83	0.057	**2.864**
	Negative	8	317		0.967 - 8.483
TB treatment challenges	Present	7	329	0.070	**0.216**
	Absent	7	71		0.073 - 0.635
Knowledge of of TB spread	Good	10	367	0.028	**0.225**
	Poor	4	33		0.067 – 0.756
Knowledge of TB causation	Good	10	289	0.626	**1.009**
	Poor	4	115		0.310 – 3.282

The source case factors associated with occurrence of TB disease were crowding index >5 at night (p = 0.043), cough symptoms in source (p = 0.049), duration of symptoms prior to diagnosis (p = 0.000) and knowledge of TB spread (p = 0.028). The details of association of source case factors and risk of TB disease is presented in Table 4.4.

4.2 IPT effectiveness as a child TB prevention strategy

4.2.1 Characteristics of the contacts' households completing IPT

A total of 414 contacts were started on IPT, but only 368 (88.8%) completed the one year follow-up. This consisted of 136 (36.9%) from Dandora, 129 (35.1%) from Kayole and 103 (27.9%) from Mukuru. Their mean age was 21.4 months. The male to female ratio was 1:1. Most (93.7%) of the children were still breast feeding. The majority, (79.6%) of the contacts had attended social places. At least 126 (34.2%) had been symptomatic at enrollment. While some morbidity was reported in 50(13.6%) of these contacts in the previous 3 months, only 41 (11.1%) had least 1 previous hospital admission. Twenty five (6.7%) of them tested positive for the HIV RNA PCR test, while the TST was positive in 76 (20.6%).

The source cases of these contacts were aged between 13 and 62 years, with a mean of 26.7 years. The male to female ratio was 1:1. Most 281 (76.4%) of the source cases were married and 312 (85%) had secondary education and below. Most 256 (70.1%) of them were unemployed. The majority 270 (73.4%) resided in the neighboring slums. In 275 (74.7%), the source case was the biological parent of the child. Some 273 (74.1%) lived in stone houses, 63 (17.1) lived in houses made of corrugated iron sheets, while the rest were in temporary shelters. Most source cases 289 (78.5%) lived in small single roomed houses of between 3 - 4 m^2. The source always shared sleeping room

with the contact in 298 (80.9%) of the cases. Majority (85.6%) used smoky cooking fuels, like kerosene, charcoal or wood. All source cases were on first line anti-TB treatment. In at least 39 (10.6%) of the households, there was more than one adult case with TB. Most of the source cases had good knowledge of TB the majority 261 (70.9%) knew the cause of TB to be bacteria, 119 (32.3%) had good knowledge of the risks of TB transmission to children and majority (55.2%) knew of the relationship between TB and HIV infection. Although all believed that TB was curable, at least 63 (17.1%) cases had misconceptions and myths regarding TB. Among the misconceptions reported were that TB was a bad omen, it connoted death, indicated HIV infection and was related to witchcraft. Characteristics of contacts completing IPT are presented in Table 4.5

Table 4.5: Characteristics of contacts completing IPT

Characteristic	**Sub -grouping**	**N = 368 N (%)**
Gender	Male	189 (51.3)
	Female	179 (49.7)
Birth order	1st	154 (41.8)
	2nd	126 (34.2)
	3rd and above	88 (23.9)
Birth weight	< 2500g	10 (2.7)
	2500 – 4000g	316 (85.9)
	> 4000g	42 (11.1)
Attendance of social places	Yes	292 (79.3)
	No	76 (20.7)
Morbidity patterns	Out-patient clinic attendance	50 (13.6)
	Previous admission	41 (11.1)
Breastfeeding	Exclusive	44 (12.0)
	Current status	126 (34.2)
Weaning age	Inappropriate(<4 months)	123 (33.4)
	Appropriate(4- 6months)	197 (53.5)
Child welfare attendance	Regular	174 (47.3)
Immunization status	Up to date	349 (94.8)
	Missed doses	19 (5.2)
BCG scar	Present	281 (76.4)
	Absent	87 (23.6)
HIV RNA PCR	Positive	25 (6.7)
	Negative	345(93.8)
ARV exposure	PMTCT- NVP	34 (9.2)
	HAART	17 (4.6)
	None	317 (86.1)
TST reaction	positive	76 (20.6)
	Negative	292 (79.4)

4.2.2 Effectiveness of IPT in preventing TB

This study focused on effectiveness 'as per protocol completion', hence only contacts completing the follow up period (368) were considered. By endpoint, 6 (1.6%) contacts had developed TB disease during the one year follow up period, hence considered to have IPT failure. The baseline point prevalence of TB disease of 3.2% was estimated to have been equivalent to the incidence of TB since TB is a curable disease, and childhood TB epidemiologically represents recent infection given the short progression period in children from infection to disease. In addition pre-diagnosed child TB cases were not included in the analysis. A comparison was therefore made of the endpoint TB incidence, to the baseline incidence of TB disease in contacts (not on IPT). IPT was shown to be protective to exposed contacts developing TB disease, with a relative risk of 0.49, (95% CI = 0.21 - 0.86) (see Table 4.6).

Table 4.6: Risk of TB disease in contacts on IPT

		TB disease	**No TB disease**	
On IPT	Yes	6 (1.6%)	362 (98.4%)	RR = 0.49 95% CI = 0.21 - 0.86
	No	14 (3.2%)	404 (96.3%)	

The focus of the study was to determine the IPT effectiveness as per protocol completion. This was determined by the net protection accorded against TB morbidity to the study population with IPT, compared to pre-IPT era. This was given by the change in proportion of contacts with TB at endpoint (with IPT) and contacts with TB at baseline (without IPT), calculated as follows;

$$\text{Effectiveness} = \frac{[\text{TB disease without IPT}] - [\text{TB disease with IPT}]}{\text{TB disease without IPT}} \times 100\% = 50\%$$

Hence the effectiveness of IPT in preventing TB disease in this cohort was 50%.

4.2.3 Characteristics of contacts with IPT failure

Of the 6 (1.6%) diagnosed with TB, the diagnosis was made during the treatment phase for 1 case, while the other 5 were diagnosed during the follow-up phase. They all had received BCG vaccine, but only 4 had a visible BCG scar. While they were all asymptomatic at enrollment, subsequently, 2 developed persistent cough lasting more than 2 weeks, 4 reported persistent fevers, and 4 had poor weight gain; with weight for age was below 2 Z score by WHO standard charts in 3 cases. The initial examinations had been unremarkable, but on subsequent assessments, 5 had fever, 4 had generalized lymphadenitis, 2 had wet chests on auscultation and 4 had weight loss. Three of these contacts had a negative TST at baseline, however, a repeat TST done tested positive. All the 6 cases had sputum samples obtained and they were all smear negative. Two of them had histology of FNA done that revealed granulomatous lesions suggestive of TB adenitis. Chest radiography was done for all these 6 case, of which 4 cases had suggestive chest radiographs. Three out of the 6 (50%) had tested positive for HIV PCR RNA.

Their mean age was 17.2 months and the male: female ratio was 1:2. They all had at least 1month of exposure to source case before the diagnosis of TB was made. All of them had been started on IPT within 3 weeks of TB diagnosis of source case. The source case was the mother in 5 cases. The average room density was 3 and 5 for day and night, respectively. The mothers were responsible for administering IPT in 5 cases,

while in 1 case it was a relative. IPT compliance rates among these contacts were generally high, at 90% and 81% after the first month and sixth month, respectively.

4.3 Factors influencing effectiveness of IPT

4.3.1 Contact factors influencing IPT effectiveness

On bivariate analysis, 4 contact factors were shown to predict IPT failure. These were weight faltering ($p = 0.023$), presence of symptoms at enrollment ($p = 0.018$), HIV status ($p = 0.005$) and a positive TST test ($p = 0.018$). The details of how contact factors that influenced IPT effectiveness are illustrated in Table 4.7.

4.3.2 Source case factors influencing IPT effectiveness

On bivariate analysis of source case factors that determined IPT failure, only 5 factors showed statistical significance. These were the female gender in source ($p = 0.015$), crowding index of more than 5 at night ($p = 0.02$), number of source cases in the house hold ($P = 0.01$), HIV status ($p = 0.02$) and knowledge of the TB/HIV relationship ($p = 0.042$). The detail of how the source case factors influenced IPT effectiveness is presented in Table 4.8.

Table 4.7: Contacts' factors that influenced IPT effectiveness

Characteristic		**TB disease (n=6)**	**No TB disease (n = 362)**	**Fishers exact test (p value)**	**OR**
					95%CI
Gender	Male	2	187	0.438	**2.137**
	Female	4	175		0.387 -11.814
Age of contact	≤ 24 months	2	204	0.701	**1.549**
	>24 months	4	158		0.280 – 8.565
Nutrition status contacts	Wt faltering	3	40	0.023	**0.124**
	Normal	3	322		0.024 – 0.636
BGC scar	Positive	5	295	1.000	**1.136**
	Negative	1	67		0.131- 9.880
Breastfeeding currently	Yes	3	230	0.673	**1.743**
	No	3	132		0.347 – 8.757
Appropriate weaning	Yes	4	236	1.000	**1.068**
	No	2	126		0.193 – 5.910
Symptomatic at enrollment	Yes	5	121	0.019	**0.100**
	No	1	241		0.012- 0.869
Birth weight (BWT)	LBW	1	12	0.195	**5.833**
	Normal	5	350		0.632 – 53.86
Recent morbidity	Yes	1	40	0.510	**0.621**
	No	5	322		0.071 – 5.451
Past morbidity/ admissions	Yes	5	49	0.586	**0.783**
	No	1	313		0.090 – 6.842
Social places attendance	Yes	5	288	1.000	**0.778**
	No	1	74		0.90 – 6.74
HIV RNA PCR	Positive	3	22	0.005	**0.065**
	Negative	3	340		0.012 – 0.339
TST reaction	Positive	4	72	0.018	**0.124**
	Negative	2	290		0.022 – 0.691

Table 4.8: Source case factors that influenced IPT effectiveness

Characteristics		**TB disease (n = 6)**	**No TB disease (n = 362)**	**Fisher's exact (P value)**	**OR**
					95%CI
Age	<30 years	6	279	0.186	-
	30+ years	0	83		
Gender	Female	6	177	0.015	-
	Male	0	185		
Residence	Slum	5	261	1.000	**1.935**
	Periurban	1	101		0.549 -16.765
Marital status	Married	5	276	1.000	**1.558**
	Single	1	86		0.180 – 13.518
Level of education	≤ Secondary	6	308	0.598	-
	Tertiary	0	54		
Occupation	Unemployed	2	256	0.068	**4.830**
	employed	4	106		0.872 – 26.770
Relationship to child	Parent	5	270	1.000	**1.704**
	Other	1	92		0.196 – 14.774
Crowding index - Nights	≤5	4	74	0.020	**7.784**
	<4	2	288		1.399 – 43.317
Number of source cases in household	1	2	326	0.001	**0.541**
	≥2	4	35		0.009 – 0.304
Share bedroom with child contact	Always	5	293	1.000	**0.849**
	Sometimes	1	69		0.098 – 7.386
Separate Cooking room	Yes	1	79	1.000	**1.396**
	No	5	283		0.161 -12. 121
Duration of symptoms prior to TB diagnosis	< 4weeks	0	107	0.187	-
	>4 weeks	6	255		
HIV status of source	Positive	4	74	0.020	**7.784**
	Negative	2	288		0.019- 43. 317
Knowledge on causation of TB	Bacteria	5	256	0.676	**2.070**
	Other	1	106		0.239- 17.933
Knowledge of TB risks to children	Good	3	116	0.638	**2.070**
	Poor	3	246		0.239 -17. 933
TB/HIV relationship knowledge	Good	3	200	0.042	**0.954**
	Poor	3	304		0.109- 8.316
TB myths and attitudes	None	1	304	0.625	**0.954**
	Present	5	58		0.109- 8.316

4.3.3 Social challenges to IPT uptake

Various challenges were expressed by clients during FGDs and KI interviews. Most (76.9%) households depended on the mothers for drug administration to the child. This meant that the treatment was likely to be interrupted whenever the mother was not available; either had travelled or was too unwell. Unlike the adults cases that were required to have a treatment supporter, poor social support was reported by 102 (27.8%) of households. Lack of the women decision making autonomy for their child's health played out in all these sites. There was internal stigma of TB diagnosis within families in at least 35 (9.5%) cases. This was a barrier to couples disclosing their status to each other, and especially where the source case was female. At least 18 (5%) of females did not also disclose the child's uptake of the IPT to their spouses, fearing social isolation and discrimination. Furthermore, external stigma was a concern in 45(12.2%) cases, who felt that the many health facility visits were revealing their status to the public. Political uncertainties arising from the impending general elections at the end of 2012 did contribute to some failing to honor their appointments or to collect the drug as scheduled. In the latter months of 2012, some of the clients from the Luo and Luhya communities migrated to their rural homes. The uncertain political scenario also led to frequent absenteeism of staff, and hence postponement of IPT clinics and the temporary suspension of CHW visits to the homes to enforce compliance.

4.3.4 Health facility factors influencing IPT outcomes

In one of the FGD with TB clinic staff, most of the staff perceived IPT program as an extra workload with no additional motivations or incentives. Poor staff remuneration led to work apathy among the clinical staff. Some staff preferred to be engaged in other

areas that promised better incomes. This was seen as a major barrier to implementation of the IPT program. Most staff reported that they had inadequacies in their knowledge of childhood TB. Specific knowledge gaps included how to measure and dispense paediatric doses using tablets, how to identify contacts with TB disease and when to change contacts from prophylaxis to full TB therapy. One TB nurse actually said, "*We have undergone various short trainings on adult TB diagnosis and management, but there was hardly any mention of childhood TB issues. In fact, we have not even seen a copy of the pediatric TB guidelines in this center".*

Other concerns raised were that the TB guidelines did not consider the available resources at the grassroots, other co- existing service delivery programs and available support structures at the facilities before it was rolled out. Indeed a large gap exists between policy and translation of policy into field programs. During key informant interviews with the laboratory in-charges, they reported lack of appropriate diagnostic reagents for paediatric TB. Examples of this included lack of TST reagents and lack of the base used for neutralizing gastric aspirate sputum samples in the laboratory to enable the handling of pediatric sputum samples. They all had no prior training of handling the gastric aspirate samples.

The TB clinic staff decried that there were no concrete public health laws for enforcing contact tracing of all exposed contacts to TB cases. This was a big hindrance to IPT program implementation. As one nurse put it, "*Even when a TB case has a child contact and declines this IPT, we do not have any teeth to enforce its administration. No penalty can be implemented on those who default such crucial public health interventions'.*

Across all sites, there was generally poor knowledge of public health legislations that could be used to enforce the guidelines.

Staff shortage was a constant concern across all the 3 centers. There was only one nurse assigned to the TB clinic at a time. The responsibilities of the TB nurse included counseling of TB clients, giving health talks, dispensing TB drugs, monitoring TB treatment defaulters, maintaining TB clients' records and attending regular workshops or community campaigns organized by the DLTLD. The adult TB clinics ran on at least 3 working days per week. These staffs were therefore assigned to do other duties on non-TB clinic days. During key informant interviews with all the facility in- charges, the overall impression was that the addition of child contact clinics would pose greater demands on existing staffing shortages. One Nurse in- charge reckoned, *"We have so many crucial programs that must of necessity run at the center weekly, some very sensitive and some well supported by donors. The additional clinic of following up well babies beyond their routine child welfare clinic cannot be considered a priority given our staffing limitations"* Sometimes, prevailing staff shortages often called for withdrawal of the TB clinic nurse, to step in and work at other clinics. This then meant that the CHW would be left to run the TB clinic all alone, despite having very scanty knowledge of TB, and especially pediatric TB. Furthermore, the TB nurse had additional responsibilities. They were expected to track and screen exposed contacts, to maintain regular follow-up and monitoring of contacts, had to dispense IPT and monitor adherance. All this left them overstretched. The DLTLD had to engage at least 2 community health workers per site to assist in the contacts tracing.

4.3.5 Programmatic challenges to IPT uptake.

All the 3 health facilities offered level 2 health care services. Programmatic concerns were reported by 316 (86%) of source cases. Although TB drugs collection for source case and isoniazid for the contact(s) tended to be coincided, 240 (65.2 %) cases felt that there were too many hospital visits, and especially at one site where weekly drug collection schedules were strictly followed. Some 108 (29.3%) cases decried the 'real treatment costs', especially the transport costs to the health center, which was not being met by the program. At least 84 (22.8%) of the clients requested for bus fare to enable them come for follow up visits. Some 78 (21.2%) complained about man hours lost coming to the facility, which interfered with their daily livelihoods. Moreover, this was worsened when TB staffs had to be engaged in other duties within the health facility. Inconveniences caused by bringing children to the facility may have contributed to some of the drop outs. A few reported that their illness had caused them to change jobs or even lose their jobs due to frequent absenteeism, in order to come to the health facility.

Some requested for incentives such as child food, or subsistence money to come to the center, as they had to put on hold their routine sources of livelihood. One site had to introduce provision of a packet of milk to the child during every visit especially during the intensive phase in order to improve compliance. There were concerns of crowding at the contacts' clinics with TB infected adults. Inconsistency in drug supplies was reported at all the centers, due to stocks running out, especially during weekend and public holidays, resulting from interrupted supply chain. There were abrupt changes in scheduled appointments, especially observed at one of the sites. This was mainly due to

the staff shortages. A few clients 20 (5.6%) complained about staff perceptions. Some reported staff indifference to their plight, others felt that the staffs had poor attitudes, while others decried poor public relations of the staff. One client lamented *" I had to pick the child from school, before her lunch was serve so as to get her here by 2pm. Once here, nothing was done till 5pm when someone told us to come the following week, but they never bothered explain what was happening despite my questioning'.* Moreover, impromptu change of clinic venue was a concern at one site, mainly due to limited room space available at the facility. This led to clients frustrations and unnecessary delays. The programmatic and drug related challenges reported are presented in Table 4.9.

Table 4.9: Programmatic and drug related challenges reported

	CHALLENGES	**n (%)**
Programmatic challenges	Too many hospital visits	240 (65.2%)
	Uncommitted staff	54 (14.7%)
	Long stay at facility	78 (21.2%)
	Duration too long	178 (48.4%)
	Too many drugs for child	23 (6.3%)
	Stocks ran out	213 (57.9)
	Lack of enablers	108 (29.3%)
	Other	11 (2.9%)
Drug related challenges	Difficulty in administering tablets to children	163 (44.3%)
	Bitter taste	33 (8.9%)
	Difficulty in establishing dose	48 (13.0%)
	Side effects	82 (22.2%)
	Child refused	89 (24.1%)
	Child vomits	36 (9.7%)
	Other (spillage, crumbled)	33 (9.0%)

4.3.6 Drug related factors influencing IPT outcomes

Drug related challenges were reported in (258) 70.1% of the cases. Majority, 163 (44.3%), had difficulties in administering tablets to children, as most were not familiar with how to crush the tablet for the child. Difficulty in establishing the dose for children aged less than 10kg was a concern in 48 (13%) cases. The tablets provided were not scored, and this posed a challenge whenever there was need to break the tablet, either into halves or quarters. Many reported that the tablet crumbled on attempt to crush it; hence the exact dose could not be accurately determined. Although the tablet is not bitter, 33 (8.9%) of caretakers reported that their children experienced difficulty attributable to the taste of the tablet. Another 89 (24.1%) of caregivers reported that children refused to take and another 36 (9.7%) of them said the children vomited the drug. However, some parents had to devise a way of masking the taste through mixing crushed powder with other flavored drinks such as milk, porridge or fruit juice. At one site, donation of syrup formulation of isoniazid from an NGO seemed to have briefly improved adherence, with mothers reporting improved child uptake. However, on bivariate analysis, the existence of reported IPT challenges in the source case was not found influence IPT outcomes ($p = 0.791$). The summary of the challenges expressed by the clients are presented in Table 4.9.

4.3.7 Safety of IPT

Majority 286 (77.8%) of contacts tolerated the drug well, but 82 (22.2%) of the contacts reported to have side effects. The leading side effect reported in this cohort was a transient skin rash reported in 46 (12.5 %), followed by a gastro-intestinal symptoms, ranging from nausea, anorexia, vomiting in 35 (9.5%) and increased appetite reported in

15(0.4%). At least, 20 (5.4%) had neurologic symptoms such as irritability and/or weakness, paraesthesias, painful limbs, altered sleeping patterns, reduced play or regression in milestones. Only 26 (0.07%) reported yellow discoloration of eyes or urine. This was more common in the malnourished children. Baseline liver enzymes were normal in 361(94%) of the children. The mean baseline AST level was 46.1mmo/l, while the baseline mean ALT was 29.6mmol/l. On repeat of LFTs after 1 month on isoniazid, the mean AST level rose to 90.9mmo/l, while the mean ALT also rose to 54.1mmol/l. However, only 3 (0.08%) children had elevations of greater than 3 times of the baseline level, necessitating discontinuation of IPT. Two of these children were also on HAART, while the other had malnutrition. The details of IPT related side effects are illustrated in Table 4.10.

Table 4.10: IPT related side effects

System	**Side effect**	**Total (N = 368)**
Gastro-intestinal system	Poor feeding/anorexia	16 (4.3%)
	Vomiting	10 (2.7%)
	Diarrhea	3 (0.8%)
	Yellow discoloration of eyes	6 (1.6%)
Central Nervous system	Weakness /lethargy	8 (2.1%)
	Irritability	8 (2.1%)
	Neuropathy	4 (1.1%)
Skin	Skin rash	46 (12.5%)

On analysis of the factors that were associated with the occurrence of side effects, only 3 factors were found to be statistically significant. These were the knowledge of TB causation ($p = 0.016$) and knowledge of risk factors to TB ($p = 0.005$) and cases where

the mother was responsible for administering the treatment to the child (p = 0.006). The following key factors were not found to be associated with occurrence of side effects; optimal compliance (p = 0.403), age of contacts (p = 0.404), HIV status of contact (p = 0.143), and under-weight status (p = 0.499).

4.4. IPT adherence

Three levels of adherence were assessed. First level assessed was the acceptance of IPT by eligible source cases (those that gave consent). The second level was the completion rate of the 6 months isoniazid course and the 6 months follow- up period. Lastly, the compliance to the recommended prophylaxis regime was assessed.

4.4.1 IPT acceptance rates

Following explanation of IPT benefit and study expectations, those source cases that accepted to be enrolled were requested to sign a written consent form. The rest were given more time of up to 1 week to make a decision, and to bring the form back on the second visit. Overall, IPT acceptance rate in this cohort was 87.4%, with the highest acceptance noted at Mukuru site at 90.3%, followed by Kayole site at 87.1%, and lastly, the Dandora site which had an acceptance rate at 85.5%. The details of the IPT acceptance and completion rates per study site are illustrated in Table 4.11.

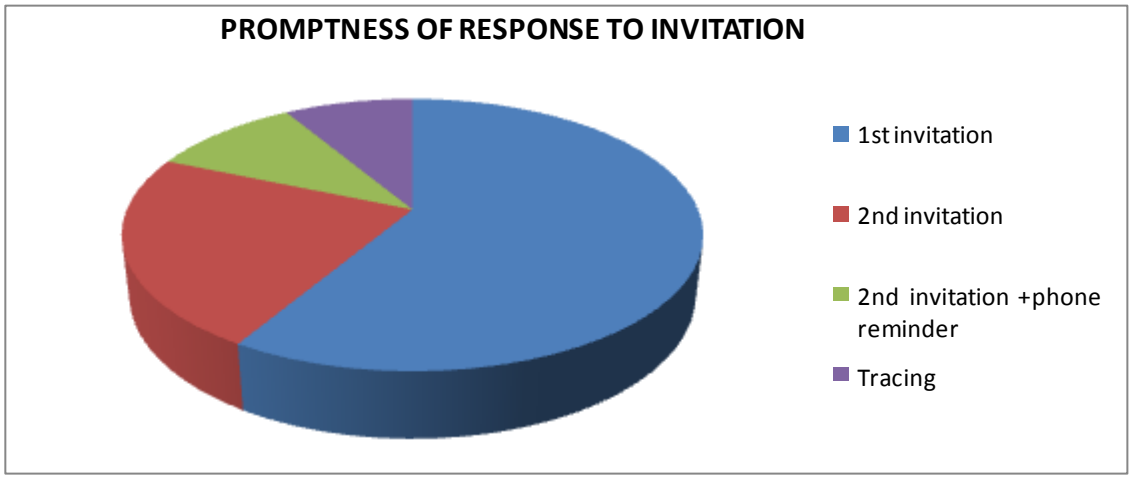
Table 4.11 IPT acceptance and completion rates

		Kayole	**Dandora**	**Mukuru**	**Total**
Eligible adults	Smear +ve PTB, + child contacts	124	138	104	366
Adult source cases	Consented	108 (87.1%)	118 (85.5%)	94 (90.3%)	320 (87.4%)
	No consent	16 (12.9%)	20 (14.5%)	10 (9.7%)	46 (12.6%)
Contacts enrolled		148	158	122	428
Contacts with TB disease	Excluded	4	5	5	14
Contacts put on IPT		144	153	117	414
Children on IPT	Defaulted IPT	15 (10.4%)	22 (14.4%)	14 (11.9%)	46 (12.5%)
	Completed IPT	129 (89.5%)	136 (85.6%)	103 (89.1%)	368 (88.8%)
Reasons for non-consenting of source case (n = 46)	Lack of time	4 (8.6%)	5 (10.9%)	4 (8.6%)	13 (28.3%)
	Fear of side effects	3 (6.5%)	4 (8.6%)	3 (6.5%)	10 (21.7%)
	Stigma	4 (8.6%)	2 (4.3%)	2 (4.3%)	8 (17.3%)
	Expensive	2 (4.3%)	2 (4.3%)	2 (4.3%)	6 (13.1%)
	Spouse refusal	2 (4.3%)	3 (6.5%)	2 (4.3%)	7 (15.2%)
	Other	1 (2.2%)	1 (2.2%)	-	2 (4.3%)

Of those that declined participation, reasons cited ranged from; fear of giving long term treatments to well children, lack of time to bring children for follow up visits, especially when the source cases were in formal employment, fear of side effects, among others. Spouses to some 8 married ladies with TB declined their participation in this study. Those that consented were requested to bring their contacts for assessment.

The promptness of acceptance varied. Only 158 (42.9%) brought in contacts on first invitation, within 7 days of the diagnosis. Another 130 (35.3%) responded 1 week later, following a second invitation. There were 58 (15.8%) who still did not bring the contacts, until a further telephone call reminder during their second week of treatment. Twenty two (6.9%) did not bring the child contacts up to 2 weeks later, despite signing the consent form, and despite telephone remainders, and until the CHW visited their homes (tracing). The details of the promptness of response to IPT invitation are presented in a pie chart below (Figure 3).

Figure 3: Promptness of response to invitation



4.4.2 IPT completion rates

The overall completion rate was 368 out of 414 (88.8%) contacts put on IPT. The completion rates across all sites were similar. This was attributed to the strict follow- up and support accorded by the CHWs. Contacts that missed dose collection or their follow- up sessions were called up and those who had minor challenges were assisted with enablers. Forty six (12.5%) contacts did not complete IPT follow- ups and were

therefore counted as IPT defaulters. Among these were 2 contacts that died of non- TB related causes; one of trauma and the other of acute gastroenteritis. In 9 cases, though their mothers had consented to their participation, they were later discontinued by their fathers. Five contacts lost their parents during the same period and had to relocate to their rural homes. There were 6 documented transfers- out from the study sites to other distant TB treatment sites. The rest (24) were lost to follow up and could not be reached either by either telephone or be traced to their residences.

Completion rates were also assessed based on attendance of the scheduled follow- up clinic schedules. Every contact was expected to attend a minimum of 6 scheduled pediatrician's clinics by the end of the study period, but only 22 (5.9%) contacts achieved this. Majority 208 (56%) attended 5 clinics, 87 (23.6%) attended 4 and 51 (13.8%) attended only 3 clinics. However, most of them collected the drugs as scheduled from the TB clinic nurses.

4.4.3 IPT compliance rates

Compliance to drug intake was assessed based on supervision of drug administration and pill count. The person responsible for administering the drug to the child was the mother in 283 (76.9%), the father in 26 (7.1%), a relative in 29 (7.9%), a grandparent in 15 (4.1%), a house-help in 13 (3.5%) and a sibling in 2 (0.5%). The drug was administered in the mornings in 158 (42.9%), 199 (54.1%) gave at bedtime and 11 (3.0%) gave it at varying times.

Pill count was monitored after 1 month of treatment of source case and monthly thereafter. The compliance rates after 1 month was very good; 34% had not missed any dose, 156 (42.4%) had missed 1-2 doses, 47 (12.8%) had missed 3-4 doses, 13 (3.5%) had missed 5-6 doses and only 17 (4.7%) had missed 7-10 doses. The average compliance level for this phase was 93.3%. Reasons for missing dose were that the child refused to take in 71 (19.3%), stocks ran out in 61 (16.6%), 47 (12.8%) forgot to give the drug, 17 (4.6%) reported that the child was unwell and therefore it was not given, and in 15 (4.1%) it was the absence of caretaker. Other reasons cited included caretaker was too tired or unwell and fear of side effects in 3 (2.2%). However after the sixth month assessment, compliance dropped across all sites; 62 (16.8%) had not missed any dose, 148 (40.2%) had missed 1-2 doses, 77 (20.9%) missed 3-4 doses, 53 (14.4%) had missed 5-6 doses and 28 (7.6%) missed 7-10 doses. The average compliance level for this phase was 82.4%. The main reasons for missing dose in the latter phase was stocks ran out in 213 (57.9%), and 59 (16.0%) forgot. In 22 (5.9%) it was reported that the fathers stopped the treatment and 12 (3.2%) gave others reasons. Table 4.12 indicates a summary of the adherence factors. The overall compliance across the study

period was 89%. A summary of the compliance rates at the various sites at the end of first and sixth month are presented in Figure 4.

Figure 4: Compliance rates at the various sites at the end of first and sixth months.

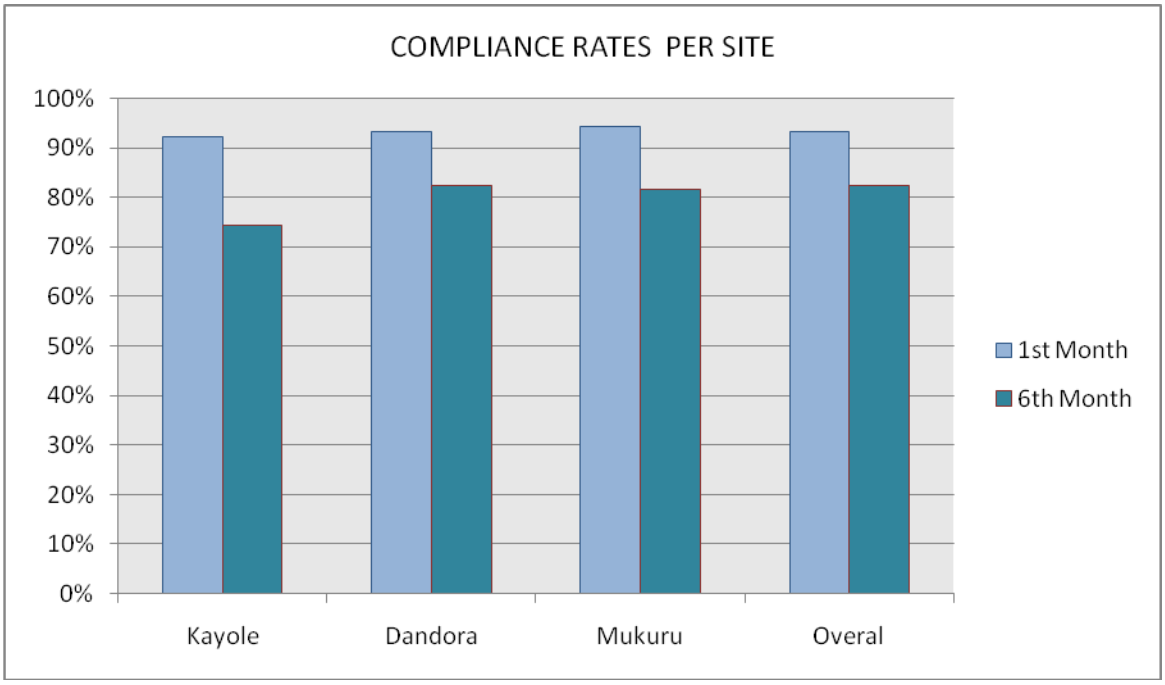


Table 4.12: IPT adherence summary

Characteristic	**Sub- group**	**Total (N = 368)**
Primary drug administrator	Mother	283 (76.9%)
	Father	26 (7.1%)
	Relative	44 (12.0%)
	Other	13 (3.5%)
Timing of drug administration	Morning	158 (42.9%)
	Evening	199 (54.1%)
	Midday	11 (3.0%)
End of month 1. Missed doses (compliance rate)	0 (100.0%)	125 (34.0%)
	1-2 (93.4%)	266 (45.4%)
	3-4 (86.7%)	47 (12.8%)
	5-6 (80.0%)	13 (3.5%)
	>/=7 (73.4%)	17 (4.7%)
	Average	82.4%
Reasons for missing doses in 1st month	Child refused	71(19.3%)
	Stocks out	61 (16.6%)
	forgot	47 (12.8%)
	Child unwell	17 (4.6%)
	Travelled	15 (4.1%)
	Caretaker ill	14 (3.8%)
	Side effects	3 (2.3%)
	Other	18 (4.9%)
End of month 6. Missed doses (compliance rate)	0 (100.0%)	62 (16.8%)
	1-2 (93.4%)	148 (40.2%)
	3-4 (86.7%)	77 (20.9%)
	5-6 (80.0%)	53 (14.4%)
	>/= 7 (73.4)	28 (7.6%)
	Average	82.4%
Reasons for missing dose in 6th month	Stocks out	213 (57.9)
	Forgot	59 (16.0%)
	Dad refused	22 (5.9%)
	Other	12 (3.2%)

On bivariate analysis of factors that influenced compliance, 3 factors were statistically significant; source case knowledge of TB causation ($p = 0.04$), knowledge of TB/HIV relationships ($p = 0.04$), and birth order ($p = 0.022$). This is presented in Table 4.13.

Table 4.13: Factors influencing compliance

Characteristics		**Optimal compliance**	**Sub-optimal compliance**	**Fisher's exact (p value)**	**OR** **95%CI**
Age of contact	< 24 months	180	28	0.753	**0.866**
	>24 months	141	19		0.465- 1.615
Nutrition status of contacts	Malnutrition	34	9	0.093	**1.999**
	Normal	287	38		0.890 – 4.489
HIV infection in contact	Positive	20	5	0.201	**1.792**
	Negative	301	42		0.638 – 5.028
Occurrence of side effects	Yes	222	34	0.399	**1.166**
	No	99	13		0.590- 2.306
Birth order	First born	142	13	0.039	**2.075**
	>Second	179	34		0.055 – 4.79
Source case age	≤ 30 years	246	39	0.454	**0.673**
	> 30 years	75	8		0.301- 1.503
Relation with source	Parent	236	39	0.209	**0.570**
	Other	85	8		0.256 -1.268
Level of education	≤ Secondary	275	39	0.059	**1.226**
	Tertiary	46	8		0.539 – 2.791
Occupation of source	Employed	93	17	0.200	**0.720**
	Un-employed	228	30		0.379 – 1.368
Residence	Slum	236	30	0.114	**1.573**
	Peri- urban	85	17		0.826- 2.998
Primary drug administrator	Mother	251	34	0.463	
	other	70	13		
Crowding index - day	≥ 5	67	11	0.704	**0.863**
	< 5	254	36		0.417 -1.786
Knowledge of TB causation	Yes	236	25	0.044	**2.443**
	No	85	22		1.309 – 4.561
Knowledge of TB/HIV relationship	Yes	184	19	0.022	**1.979**
	No	137	28		1.061- 3.691
TB myths	None	270	39	0.832	**1.086**
	yes	51	8		0.480- 2.459

Sub-optimal compliance was not shown to significantly influence risk of occurrence of IPT failure (p = 0.562). Those with sub-optimal compliance had an odds ratio of 0.728 of developing IPT failure. Households with the mother as the primary drug administrator had odd of 1.236 of developing TB. The summary of the effect of adherence on IPT outcomes is provided in Table 4.14.

Table 4.14: Effect of adherence on IPT outcomes

Adherence		**TB disease N = 6**	**No TB disease N = 362**	**Fisher's exact (p- value)**	**OR**
					95% CI
Compliance rate	Sub-optimal	1	46	0.562	**0.728**
	Optimal	5	316		0.083 - 6.370
Timing of drug administration	Morning	4	153	0.440	_
	Bedtime	2	198		
	Midday	0	11		
Person responsible	mother	5	280	0.481	**1.236**
	other	1	82		0.321 - 9.880

4.5 Multivariate logistic regression

The independent variables that had showed statistical significance were all entered into the multivariate logistic regression model to determine if they had a relationship with IPT failure- the dependant variable. Only weight faltering was significant (p = 0.05, CI 0.998- 200.237). Table 15 shows the variables in the equation on multivariate logistic regression.

Table 15: Variables in the equation on multivariate logistic regression

	B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I. for EXP (B)	
							Lower	Upper
Number of TB sources							0.013	1.199
Room density night	0.017	0.373	0.002	1	0.963	0.983	0.473	2.044
HIV status	-1.299	1.517	0.734	1	0.392	0.273	0.014	5.330
Weight faltering	2.649	1.352	3.836	1	0.050	14.137	0.998	200.237
HIV PCR	2.504	1.705	2.157	1	0.142	12.225	0.433	345.312
Mantoux	2.275	1.312	3.006	1	0.083	9.731	0.743	127.444
Gender of source	-18.892	2295.193	0.000	1	0.993	0.000	0.000	.
Cough symptom	-14.923	4064.238	0.000	1	0.997	0.000	0.000	.
Constant	32.920	4667.541	0.000	1	0.994	1.981E 14		

CHAPTER FIVE: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

5.1 DISCUSSION

5.1.1 Baseline child TB infection and disease prevalence

Various studies have assessed the risk of TB transmission to children in congregate communities. This study focused on informal settlements, areas of high adult TB burden, small crowded residences, hence TB predisposing environments. The baseline TB infection rate was 22.2% and that of TB disease was 3.2%. Much higher rates were reported from the Indian academy study which showed infection rates of 71% and disease risk of 33% (Castan Vindal *et al*., 1991). Similarly, higher TST positivity was reported among household contacts in a Pakistan study at 49.4% (Rathi *et al*., 2002). In a study done in Uganda, the prevalence of TB disease in child population was 10% (Jaganath *et al.*, 2013). A pooled analysis of contact studies in low and middle-income countries demonstrated a yield of 7% (Swaminathan *et al.*, 2010). These variations among high burden settings may be attributed to factors such as variations in HIV prevalence, nutrition status of the children, environmental factors, and infectivity of the mycobacteria, among others. In this cohort, 6.3% contacts were HIV positive, while 14.5% were malnourished. Some of them may have been anergic, resulting in low TST positivity observed. Intensive cough management strategies instituted in our study sites may have also contributed to the lower TB rates observed. These findings support occurrence of continuous transmission in informal settlings, and therefore potential benefit of contact tracing in preventing childhood TB in informal settlings.

The risk of TB transmission was proportionate to intensity of internal exposures, which included the crowding index of ≥ 5 persons at night (p = 0.043), presence of cough symptom in source case (p = 0.049), and prolonged contact time of ≥ 1 month prior to TB diagnosis (p = 0.000). However, sharing sleeping room with source case was not significant (p = 0.471). This is corroborated by findings from a Gambian study which found the risk of TST positivity in the child increased with geographic proximity of the child to the source case within the household and with the degree of activities shared with the TB source case. It was also associated with the clinical severity of the disease in the index case (Leinhardt *et al*, 2003). On the other hand, vulnerability of contacts was related to weight faltering (p = 0.000), BCG negativity (p = 0.000), low birth weight (p = 0.000), inappropriate weaning (p = 0.011), HIV positivity (p = 0.000), and recent morbidity (p = 0.000). Similar findings were reported in the Uganda study, where suggested risk factors were HIV status (OR, 7.90; p < 0.001), and baseline positive TST (OR, 2.21; p = 0.03) (Jaganath *et al.*, 2013). In this study, the adult source characteristics such as sex, HIV status, and extent or severity of disease were not associated with childhood disease. Similarly, in a Pakistan study, source case age, sleeping site relative to index case, intensity of index case AAFB sputum smear positivity, and contacts BCG status were found to be independent predictors of TST positivity (Rathi *et al*., 2002).

Interventions targeting to reduce TB transmission in informal settlings, should sensitize urban dwellers on reducing crowding, improving ventilation, and reduction of infectious period of source case by early case diagnosis and promotion the practice of cough

etiquette. Moreover, transmission from external TB exposures to children is on the increase, and needs to be monitored closely.

5.1.2 IPT as a child TB prevention strategy

BCG vaccination was the child TB prevention strategy adopted in these sites, with 96.7% of contacts having received BCG vaccination at birth. However, only 77.1% had the BCG scar on their left forearms, as evidence of vaccine uptake. The poor uptake was probably related to high numbers of immune-compromised susceptible hosts, including the HIV infected, those born low birth weight and the malnourished. BCG positivity was protective in reducing the risk of TB disease at baseline (OR- 0.000, 95% CI 0.028 – 0.297). However, 5 out of 6 contacts with IPT failure at endpoint had BCG scar. BCG vaccination did not therefore prevent of progression of primary infection in this cohort. Constant exposures in high burden settings leads to continuous TB transmission hence increased risk of primary infection. There is need to adopt complementary strategies that could prevent infection progression to disease.

IPT was protective to exposed contacts developing new TB disease, with RR of 0.49 (CI = 0.21 - 0.86). Introduction of IPT lowered the incidence of new TB disease in child contacts by 50%. Many children in informal settlements get exposed to adults with TB at a very young age. Four out of the six contacts with IPT failure had a positive TST at the baseline, thus the disease may have arisen as progression of latent TB infection in these contacts. Physical or emotional stresses trigger progression of infection to disease. However, the other 2 cases of IPT failure were new TB infections, while on IPT. IPT did not prevent TB infectivity in these two. Various studies have found IPT to be effective in reducing progression to disease in TST positive individuals (Curry *et al*.,

1967, Stead *et al*., 1985, Veening *et al*., 1968). Five cases with IPT failure arose during the follow-up period, after stoppage of isoniazid, with only 1 case occurring while still taking IPT. Similar findings were observed in study by Martinson *et al*., comparing 4 secondary prophylaxis regimens among persons with TB and HIV infection in a high-risk South African setting, rates of TB in the continuous-isoniazid group markedly increased when therapy was discontinued. Similar findings were documented in a Botswana trial of continuous isoniazid; they suggested ongoing transmission and re-infection in this high-prevalence setting, as a phenomenon that is likely to compromise the long-term benefit of any chemoprophylactic regimen, regardless of short-term efficacy.

The 50% effectiveness of IPT was achieved under strict monitoring and follow-up of a research study set-up. However, this still fell short of the recommended cut off of effectiveness of a good prophylaxis agent by WHO of 80%. Many studies from low burden settings reported similar effectiveness (USA advisory committee 1990). However, variable IPT protection was reported in high burden settings. In a study from Uganda, 483 of 490 children (99%) started on IPT did not develop disease (Jaganath *et al.*, 2013). However, this study included children up to 15 years of age. Two metanalysis of RCT which found protective benefit with RR of 0.40, (95% CI 0.31 to 0.52), (Smieja *et al.*, 2000) and RR of 0.65 (95% CI 0.47, 0.89) $p = 0.004$ (Ayieko *et al*., 2014). However, one study form South Africa failed to demonstrate protective benefit especially among very young children when IPT was administered for primary prevention (Madhi *et al*., 2011). They attributed this to lack of definitive diagnostic tool for this group, which could have led to over-diagnosis of TB in contacts.

Overall, the cost-effective benefit for IPT in child TB control ought to be the biggest consideration. A South Africa study modeling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting by Mandalakas *et al.*, did demonstrate that screening for *M. tuberculosis* infection and provision of IPT in young children is a highly cost-effective intervention, and lack of testing capacity should therefore not be a barrier to IPT delivery (2013). The population of contacts in informal settlings that could benefit from this strategy makes it a highly cost effective strategy that would have a large public health benefit.

However, there are 2 perspectives of effectiveness of IPT. The first is the effectiveness based on protocol completion, and secondly, is the effectiveness based on intention to treat basis. This study focused on the first. The latter could have considered overall effectiveness in all contacts that required to be started on IPT, including the 46 that defaulted treatment. This could have seen the IPT failure rate would rise to 14.13%, hence lower effectiveness. This would have further been lowered by relatively high non- acceptance rates at the enrollment stage. Hence, the effectiveness on intention to treat basis was much lower than that reported in studies from high burden settings.

The biggest contributor to this high failure rate in this setting was related to the health facility and programmatic challenges which are the biggest barriers to this strategy. Improved benefit may be achievable when most impediments to its success are addressed. Indeed, IPT failure in congregate settings could be best reduced by intensified case finding, rapid diagnosis, and prompt institution of effective therapy; fully supervised and based on rapid drug-susceptibility testing.

5.1.3 Risk factors of IPT failure

The contact factors associated with IPT failure were weight faltering (p = 0.023), presence of symptoms at enrollment (p = 0.018), HIV status (p = 0.005) and a positive TST test (p = 0.018). The source case factors associated with IPT failure were female gender (p = 0.015), crowding index >5 at night (p = 0.020), number of source cases per household (p = 0.010), HIV status (p = 0.020) and knowledge of the TB/HIV relationship (p = 0.042). The female source cases spent more hours at home with the contacts, hence the higher risk of IPT failure. Crowding of households, especially at night resulted in more transmission and hence higher likelihood of failure. Improved screening procedures for children would also go a long way in reducing cases of putting children with TB on IPT resulting in IPT failures. In contradiction to the expected, sub-optimal compliance (p = 0.562) and side effects (p = 0.23) were not associated with IPT failure. On multivariate logistic regression, only weight faltering was significant (p = 0.05. CI 0.998 - 200.237). These findings also contradict the study by Madhi *et al.*, 2011 that showed a surprising lack of efficacy of continuous isoniazid as primary prevention in very young children of HIV-positive mothers, regardless of HIV status. Under nutrition which is common in informal settlings, needs to be addressed if the IPT strategy is to succeed.

The contribution of Mycobacterial drug resistance to IPT failure was not assessed. This remains a key factor in cases of failed INH chemoprophylaxis for patients infected with INH-resistant organisms. This study did not go into the details of establishing the drug sensitivity of cases.

5.1.4 Challenges thwarting IPT strategy

At all the study sites, IPT for under 5s program was being launched for the first time. Therefore, teething problems and logistical hitches posed a challenges to the roll out course. IPT delivery to children remains an operational challenge in both high and low HIV prevalence settings, due to a wide range of health system barriers (Getahun *et al.*, 2010), with only 16% – 66% of eligible contacts receiving the drug (Banu Rekha *et al*., 2009, Marais *et al*., 2006, Pothukuchi *et al*., 2011, Zachariah *et al.*, 2003,). In this study, social, health facility and programmatic challenges limited the adherence and completion rates. Limited resources were the main underpinning challenge. Program rollout was fraught with challenges to both the source cases and the health facilities; these included limited human resource, limited support infrastructure in terms of clinic space, storage space, time allocation, documentation, and monetary resources, among others. Due to space limitations, child contact clinics were operating at the same venues as the adult TB clinics. Vulnerable child contacts were constantly exposed to a group of coughing smear positive adults, in crowded interior waiting areas every 2 weekly! Separation of high risk adults and susceptible child hosts is important. Time separation and space separation of the index and contact clinics should be enforced. An isolated office space away from adult TB clinics, for child contacts' clinic would be ideal, to reduce the risk of exposure of these children in hospital settings. Precautions to minimize infection in hospital settings need to be enforced. Small crowded clinics should be discouraged. Environmental control measures such as keeping all windows and doors open to allow natural ventilation should be emphasized. In addition, aggressive cough etiquettes among patients should be instituted. Patients should be

handed with tissues (or pieces of cloth) and instructed to cover their mouths and noses when they cough. Alternatively face masks should have been provided to wear when at the facility. Non touch receptacles for disposal of used tissues and masks should be made available in waiting areas.

Effective IPT implementation requires proper documentation, child health monitoring, TB diagnostic procedures, compliance and toxicity monitoring. Most of these data collection and storage tools remain undeveloped in public clinics. Supporting computer software programs, contacts record cards and registers have not been put in place yet. Tracking of contacts is still not streamlined. With many other competing hospital programs, IPT program was not getting priority. This is partly related to limited child TB advocacy and less support by NGOs and multinational companies.

The IPT program is a labor intensive venture and its addition to the already resource strained facilities, posed a big challenge. For most sites had only one nurse assigned to the TB clinic, with assistance of CHWs. Occasionally the nurse was required to serve in other hospital departments. Frequent change over to work in departments, and with high staff turnovers led to inconsistency of trained personnel. It is necessary to keep log of the trained staffs, and retain them, in order to avoid wasted efforts. Annual re-training on TB control measures was useful for these staff. None of the sites had a clinician attached to the TB clinic. Basic personnel capacity needed for such a program was a full time nurse, a clinician and at least 2 community health workers.

Pediatric TB diagnostic challenges were a bottleneck to the effective roll out of the program, especially at these level 1 facilities. The site laboratories were not equipped

for diagnosing Pediatric TB. Most staff had incompetent pediatric TB diagnostic skills and Pediatric TB treatment guidelines were ironically missing at all implementing sites. These led to contacts' referrals to higher level centers for further evaluations. However, referral systems are not streamlined, and some children referred did not come back to the facility, hence their outcomes were poorly documented. There is need to strengthen laboratory services and improve X-ray access. Demoralized staff, poor staff attitudes and stigma were rampant. Institutional policies should be developed and appropriate incentives put in place. Resources need for various purchases including reagents, the drug isoniazid, consumables such as gloves, nasogastric tubes, nebulizers were not put in place. Infection control measures expected of an ideal "Contact clinic' such as fans, tissues, non touch receptacle bins, setting aside of sputum induction rooms, and waiting areas with room air cleaners with ultraviolent germicidal irradiation or Highly efficient particulate air (HEPA) filters were not in place.

5.1.5 Safety of isoniazid

Isoniazid was well tolerated in this cohort, with side effects reported in only 82 (22.2%) of the cases. The leading side effect reported was a transient skin rash in 46 (12.5 %), followed by gastro-intestinal symptoms in 35 (9.5%), increased appetite in 0.4%, and 20 (5.4%) had neurologic symptoms. Only 6 (1.6%) reported yellow discoloration of eyes or urine. Three factors predicted occurrence of side effects; knowledge of TB causation ($p = 0.016$), knowledge of risk factors to TB spread ($p = 0.005$) and person responsible for administering the treatment to the child ($p = 0.006$). These were the groups that were likely to be more knowledgeable, hence had a higher index of suspicion. Vulnerable contacts such as those malnourished, LBW babies, and the HIV positive

contacts, were not significantly associated with side effects. The mean AST and ALT levels showed a 2 fold increase after 1 month on IPT. However, only 3 (0.008%) of the children experienced 3 fold increase in liver enzyme levels, 2 of who were on HAART and 1 was underweight (>2 Z-score weight for height). Most of toxicities reported were transient and did not require discontinuation of therapy. Similar findings were reported in a study done by Kopanoff, where only 15% of patients experienced a transient asymptomatic increase in their liver transaminases while on treatment (1978). Clinical hepatitis was much less common and rarely fatal. Most of these were older patients. In the IUAT trial, 1982, the risk of INH-related hepatitis was 0.5%, with a mortality rate of 14 per 100,000, but significant liver toxicity was more likely in those who were malnourished or severely ill at diagnosis. In a meta-analysis of 11 RTCs evaluating IPT in non-HIV infected persons, hepatotoxicity was observed in 0.36% of people on 6 months treatment and in 0.52% of people treated for 12 months (Smieja *et al*, 2000). Children on concurrent medications such as anticonvulsants are at higher risk. Monitoring of liver function would be indicated only if there was another co- morbid states that predisposed to hepatocyte injury. Variability in drug acetylator status may have contributed to lower rates of hepatitis and higher rates of neuropathy observed in this study. This means that routine supplementation of pyridoxine was not necessary in all children on IPT, unless the child is malnourished, preterm, or a breastfed infant.

5.1.6 Adherence to contact tracing and IPT.

Compliance remains an important barrier to effective chemoprophylaxis. Despite the knowledge of IPT benefit, and despite existence of the Kenya Paediatric TB treatment guidelines (2012) recommending use of IPT among contacts aged below 5 years, IPT

acceptability was relatively low, with 12.6% of eligible source cases declining IPT for their contacts. The commonest reasons cited were fear of giving long term treatments to well children, lack of time, fear of side effects, self and external stigma, expenses, and spousal refusal in 8 cases. While majority (77.2%), required only verbal invitations to bring in their child contacts, others required a further telephone call reminder to bring in their contacts. However, there were a few that had to be tracked by CHWs to their residences, before their contacts were brought in. Most households adhered to their appointments and therapy schedules, but some required close monitoring and support by CHWs. Non-the-less, the researcher was not able enforce IPT for all eligible contacts due to lack of legislations that could be enforced. This strategy needs to be further supported by putting in place supporting public health laws.

The IPT completion rate was 88.8%, therefore the dropout (attrition) rate observed was 12.5%. Only half of the drop outs could be accounted for, while the rest were lost due to unknown circumstances. However, programmatic challenges were the most likely reasons for this. The same also had a bearing on compliance. The leading challenge reported was the inconvenience caused by too many facility visits. Attrition represents the worst form of non adherence. Hence the overall adherence, stated in this study may be an overestimate, as these defaulters were not accounted for in the analysis.

There is no gold standard for adherence (Osterberge *et al*., 2005). As with adherence to HAART, comparing estimates of adherence to TB prophylaxis between studies has been complicated by varying definitions of adherence and the use of different adherence tools (Mills *et al*., 2006, Vreeman *et al*., 2008). Traditionally, completion rates (based

on taking > 80% of the prescribed doses) have been used to describe adherence to TB prophylaxis (Ferebee, 1970). The overall compliance among those that completed follow up was 89%, with better compliance (93%) observed after the first month, but dropped to 85% in the sixth month. This may have been a reflection of lack of pressure from ill health status that occasioned lack of commitment to the treatment. Most contacts were dependant on their mothers for drug administration, who gave it at bed time. However, both factors were not statistically significant. The factors that were found to influence compliance were knowledge of TB causation ($p = 0.04$), knowledge of TB/HIV relationships ($p = 0.04$), age of contacts ($p = 0.04$) and birth order ($p = 0.022$). However, most contacts are dependent on their fathers to make decisions pertaining to their IPT completion. At least, 8 fathers in this cohort declined their spouses' and children's participation, while in 9 cases, the fathers withdrew the contacts from IPT use. Side effects were not a predictor to poor compliance. In various clinical trials, compliance ranged from 50-75% through one year of preventive therapy, (Marais *et al*., 2006, Nabukeera-Barungi, 2007, Szakacs *et al*., 2006, van Zyl *et al*., 2006,).

These compliance rates are much higher compared to studies done in similar cities from developing countries. Average compliance in India was only 75%. Recall errors may have contributed to better reported rates, but also the study framework pushed the caretakers to come for follow up. In operational settings, as in a general population, much lower rates are reported compared to trial settings. However, both self report measures and clinic based pill counts have been reported to overestimate adherence in most studies (Steele *et al.*, 2001, Berg *et al*., 2006). Death and lost-to-follow up might represent non-adherence in the extreme and are not accounted for by pill counts or self-

report. In one prospective and one retrospective study evaluating adherence to INH prophylaxis in operational settings in Cape Town, South Africa, only 15% and 27% respectively of the children completed 5-6 months of INH (Marais *et al*., 2006, van Zyl *et al*., 2006). However, for more accurate compliance monitoring, urine testing for isoniazid could have been utilized.

In this cohort, parents / caregivers were provided with substantial adherence support. In particular, the adherence measures we used allowed for immediate feedback and counseling. This allowed the care providers to focus attention on those children and caregivers who were struggling and may, at least in part, explain our high completion rates. There were several challenges that affected compliance. After first month the main challenge reported was that child refusal to take in 71(19.3%) and difficulty in administering tablets to children due to lack of an acceptable syrup formation 168 (44.3%). However, in the latter months, stocks running out were reported in 61 (16.6%), while caretaker forgetting to administer was reported in 47 (12.8%). The lack of sickness pressure may have been the biggest contributor to this, since the source had much improved by then.

Asked the best way to improve compliance, most stated the availability of syrup formulation, provision of enablers such as bus fare and child food and treatment supporters. The program had no provisions for these concerns; yet meeting of basic physical needs of contacts must be addressed to ensure sustainability of this program. In addition, patient education through regular health talks and posters, would greatly improve acceptability and compliance. This study adopted the 6 month regime; shorter

regimes are as effective as a 9-month course of isoniazid monotherapy, according to results of a prospective, randomized trial (Whalen *et al*., 1997). Shorter regimes may result in better completion rates. However, they ma have a higher relapse rate compared to 9 month course. Although DOT improves completion rates (Marks *et al*., 2000, Wobeser *et al*., 1989), it is a resource-intensive intervention that might not be feasible for all infected contacts and may not be sustained after observation is discontinued. Furthermore, overburdened and demoralized clinic staff members were unlikely, and in many cases simply unable, to provide vigilant adherence support such as written or telephonic reminders. Such support, however, is integral to a prospective study protocol. Patients are more likely to be subjected to long waiting times, interrupted drug supplies and worse interpersonal experiences with care providers in resource poor health care centers outside of a study setting (Munro *et al*, 2007). Many of these adherence barriers are being addressed and successfully overcome in the context of HIV and HAART (Stanzi *et al*, 2007). Likewise, our study suggests with minimal support, high levels of adherence to IPT can be achieved among selected TB exposed children, despite poor socio-economic circumstances and a prolonged period of prophylaxis.

Gender issues played out in this study. The female source cases tended to spent more time (mean 16.7 hrs) with the child contacts than the males (mean 12.5 hrs), hence higher exposures. There was better IPT acceptability among female source cases than the males (2:1). In Majority of households (82%), the primary drug administrator to the child was either the mother (76.9%) or a female relative. Though not statistically significant, better IPT compliance was observed among female source cases ($p = 0.209$), but severe ill health of mother may have been a confounder, as this tended to be

associated with poor compliance. In households where the source case was the mother, the fathers consent had to be additionally sought to allow participation of the child. In this cohort, 6 fathers declined to give consent, while 9 fathers stopped ongoing the ITP. The reverse however was not reported. A few mothers, 18 (5%) went ahead and administered IPT secretly, without spousal knowledge. Similar findings were reported by a South African study (Stanzi *et al*., 2009).

5.2 IMPLICATIONS OF THE FINDINGS

Many children in informal settlements are constantly exposed to TB. Health care providers in these settings need to be cognizant of this fact, by having a high index of suspicion. Protection conferred by BCG vaccination is not enough to prevent new infections in exposed contacts, and therefore needs to be boosted by adoption of contact tracing and IPT strategy. Maximum benefit is however not achievable without addressing basic physical needs of clients, as well as addressing prevailing programmatic and health system challenges. A well running IPT program puts enormous stress to existing scarce resources at health facilities, and especially the level 2 facilities. However, poorly structured contact clinic only serve to further expose vulnerable children to TB. There is therefore need to ensure that contact clinics are properly set up, and that logistical issues are streamlined to ensure sustainable supplies chains and access to IPT. Further, adherence could be optimized by investing in public and patient education, availing of paediatric formulations and reduction of frequency health facility visits. In order to maximize IPT benefits, strengthening of child nutrition support programs would reduce IPT failure, and therefore significantly improve IPT effectiveness.

5.3 CONCLUSIONS

Based on the stated specific objectives, this study makes recommendations as below elucidated:

1. The prevalence TB infection in children 5 under years, in household contacts of smear positive adults with PTB in informal settlements in Nairobi remains high, at about 22.2% and that of TB disease at 3.2%.
2. IPT use in children under 5 in close contact to adults with PTB reduced risk of child TB disease in informal settlings by 50% (RR = 0.49, CI - 0.21 – 0.86). The hypothesis that there is no difference in the prevalence of TB disease in contacts to smear positive PTB infected adults who received IPT as compared to those who do not was therefore rejected.
3. The main contact factor that predicted IPT failure in this cohort was weight faltering in contacts (p = 0.023). Various challenges limited optimum effectiveness of IPT. The main social challenges observed were mainly lack of female autonomy in healthcare decisions and stigma. The leading health system challenge was staff shortages and demoralized staff. The leading programmatic challenges reported were too frequent clinic visits, lack of pediatric formulations of isoniazid, and lack of enablers. IPT was safe, with minor transient side effects reported in 22.2% of contacts. Significant hepatotoxicity was rare, documented in only 0.008% contacts.
4. Fairly good IPT acceptance was documented in this cohort at 87.4%. IPT completion rate was 88.8%, while overall drug compliance at 89%. Programmatic, drug related and social challenges limited IPT acceptance. The

mothers were the primary drug administrators. The commonest drug challenge reported was difficulty in administering tablets to children. Good knowledge in source and small birth order of contact were associated with better compliance.

5.4 RECOMMENDATIONS

This study proposes several recommendations for both national and county governments and other stakeholders to improve IPT child TB prevention strategy as follows:

5.4.1 Recommendations for policy and practice

1. This study largely informs policy makers at the national level, at the Ministry of Health, through the DLTLD of the need to raise awareness among child health practitioners on risks and magnitude of childhood TB in informal settlements within urban centers. These children should be prioritized in TB tracing and screening programs.

2. The National TB control program should begin to cascade contact screening and IPT to all congregate settings to further support existing child TB prevention strategies, and eventually to roll it out to all areas countrywide.

3. In order to optimize effectiveness of IPT, the National TB control program needs to adopt a multi-sectoral approach. One key sector that needs to be brought on board is the Division of Child and Adolescent health, which needs to work towards improving child nutrition in informal settlements, by linking routine growth monitoring, food supplementation programs to IPT program activities. Children with growth faltering from informal settlings should be

routinely screened for TB. The other sector is the Ministry of planning and Housing, who should work to address city planning and to improve of housing in informal settlings in view of improving ventilation and lighting in the houses.

4. The National TB control program should advocate for the in-cooperation of TB control interventions in the public health act, such as contact tracing and IPT for all vulnerable exposed persons, through enacting of relevant health legislations in parliament.

5. The National TB control program should seek ways to improve IPT adherence in order to minimize development of INH resistant TB organisms in our communities. Key strategies include availing of shorter prophylaxis regimes, and/or investing in product development of pediatric formulations of INH.

6. The National TB control program needs to address programmatic challenges. Issues pertaining to logistics, sustainable supplies chains, and adequate resource allocation should be addressed. They should also provide guidance on staffing requirements for TB clinics that would match anticipated workloads. They should also provide minimum guidelines for setting up of contact clinics.

7. The National TB control program needs to prioritize capacity building for technical staff working on child TB programs, by raising their skills towards child TB diagnosis and treatment. In addition, there need to budget for motivation tokens to be given to those that accept to work in these essential programs, as this would booster commitment and help change staff attitudes.

5.4.2 Recommendations for county health officers

1. At county level, the county health officers need to systematically embrace contacts' tracing and IPT as child TB prevention strategy in all health facilities, and especially at centers in congregate settings, like informal settlements.

2. Following devolution of health care, county health officers need to address regional programmatic issues pertaining to logistics; supply chains, and ensure adequate resource allocation for the establishment of proper 'contact clinics". This would improve the adherence and therefore effectiveness of IPT. Routine monitoring for isoniazid toxicity need not be a barrier in roll out of IPT strategy.

3. County health officers should optimize patient adherence by investing in patient education forums, and by providing adherence support to households.

4. County health officers must ensure routine supervision of TB and contact clinics to ensure vulnerable contacts are not unduly exposed to infectious adults during screening. Improved child TB diagnostics need to be put in place to minimize cases of misdiagnosis of children.

5. At community level, the strategy could be enhanced by engagement of CHWs, who could take up further roles like public education on child TB control measures, thereby empowering women to make health care decisions in their households, as well as contact tracing and adherence support. Community based DOTS may be alternative options to support this strategy through use of CHWs in drug distribution. This would significantly improve IPT effectiveness

5.4.3 Recommendations for further research

The study noted various areas that could be subject to further research as follow:

1. Research to evaluate the factors that influence IPT failure in a larger case - control study.

2. Operational research to investigate health system and programmatic strategies that would further improve IPT uptake and compliance rates and hence the overall effectiveness of this strategy.

3. Research to evaluate the contribution of mycobacterial anti- TB drug resistance patterns on occurrence of IPT failure.

4. Research to evaluate the long term impact of widespread use of IPT on emergence of isoniazid resistance mycobacteria tuberculosis organisms in the communities.

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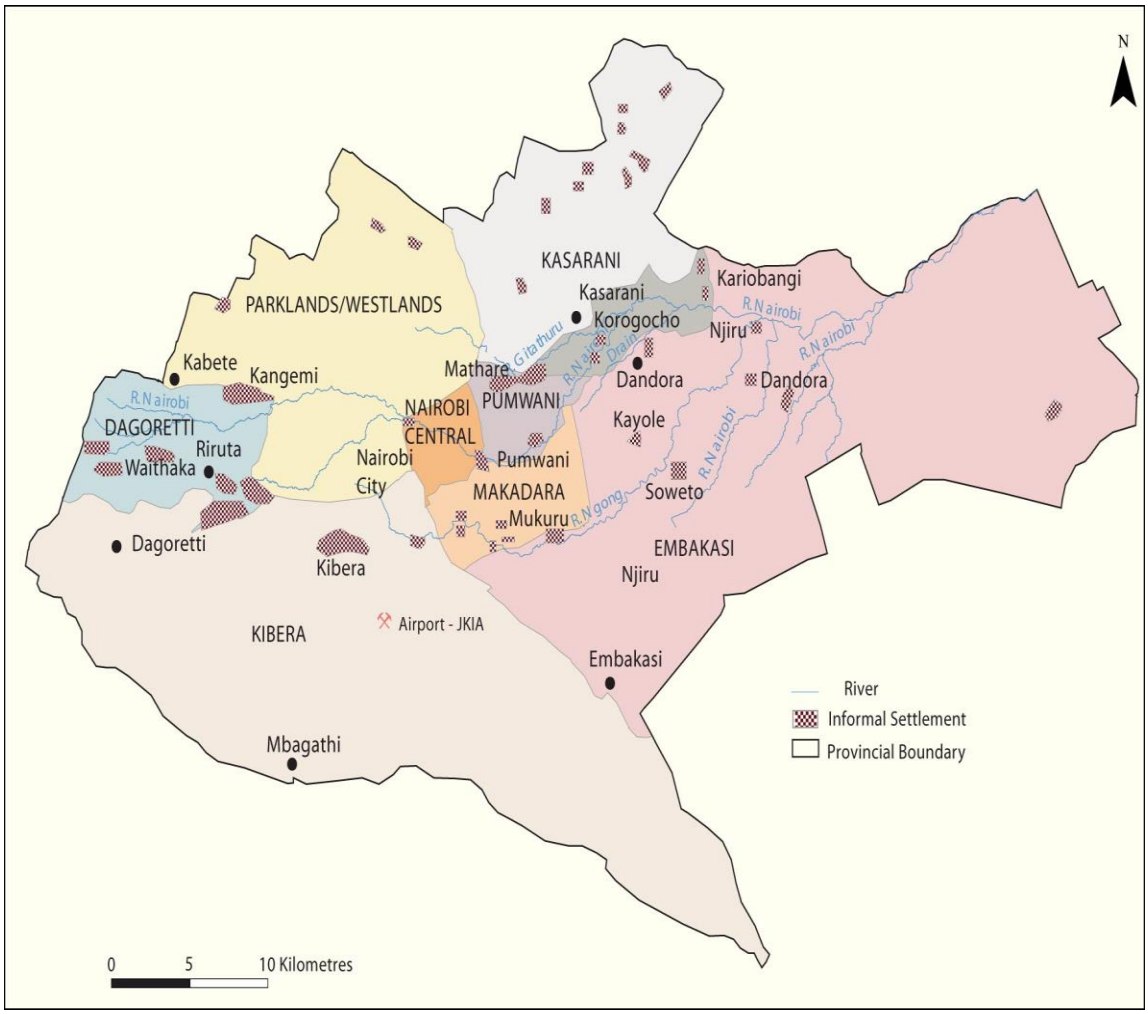
APPENDICES AND ANNEXES

APPENDIX 1. Map of Nairobi province



APPENDIX 2

APPENDIX 2.1 CONSENT FORM (English version)

Study explanation Form

I am Dr. Florence Okwara, a post-graduate student at Kenyatta University. We know that children commonly contract tuberculosis (TB) by inhaling the bacteria from TB infected adults in their households. Isoniazid is a drug that has been shown to be effective in treating and preventing TB. I am carrying out a research to evaluate the role of using this drug for the prevention of TB in children exposed to TB infected adults in their households. As one of the adult TB patients on treatment, you have been identified as a respondent to assist us towards this goal. You will be expected to inform us about all children less than 4 years old living in your household and therefore exposed to TB and respond to a set of questions.

After an initial examination by a doctor, these children will undergo a skin test on their right arm, have a blood sample drawn to test for HIV infection and to monitor the functioning of their liver. They will then have a sputum sample obtained either directly or stimulating production after inhaling some salt solution, or aspirating from their stomachs, in order to exclude existing TB disease. They will then receive a tablet of the drug isoniazid at their appropriate dosage, to be given daily for a period of 6 months. They will be followed up once every 2 months over a period of 1 year for development of any new symptoms or side effects of the drug. During these routine visits, the children will also undergo a clinical examination by a health worker and then a blood and sputum sample will be obtained another 2 times. X- rays or any other tests towards diagnosis of TB will only be recommended if there is suspicion of TB disease in the child.

Please note that here are no major risks involved in participating in this research, except for occasional side effects of the drug, which we shall be monitoring and advice you in case it happens. The Sputum induction process may be a bit uncomfortable but not painful. You will not receive any direct compensation for participating in the study. However, there may be benefits for the children participating in the study such as growth monitoring, updates of immunizations, routine health checks and early diagnosis and treatment of TB if it occurs. You will be free to withdraw from the study if you wish to, with no repercussions. All information obtained will be held in strict confidence and only used for purposes of this study. Results from the study will go a long way in informing health workers on how to prevent TB in children living in households with adults with TB. Your assistance in bringing these children for follow up and responding accurately to the questions raised will be highly appreciated. In case you have any specific questions, please feel free to call me on this number; 0722322363, or contact the Kenyatta University ethics review board.

If you have understood these requirements and agreed to participate in this study, please sign in the consent form below:

Consent form

Title of study: Role of role of isoniazid prophylaxis therapy in prevention of tuberculosis in children under 4 years of age in household contact with adults with tuberculosis in Nairobi county, Kenya.

I have been given adequate information about this research. I have been given a good explanation of all the concerns that I had, and I understand the person(s) I can contact in case I need further clarification. I understand that confidentiality will be maintained about my issues. I also understand that I may withdraw from the study at any time without compromising my rights and without any victimization. I accept to participate in this research according to the explanations given to me in the forms of explanation. I understand that I will be given the study information form and the consent form.

Name ;_____

Address:_____

Signature;_____

Date; _____

Researchers statement

I, who has appended my signature below, do confirm that I have clearly explained to this client about this research, in a language that they understand best. I have explained that strict confidentiality will be observed during the study, and the client has a right to withdraw their participation at any time of the study without victimization. I do swear that, I will adhere to the facts documented in this study only. I will not disclose any information regarding the client, told to me in confidence. And I will respect his/her rights. I will also respect his/her freedom.

Name of research assistant: _____

Signature of research assistant;_____

Date ;_____

APPENDIX 2.2 FORMU YA RIDHAA (Swahili translation)

Nakala ya maelezo ya utafiti

Mimi daktari Florence Okwara ni mwanafunzi wa udaktari katika Chuo Kikuu cha Kenyatta. Twajua kuwa watoto huambukizwa ugonwa wa kifua kikuu kutoka kwa

kupumuliwa na viini vya kifua kikuu kutoka kwa watu wazima walio na ugonjwa huu nyumbani wanapokaa. Isoniazide ni dawa ambayo imedihirishwa kutibu na kuzuiya huu ugonjwa. Tunafanya utafiti kuchunguza umuhimu wa utumiaji wa dawa hii kwa kuzuia uambukizaji wa ugonjwa wa kifua kikuu kwa watoto wanaoishi katika nyumba moja na watu wazima walio na huu ugonjwa. Wewe kama mmoja wapo wa waadhiriwa wa ugonjwa huu, na ambaye ameanzishwa matibabu, waeza tusaidia kwa kuwa mshirika katika utafiti huu. Tungependa utujulishe ikiwa kuna watoto chini ya miaka minne ambao wanaishi pamoja nawe, na kwa hivyo wako hatarini ya kuambukizwa. Kuna maswali tungependa uyajibu.

Watoto wote tutakaojulishwa wataangaliwa na dakitari, kisha watafanyiwa kipimo cha ngozi cha mantoux kwenye mkono wao wa kulia. Pia mwanzoni, hawa watoto watatolewa damu kidogo ya kupima uwepo wa ugonjwa wa Ukimwi, na kuangalia utendakazi wa maini yao. Ikiwezakana, wataulizwa kutoa kikohozi kwa ihari yao, au itolewe kwa kuingiza mpira mdogo kwenye tumbo lao kupitia kwenye pua. Baadaye watapewa dawa ya tebe ya isoniazide kulingana na uzito wao, kuitumiwa kila siku kwa mda wa miezi sita. Wanapotumia hii dawa, watakuwa wakiangalia kwenye kliniki ya kifua kikuu mara moja kwa kila miezi mbili, kwa mda wa mwaka moja. Wakija kwenye hii kliniki, watachunguzwa na daktari, na damu kidogo kutole tena. Picha ya kifua , au uchunguzi mwingine wowote itaweza tu kufanywa panapo kuwa na haja yake, ambapo utajualishwa.

Hakuna tatizo lolote lawezatokea kwa sababu ya kuhusika kwako kwenye utafiti huu, ijapakuwa tatizo ndogo za dawa ambazo tutakuwa tukichunguza na kukuharifu ikitokea. Kutolewa kwa kikohozi kwaweza sababisha uchungu mdogo tu. Hakutakuwa na marupurupu yoyote ya kushiriki kwa utafiti huu. Hata hivyo, kutakuwa na faida kwa watoto watakaoshiriki kama uchunguzi wa ukuagi wao, kuhakikisha wamepewa chanjo halisi, uchunguzi wa mara kwa mara na daktari, na kuanzishwa matibu ya kifua kikuu mapema iwezekanavyo ikiwa watakuwa wameambukizwa. Utakua huru kujitoa kwenye utafiti huu wakati wowote bila kuhatarisha haki zako, na bila kulaumiwa. Siri ya hali ya juu itadumishwa kuhusu mambo yako, na kutumiwa tuu kwa ajili ya utafiti huu pekee. Matokeo ya utafifiti huu itasaidia wahudumu wa afya kujua kuhusu njia za kuzuia watoto wanaoishi katika nyumba moja na watu wazima walio na ugonjwa wa kifua kikuu kuambukizwa. Twaomba ushiriki wako kwa kuwaleta hawa watoto kwa kliniki, na kwa kujibu maswali utakayoulizwa. Ukiwa na swali lolote kuhusu utafiti huu, waweza kuniuliza kwa njia ya simu kwa nambari 0722322363, au kuwasiliana na idara ya utafiti katika chuo kikuu cha Kenyata.

Ukikubali kushiriki, tafadhali weka sahihi kwenye formu ya kukubali kushiriki.

Formu ya Kukubali

Jina la utafiti: Umuhimu wa utumiaji wa dawa ya isoniazide kwa kuzuia uambukizaji wa ugonjwa wa kifua kikuu kwa watoto wanaoishi katika nyumba moja na watu wazima wanaougua ugonjwa wa kifua kikuu.

Nimejulishwa kinaganaga kwa kuambiwa na kwa kusoma kuhusu utafiti huu. Nimeelewa kikamilifu kuhusu utafiti huu. Nimepewa maelezo ya kuunitosheleza ya maswali niliyokua nayo na ninafahamu vyema mtu au watu ninaoweza kuasiliana nao iwapo nitahitaji maelezo zaidi. Ninaelewa kwamba, siri itadumishwa kuhusu mambo yangu. Nina elewa kwaba, ninao uhuru wa kujitoa kwenye utafiti huu wakati wowote bila kuhatarisha haki zangu, na bila kulaumiwa. Nimekubali kwa hiari yangu kushiriki kwenye utafiti huu kulingana na mipango nilioona kwenye formu ya maelezo. Ninajua kwamba nitapewa nakala ya formu ya maelezo, na formu hii ya kukubali kushiriki kwenye utafiti huu.

Jina la mshiriki:_____

Anwani ya mshiriki_____

Saini ya mshiriki _____

Tarehe_____

Kauli ya mtafiti

Mimi, ambaye nimeweka sahini yangu hapa, nathibitisha kwamba, nimemueleza mshiriki huyu kuhusu utafiti huu, kwa lugha ambayo anaielewa. Nimemueleza mshiriki kwamba, siri ya hali ya juu itaimarishwa kwa utafititi huu, na kwamba mshiriki huyu anaweza kujiondoa kutoka kwa utafiti huu wakati wowote bila kulaumiwa. Nina apa kuzingatia mipangilio iliyowekwa ya utafiti huu. Sitayatoa mambo ya mshiriki huyu nilivyoyajua kwa hali ya siri, na nitaheshimu haki aliyonayo mshiriki huyu. Pia, nitaheshimu uhuru alio nao mshiriki huyu.

Jina la mtafiti_____

Saini ya mtafiti_____

Tarehe_____

APPENDIX 3. Source case baseline questionnaire

1.0 Vital data

TB clinic No. _____Serial No: _____ Date _____

1.1 Name of TB Patient:_____ Age (yrs):_____ Sex: M/F

1.2 Marital status: Married □ Divorced □ Separated □ Single □

1.3 Occupation: Unemployed □ Self employed □ Employed □ In training □

1.4 Tel Contacts:_____ Residence _____

2.0 Source case TB diagnosis and treatment record (check TB record card)

2.1 Duration since TB diagnosis (weeks)? < 2 □ 2 < 4 □ 4 < 6 □ 6 < 8 □

2.2 Symptoms at diagnosis of TB? Cough □ Fever □ Weight loss □ Swellings □ Chest pain □ Malaise □ Others □

2.3 Duration of symptoms prior to diagnosis (weeks)? _____

2.4 How was TB diagnosis made? Chest X-ray □ Sputum report □ 1/ 2 / 3 Skin test □ Blood test □ All the above □ Unknown □

2.5 Sites where TB was found? Lungs □ Abdomen □ Bones/spine □ Brain □ Lymph nodes □

2.6 Sputum report? Smear Positive □ Smear negative □ Unknown □

2.7 HIV status ? Positive □ Negative □ Unknown □

2.8 If unknown, can you take the test now? Yes □ No □

2.9 If yes, are you on any treatment for HIV? No □, Yes □ Regime_____

2.10 Is this the first time you are on treatment for TB? Yes □ No □

2.11 What treatment regimen is patient taking? 1st line □ 2nd line □

2.12 What challenges have you experienced with TB treatment? Too long□ Bad taste□ Too many drugs □ Too many hospital visits □ Side effects □ Stigma □ Others__

2.13 Any side effects of TB drugs experienced? None □ Rashes □ Nausea □ Vomiting□ Anorexia □ Increased appetite □ Yellow eyes □ Pains in limbs □ Orange urine/tears □ Poor colour vision □ Memory loss □ Psychosis □ Others__

2.14 Have you missed any doses and why?

None □ Forgot □ Stock out □ Travelled □ Others _____

2.15 How often are you seen at the TB clinic? Daily□ Weekly □ Monthly □ Others __

2.16 Have you ever been asked to take your children < 5yrs for TB check at the health center? Yes □ No □

3.0 Source case TB knowledge and attitudes

3.1 What is your main source of information about TB? Radio □ Television □ Newspapers □ Health center □ CHW□ Friends/Neighbors □ Others_____

3.2 What causes TB? Bacteria □ Virus□ Germs □ Unknown □ Others _____

3.3 What sites can get affected by TB? Lungs □ Abdomen □ Bones □ Blood □ Brain □ Lymph nodes □ Spine □ Joints □ Any part of the body □

3.3 What are the symptoms of TB? Cough □ Haemoptysis □ Fever □ Anorexia □ Malaise □ Weight loss □ Swellings □ Chest pain □ Night sweats □ Others □

3.5 How is TB spread? Airborne □ Food borne □ Water borne □ Skin contacts □ Kissing □ Sex □ Breastfeeding □ Unknown □ Others □ _____

3.6 What factors predisposes one to TB? Crowding□ Poor ventilation □ HIV □ Immunosuppression □ Malnutrition□ Poor sanitation□ Careless cough □ Others□

3.7 What is the relationship between TB and HIV infection? HIV causes TB □ TB causes HIV □ TB common in HIV+ patients □ I don't know □ Other□_____

3.8 How can TB be diagnosed in children? Doctor evaluation □ Chest X- ray □ Sputum testing □ Blood tests □ Skin test □ All the above □ I don't know □

3.9 Do you have any cultural beliefs about TB?_____

3.10 What concerns you about your diagnosis of TB? Normal □ Stigma □ Sad □ Expensive □ Poor facilities □ Incompetent staff □ Unfriendly staff □ Others□

3.11 Do you think TB is curable? Yes □ No □

3.12 How can you prevent your children from contracting TB from you? Immunization □ Treating myself □ Drug prevention □ Cover mouth during cough □ Isolate□ Adequate lighting□ Improving ventilation □ Avoiding spitting any where □ Improved nutrition □ I don't know □

3.13 Do you foresee challenges giving TB prevention treatment to children? Bearable □ Too long □ Bad taste□ Too many drugs□ Too many hospital visits □ Side effects □ Difficult to give tablets □ Difficult to get □ Others_____

4 Socio-demographic characteristics

4.1 Your social habits? Smoking □ Alcohol □ Singing □ Preaching □ Others____

4.2 Is there another adult whose had TB in your household?Yes□ No□

4.3 What is your relationship? Spouse □ Relative □ Friend □ Neighbor □ Other ___

4.4 Are there children < 5 years in your household? No □ Yes □ Number _____

4.5 What is your relationship to these children? Biological children □ Relative □ Friend □ Neighbor □ Employers' children □ Others _____

4.6 Is any of these children on TB treatment? No □ Yes □ , Number _____

4.7 Is any of these children on TB prevention treatment? No □ Yes □ Number ___

4.8 How many hours do you spent with the children? Day ___ Night ____

4.9 Has any of these children been sick and seen at the local health facility? Reason? No □ Cough/cold □ Diarrhea □ Malaria □ Fever □ Probable TB □ Malnutrition □ Others _____

4.10 Are there other children < 5 years in close contact with you, but staying in a different house? No □ Yes □ Number _____

4.11 What type of material is your house walls made of? Stone /Bricks □ Mud □ Wooden □ Iron sheets □ Reeds □ Cartons □ Polythene □ Other □_____

4.12 Number of rooms in the house? _____

4.13 Average size of rooms in your house (m^2)? <2 □ 2<3 □ 3 < 4 □ 4< 5 □ >5 □

4.14 Number of people in your household, including children? _____

4.15 Room density during the day. (No of people per room)? _____

4.16 Number of windows per room in house? None □ 1 □ 2 □ 3 □ > 4□

4.17 Do you have a separate room for cooking? Yes □ No □

4.18 Type of cooking fuel used? Firewood □ Charcoal□ kerosene □ Gas □ Electricity □

4.19 Do you share your bedroom with the children <5yrs? Always □ Sometimes□ Never□

4.20 Room density during the night? (No of people per room) _____

4.21 What is your level of education? None□ Primary□ Secondary□ College□ University□

4.22 Estimate earnings per month in Ksh? < 3000 □ 3000 - 4999 □ 5000 – 10,000 □ >20,000 □

4.23 Have you had any deaths of children < 5yrs in your house in the last 1 year, why? None □ Unknown □ Pneumonia □ TB□ Diarrhea □ Malaria □ Others _____

APPENDIX 4. Contact clinical assessment and follow–up chart.

Name: _____ Serial Number:_____ Age:_____

Birth Order _____Birth weight_____ Weaning age _____BCG scar_____

VISIT	**0**		**1**		**2**		**3**		**4**		**5**		**6**	
DATE														
Visit type: Invitation (1), Tracing (2)														
	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Breastfeeding														
CWC attendance														
Growth faltering														
Out-patient visit														
Previous admission														
Daycare attendance														
Social visits														
ARV use														
NUTRITION STATUS														
Weight														
Height														
MUAC														
Oedema														
Weight for Height/ length z score														
Weight for Age z score														
Ht /length for age z score														
TB SUGGESTIVE SYPMTOMS	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Fever > 2 weeks														
Weight loss/faltering														
Malaise														
Night sweats														
Irritability/coma														
Cough > 2 weeks														
Haemoptysis														
Wheeze														
Chest pain														
Abdominal distension														
Swellings														
Spinal deformity														

	0		1		2		3		4		5		6	
CLINICAL SIGNS	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Lethargy														
Fever $> 37.5^0$ C														
Lymphadenopathy														
Finger clubbing														
Cold abscess														
Erythema Nodosa														
Phylectanular conjunctivitis														
Jaundice														
Respiratory signs														
Tachypnoe														
Chest recessions														
Crackles														
Ronchi														
Stony dullness														
CNS signs														
Lower limb weakness														
Lower limb pains														
Altered consciousness/coma														
Confusion														
Spine deformity														
Swollen joints														
CVS signs														
Dyspnoe														
Tachycardia														
Distant heart sounds														
Abdominal signs														
Distension														
Hepatomegally														
Spleenomegally														
Ascites														
TESTS done														
Mantoux (TST) test														
CXR														
Sputum for AAFB														
Sputum culture														
HIV PCR/ Rapid														
LFT (AST)														
LFT(ALT)														
KJ clinical score														

APPENDIX 5. Compliance and toxicity monitoring chart

NAME:_____Serial Number:_____ Age _____

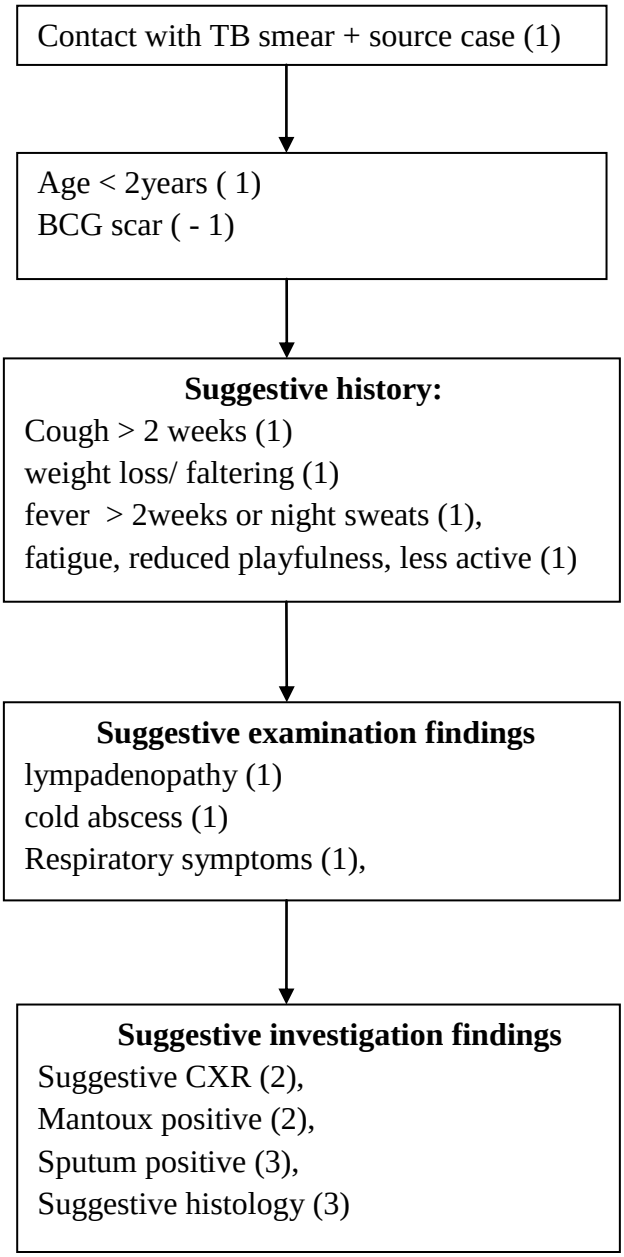
Visit number	0	1	2	3	4	5	6
Date of visit							
1. Who is responsible for administering treatment to the child?							
Mother (1) Father (2) Uncle /Aunt (3) Grandparent (4) House help (5) Sibling (6) Neighbor (7) Others(8)							
2. What time is the child given the treatment?							
Morning (1) Bed time (2) Midday (3) Anytime (4)							
3. How many doses were missed during the last one month?							
Number							
4. Why was/were the dose missed?							
Forgot (1) Stocks ran out (2) Tired (3) Travelled (4) Child refused (5) Child sick (6) Caretaker unwell (7) Side effects (8) Others (9)							
5. Have you experienced any challenges administering the treatment?							
No (0) Bad taste (1) Difficult to administer tablets (2) Child vomits (3) Child refused (4) Too many hospital visits (5) Others(6)							
6. Is there any side effects you have observed in the child?							
None (0) Rashes (1) Anorexia (2) Nausea (3) Vomiting (4) Overfeeding (5) Yellow eyes (6) Painful limbs (7) Irritability (8) Orange-red urine/ tears (9) Diarrhoe (10) Poor memory(11) Psychosis (12) Fits (13) Other (14)							
7. What measures do you think may help improve your adherence to IPT use in your child?							
Incentives (Money, favors) (1) Enablers (Clock, bus fare) (2) Syrup preparation (3) DOTs (4) Assistant (Relative, friend) (5) Others (6)							

APPENDIX 6. FGD/IDI guides

1. What are the causes of childhood illnesses and deaths in this community?
2. How common is childhood TB in this area?
3. What are the main sources of TB information in this community?
4. What factors predispose children to TB in this community?
5. What is the level of Knowledge of child TB transmission in this community?
6. Are there any myths or stigma regarding TB?
7. How common is HIV in this community, and what factors predispose people here to HIV?
8. What do you know about child TB prevention?
9. What challenges are facing IPT in this community?
10. What fears are clients having on IPT?

ANNEX 7. Modified TB clinical scoring algorithm

– adapted from Jones criteria



ANNEX 8. Tuberculin Skin Test- administering, reading and interpreting.

A TST is the intradermal injection of a combination of mycobacterial antigens which elicit an immune response (delayed-type hypersensitivity), represented by induration, which can be measured in millimetres. The TST using the Mantoux method is the standard method of identifying people infected with *M. tuberculosis*.

Details of how to administer, read and interpret a TST are given below, using 5 tuberculin units (TU) of tuberculin PPD-S. An alternative to 5 TU of tuberculin PPD-S is 2 TU of tuberculin PPD RT23.

1. Locate and clean injection site 5–10 cm (2–4 inches) below elbow joint

Place forearm palm-side up on a firm, well-lit surface.
Select an area free of barriers (e.g. scars, sores) to placing and reading.
Clean the area with an alcohol swab.

2. Prepare syringe

Check expiry date on vial and ensure vial contains tuberculin PPD-S (5 TU per 0.1 ml).
Use a single-dose tuberculin syringe with a short (¼- to ½-inch) 27-gauge needle with a short bevel.
Fill the syringe with 0.1 ml tuberculin.

3. Inject tuberculin (see Figure A1.1)

Insert the needle slowly, bevel up, at an angle of 5–15 °.
Needle bevel should be visible just below skin surface.

4. Check injection site

After injection, a flat intradermal wheal of 8–10 mm diameter should appear. If not, repeat the injection at a site at least 5 cm (2 inches) away from the original site.

5. Record information

Record all the information required by your institution for documentation (e.g. date and time of test administration, injection site location, lot number of tuberculin).

ANNEX 9. Procedures for obtaining sputum for smear microscopy

A. Expectoration

Children who can produce a sputum specimen may be infectious, so, as with adults, they should be asked to do this outside and not in enclosed spaces (such as toilets) unless there is a room especially equipped for this purpose. Three sputum specimens should be obtained: an on-the-spot specimen (at first evaluation), an early morning specimen and a second on the- spot specimen (at follow-up visit).

Procedure (adapted from Laboratory services in tuberculosis control. Part II. Microscopy)

1. Give the child confidence by explaining to him or her (and any family members) the reason for sputum collection.
2. Instruct the child to rinse his or her mouth with water before producing the specimen. This will help to remove food and any contaminating bacteria in the mouth.
3. Instruct the child to take two deep breaths, holding the breath for a few seconds after each inhalation and then exhaling slowly. Ask him or her to breathe in a third time and then forcefully blow the air out. Ask him or her to breathe in again and then cough. This produces sputum from deep in the lungs.
4. Ask the child to hold the sputum container close to the lips and to spit into it gently after a productive cough.
5. If the amount of sputum is insufficient, encourage the patient to cough again until a satisfactory specimen is obtained. Give the child sufficient time to produce an expectoration which he or she feels is produced by a deep cough.
6. If there is no expectoration, consider the container used and dispose of it in the appropriate manner.

B. Gastric aspiration

Is most useful for young hospitalized children. However, the diagnostic yield (positive culture) of a set of three gastric aspirates is only about 25–50% of children with active TB, so a negative smear or culture never excludes TB in a child. The highest-yield specimens are obtained first thing in the morning for each of three consecutive mornings. Of note, the first gastric aspirate has the highest yield. It is not an aerosol-generating procedure, hence low risk procedure. Performing the test properly usually requires two people (one doing the test and an assistant). Children not fasting for at least 4 hours (3 hours for infants) prior to the procedure and children with a low platelet count or bleeding tendency should not undergo the procedure.

The following equipment is needed:

gloves
nasogastric tube (usually 10 French or larger)

5, 10, 20 or 30 cm syringe, with appropriate connector for the nasogastric tube
litmus paper
specimen container
pen (to label specimens)
laboratory requisition forms
sterile water or normal saline (0.9% NaCl)
sodium bicarbonate solution (8%)
alcohol/chlorhexidine.

Procedure

The procedure can be carried out as an inpatient first thing in the morning when the child wakes up, at the child's bedside or in a procedure room on the ward (if one is available), or as an outpatient(provided that the facility is properly equipped). The child should have fasted for at least 4 hours (infants for 3 hours) before the procedure.

1. Find an assistant to help.
2. Prepare all equipment before starting the procedure.
3. Position the child on his or her back or side. The assistant should help to hold the child.
4. Measure the distance between the nose and stomach, to estimate distance that will be required
   to insert the tube into the stomach.
5. Attach a syringe to the nasogastric tube.
6. Gently insert the nasogastric tube through the nose and advance it into the stomach.
7. Aspirate gastric contents (2–5 ml) using the syringe attached to the nasogastric tube.
8. To check that the position of the tube is correct, test the gastric contents with litmus paper: blue litmus turns red (in response to the acidic stomach contents). (This can also be checked by pushing some air (e.g. 3–5 ml) from the syringe into the stomach and listening with a stethoscope over the stomach.)
9. If no fluid is aspirated, insert 5–10 ml sterile water or normal saline and attempt to aspirate again. If still unsuccessful, attempt this again (even if the nasogastric tube is in an incorrect position and water or normal saline is inserted into the airways, the risk of adverse events is still very small). Do not repeat more than three times.
10. Withdraw the gastric contents (ideally at least 5–10 ml).
11. Transfer gastric fluid from the syringe into a sterile container (sputum collection cup).
12. Add an equal volume of sodium bicarbonate solution to the specimen (in order to neutralize the acidic gastric contents and so prevent destruction of tubercle bacilli).

After the procedure

1. Wipe the specimen container with alcohol/chlorhexidine to prevent cross-infection and label.
2. Fill out the laboratory requisition forms.
3. Transport the specimen (in a cool box) to the laboratory for processing as soon as possible (within 4 hours).
4. If it is likely to take more than 4 hours for the specimens to be transported, place them in the refrigerator (4–8 °C) and store until transported.
5. Give the child his or her usual food.

C. Sputum induction

Is an aerosol-generating procedure, hence should be performed in an isolation room that has adequate infection control precautions (negative pressure, ultraviolet light (turned on when room is not in use) and extractor fan). It is regarded as a low-risk procedure. Very few adverse events have been reported, and they include coughing spells, mild wheezing and nosebleeds. It can safely be performed even in young infants, though staff will need to have specialized training and equipment to perform this procedure in such patients.

General approach

Examine children before the procedure to ensure they are well enough to undergo the procedure.

Children with the following characteristics should not undergo sputum induction.

- Inadequate fasting, < 3 hours.
- Severe respiratory distress (including rapid breathing, wheezing, hypoxia).
- Intubated.
- Bleeding: low platelet count, bleeding tendency, severe nosebleeds (symptomatic or Platelet count <50/ml blood).
- Reduced level of consciousness.
- History of significant asthma (diagnosed and treated by a clinician).

Procedure

1. Administer a bronchodilator (e.g. salbutamol) to reduce the risk of wheezing.
2. Administer nebulized hypertonic saline (3% NaCl) for 15 minutes or until 5 cm of solution have been fully administered.
3. Give chest physiotherapy is necessary; this is useful to mobilize secretions.
4. For older children now able to expectorate, follow procedures as described in section A above to collect expectorated sputum.
5. For children unable to expectorate (e.g. young children), carry out either: (i) suction of the nasal passages to remove nasal secretions; or (ii) nasopharyngeal aspiration to collect a suitable specimen.

Any equipment that will be reused will need to be disinfected and sterilized before use for a subsequent patient.