

**An assessment of the Isoniazid Prevention Therapy  
programme for children in a busy primary healthcare clinic  
in Nelson Mandela Bay Health District, Eastern Cape  
Province**

**By**

**FAYE TUCKER**

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**Supervisors:**

**Dr Jawaya Shea**

**Dr Feroza Amien**

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## **DEDICATION:**

This thesis is dedicated to my amazing husband whose unwavering love, encouragement and support have been instrumental in summiting this mountain. My gratitude is immeasurable to my three beautiful children, for their unconditional love, their wild passion for life and their sweet laughter that lifted my spirits when I needed it most and to my parents for instilling in me a sense of pride and dedication and for their support during the tough times.

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## **ABBREVIATIONS:**

BCG - Bacille Calmette-Guerin

CXR – Chest X-ray

DoH – Department of Health (Eastern Cape)

DOTS – Directly Observed Therapy Short course

DR-TB – Drug resistant Tuberculosis

EC – Eastern Cape Province

HIV – Human Immunodeficiency Virus

INH – Isoniazid

IPT- Isoniazid Preventative Therapy

IQR- Interquartile Range

MDG – Millennium Development Goals

MDR-TB – Multi-drug resistant tuberculosis

MTB – Mycobacterium tuberculosis

NMB – Nelson Mandela Bay

NMBHD – Nelson Mandela Bay Health District

NTCP – National Tuberculosis Control Programme

Rif – Rifampicin

SA- South Africa

NDoH- National Department of Health

SANTP – South African National Tuberculosis Programme

SD – Standard deviation

TB – Tuberculosis

TSR – Treatment success rate

TST – Tuberculin skin test

WHO – World Health Organisation

## **DEFINITIONS:**

**Pulmonary tuberculosis (PTB)** – Tuberculosis (TB) disease involving the lung parenchyma (National Department of Health [NDoH], 2014)

**Extrapulmonary tuberculosis** – TB disease involving organs other than the lungs. These may include the pleura, lymph nodes, abdomen, bone, meninges among others (NDoH, 2014).

**Index patient** - The first patient to be diagnosed with new or recurrent TB in a specific household or other comparable setting in which others may have been exposed, irrespective of age (NDoH, 2014)

**Child contacts** - For the purposes of this study, a child contact is defined as any child less than 5 years of age who is in close contact with an adult with infectious TB.

**Close contact** - A person living in the same household as, or in frequent contact with (e.g. child minder, school staff), a source case with PTB (NDoH, 2013)

**Isoniazid prevention therapy** – Isoniazid therapy given to prevent the progression of TB infection to TB disease. A six month course is recommended (WHO, 2006, NDoH, 2013). For the purpose of this study, 24 weeks is considered a complete course of IPT.

**Infectious/sputum positive TB**- Smear positive pulmonary TB is the most infectious form of the disease with smear negative/culture or GeneXpert positive disease being less infectious (NDoH, 2014). For the purposes of this study, index patients were classified as infectious or sputum positive if they had at least one positive sputum result i.e. they were either smear or culture or GeneXpert positive or a combination there of .

**Drug sensitive TB**- TB disease that is sensitive to the standard treatment regimen 1 using Rifampicin, Isoniazid, Ethambutol and Pyrazinamide (NDoH, 2014).

**Monodrug resistant TB**- TB disease that is resistant to one of the first line drugs mentioned above (NDoH, 2014)

**Multidrug resistant TB**- TB disease that is resistant to at least rifampicin and isoniazid (NDoH, 2014)

**Drug resistant TB**- For the purposes of this study, patients with monodrug resistant TB or multidrug resistant TB were classified as ‘drug resistant’

### **Diagnostic tests:**

Smear microscopy: the identification of acid fast bacilli through examination of stained sputum samples using a microscope. It has a good specificity for detecting TB disease but a low sensitivity when diagnosing patients with non-cavitary pulmonary disease and those with paucibacillary TB such as HIV positive patients and children (NDoH, 2014). Smear microscopy is a rapid test with 80% of results being available in 48 hours.

Culture: TB bacilli can be cultured on solid or liquid mediums and can be positive with only 10-100 bacilli per millilitre of sputum. Thus culture is more sensitive than smear but more expensive and slower. A positive result depends on bacillary load and most are positive within 4 weeks, however a negative result is only reported after 6 weeks of incubation. It is an important diagnostic tool in those groups with paucibacillary disease (NDoH, 2014).

GeneXpert: The test is called *Xpert MTB/RIF* and the instrument is a GeneXpert (GXP). GeneXpert is an automated molecular platform to detect *M. tuberculosis* and rifampicin resistance. It is a rapid and relatively simple test with results being available in the laboratory in 2 hours and at the health facility within 48 hours (NDoH, 2014).

Tuberculin skin test (TST): The TST measures the hypersensitivity to tuberculin purified protein derivative which is injected intradermally into the forearm of the patient. It takes a child who is infected with TB 6-12 weeks after exposure to develop a positive skin test. However, a number of conditions that weaken the patient's immune system can cause a false negative result. These include HIV infection, malnutrition and severe, disseminated TB disease. Thus, it has limited value in the clinical setting especially where TB is common (NDoH, 2013).

### **Treatment outcome definitions (relating to the index patient)** as per NDoH 2014:

Cure: Patient whose baseline smear (or culture) was positive at the beginning of the treatment and is smear/ culture negative in the last month of treatment and on at least one previous occasion at least 30 days prior.

Treatment completed: Patient whose baseline smear (or culture) was positive at the beginning and has completed treatment but does not have a negative smear/culture in

the last month of treatment and on at least one previous occasion more than 30 days prior.

Treatment failure: Patient whose baseline smear (or culture) was positive and remains or becomes positive again at 5 months or later during treatment. This excludes patients that were diagnosed with rifampicin or multidrug resistant TB.

Died: Patient who dies for any reason during the course of TB treatment

Treatment defaulted: Patient whose treatment was interrupted for two consecutive months or more during the treatment period.

Transferred out: For the purposes of this study, those patients who were transferred to another facility (whether in the same or a different district) to complete treatment were classified as being transferred out.

## **ABSTRACT**

### **Introduction**

Tuberculosis is the second leading cause of death from an infectious cause worldwide having claimed approximately 1.5 million lives in 2013. Estimates suggest that children account for about six percent of the total number of TB cases globally, however in South Africa this figure is much higher (15%). Young children are at particularly high risk of mortality and significant morbidity from TB. Despite clear evidence that Isoniazid preventative therapy (IPT) can reduce the risk of progression from TB infection to disease, IPT has been a poorly implemented component of national TB control programmes, especially in high TB-burden areas, including South Africa. This study aims to determine current practices regarding the identification and management of child contacts < 5 years in an area with an extremely high TB incidence rate where little background data exists on the topic. It will also assess the operational aspects of the TB control programme relating to the spread of TB to children.

### **Methodology**

A cross-sectional descriptive study was conducted using a retrospective review of clinic records from infectious index patients aged  $\geq 15$  years at West End clinic in the Nelson Mandela Bay health district in the Eastern Cape Province. A sample size of 246 child contacts (<5 years) was required to obtain a 95% confidence index with a 5% precision. This is based on 20% of eligible child contacts < 5years receiving IPT, as described by van Wyk, et al. (2010). 491 Index patient records were assessed in order to identify 261 child contacts < 5 years of age.

### **Results**

Contacts were generally well recorded with only 12.5% of index patient folders having no contacts documented although only 0.53 child contacts <5years were identified per index patient. A total of 261 child contacts < 5 years were identified and of these 184 (70.5%) were screened for TB. Two contacts were started on TB treatment and 108/184 (58.7%) were initiated on TB prevention therapy. For the remaining 74 (40.2%) children who were screened there was no documentation of further management. Adherence to IPT was extremely poor with only 4 (3.7%) children who started TB prevention completing the 24 week course. Female index patients were more likely to have contacts documented and to bring their contacts for screening. Contacts of index

patients who had previous TB were less likely to be screened and initiated on TB prevention therapy.

The results of the assessment of programmatic factors relating to childhood TB control showed that patients were diagnosed and were rapidly initiated on treatment (median time of 5 days from sputum collection to commencement of treatment). It took a median of 4 days for children to be screened once the index patient had started treatment and a further 2 days (median) for child contacts < 5 years to be initiated on preventative therapy.

### **Conclusion and recommendations**

The results of this study are in keeping with those obtained in other settings with a high burden of TB. Although the documentation of contacts in this setting was relatively good, child contacts <5years were poorly identified and the fall-out of children at each step from identification to preventative treatment completion was still unacceptably high. Contacts of men and retreatment index patients are at particularly high risk of poor management. Recommendations are made for interventions at national and local level to improve contact management and the documentation thereof.

## **CHAPTER 1 : BACKGROUND AND INTRODUCTION**

### **1.1 Background**

In 2013 alone there was an estimated nine million new cases of tuberculosis (TB) and 1.5 million people lost their lives as a result of the disease, making TB the second leading cause of death from an infectious cause worldwide (second only to human immunodeficiency virus [HIV] infection) (World Health Organization [WHO], 2014). The global distribution of TB infection is markedly skewed with the 22 high burden countries earmarked by the WHO contributing a staggering 82% of these infections. The WHO (2014) estimates that childhood TB accounts for approximately 6% (550 000 cases) of the total number of TB cases globally, although in high burden areas it has been shown to be significantly higher (Zar & Pai, 2011).

The strongest known risk factor for TB is HIV which, over the past 25 years, has fuelled the explosion of the TB epidemic in high HIV-burden areas (Lawn et al., 2011). This HIV-associated TB epidemic is one of the major obstacles to attaining the Millennium Development Goals (MDGs) for global TB control. These goals are to halt and reverse the rising incidence of TB and to halve the 1990 TB prevalence and death rates by 2015. The burden of HIV-related TB is shouldered mainly by the WHO Africa region which accounts for about 80% of all TB cases and deaths in HIV-infected individuals (WHO, 2014).

The WHO's "Three I's" are key strategies in reducing the impact of TB on HIV-infected individuals (WHO, 2008). As young children are also an at-risk population, these strategies could form a central role in developing plans to reduce the burden of TB in children. The concepts outlined by the WHO include:

- Intensive Case Finding: regular screening for TB
- Isoniazid Preventative Therapy (IPT): IPT in children has been shown, with good compliance, to significantly reduce the risk of developing TB disease.
- Infection Control: Infection control measures are essential to reduce the spread of TB to vulnerable populations such as children.

The burden of childhood TB is not insignificant. In 2013 there were 550 000 TB cases and 80 000 TB-related deaths in children worldwide and this figure is likely to be significantly underestimated (Graham et al., 2014; Jaganath et al., 2013; Graham,

2011). Childhood TB has, in the past, been overlooked as a health priority. The focus of global public health campaigns to control TB has aimed to reduce transmission by early case-finding and the treatment of highly infectious patients (Graham et al., 2014). As children often have paucibacillary TB, their risk of transmission is low and, thus, they have largely gone unnoticed.

The plight of children with TB has, only in the past decade, gained interest and emphasis from national TB programmes. For the first time, in 2012, the WHO made childhood TB the focus of World TB Day (Graham et al., 2014). Not only does TB have an impact on child mortality, the sequelae of the disease can cause chronic morbidity. Small children are at greater risk of severe and disseminated forms of TB (Jaganath et al., 2013). The possible morbidity resulting from some of these forms, such as TB meningitis, can be devastating; with survivors at high risk of being both mentally and physically disabled (van Well et al., 2009). The indirect effects of TB on children should also not be ignored. The WHO estimates that there are about 9.7 million orphans as a result of TB deaths in parents and this has a profound impact on child mortality (Graham et al., 2014).

Evidence for screening and preventative therapy in children who are close contacts of individuals with infectious TB has been available for more than 50 years (Graham & Triasih, 2013). Although the policy has long been in place in international and national TB control guidelines, it has been poorly implemented, especially in high-burden, poorly resourced areas. The rationale behind contact screening is two-fold. Firstly, it is to identify those individuals such as young children and those who are HIV-infected and at high risk of developing TB and to provide them with prevention therapy. Secondly, it is to actively trace those contacts that have TB and treat them appropriately (Graham & Triasih, 2013).

The successful implementation of child contact screening and management is hampered by a variety of challenges and barriers unique to each setting (Graham & Triasih, 2013). These difficulties are evident in the fact that there are very few, if any, successful large-scale contact screening programmes implemented in TB-endemic settings. To remedy this, strong political will, clear policies, appropriate tools and the strong collaboration between child health services and national TB services are required (Graham & Triasih, 2013).

## **1.2 Introduction**

In 2010 South Africa (SA) had the third highest number of new cases of TB globally (0.4 million-0.59 million), and ranked only behind the densely populated areas of India and China. Worldwide the TB incidence is falling, albeit slowly. However SA, at that time, was the only country in the WHO regions where the incidence (981/100 000) was on the increase (WHO, 2011). The latest WHO Global TB report (2014) showed that SA has managed to curb its TB incidence to 860/100 000 having achieved the first component of MDG 6 which is to halt and reduce TB incidence. However it is unlikely, given the slow attainment in TB incidence reduction, that the country will achieve the other components, namely to reduce TB prevalence and TB-related mortality to half the 1990 rate by the end of 2015.

Historically, TB was brought to SA by the European settlers as far back as the 17<sup>th</sup> century and it was the development of the country's mining sector in the late 19<sup>th</sup> century that laid the groundwork for the current epidemic (Kariem et al., 2009). Overcrowding, sub-standard working conditions and undernutrition allowed TB to spread amongst migrant labourers while returning to their families assisted the dissemination of the disease (Kariem et al., 2009). During the apartheid era the fragmented health systems placed little emphasis on managing TB and were ill-equipped to do so.

The end of apartheid in 1994 marked the beginning of the health system reform (Kariem et al., 2009; Naidoo, Taylor & Jinabhai, 2007). The development of the district health system, the formation of the South African National TB Control Programme (SANTCP) and improved funding should have translated into better TB control (Naidoo, Taylor & Jinabhai, 2007). Directly Observed Therapy Short course (DOTS) was introduced in 1996 to improve compliance and patient outcome and combination tablets were available from 1999 decreasing patients' pill burden (Naidoo, Taylor & Jinabhai, 2007).

However, with the emergence of the HIV epidemic in the 1990's, the above efforts were not enough to curb the rampant rise in TB cases. In a mere five years from 2001-2006, the number TB cases notified increased by a staggering 81% (NDoH, 2009). Consequently SA harbours one of the highest rates of HIV and TB infection in the world (Naidoo, Taylor & Jinabhai, 2007). Despite having only 0.7% of the world's

population, it carries approximately 25% of the world's HIV-associated TB cases (Lawn et al., 2011).

SA has a dual healthcare system with the private sector providing medical care to a relatively small percentage of fee-paying patients and the public sector providing healthcare to the vast majority of the country's population. There is marked disproportion between finances and beneficiaries in the two systems, resulting in the distribution of benefit being skewed in favour of the wealthiest people with the lowest burden of disease (Harrison, 2009). TB treatment is only available in the public health system. This system, in many areas, is poorly managed, understaffed, badly supervised and unequally resourced, thus compromising TB management (Naidoo, Taylor & Jinabhai, 2007).

The public health system is tiered with service delivery being divided into primary, secondary and tertiary level institutions (Dookie & Signh, 2012). There is an emphasis on access to primary care healthcare which is achieved through clinics, community health centres and midwife obstetric units which are located within communities. Secondary hospitals and district health centres provide general medical care at a higher level. Tertiary centres or referral hospitals aim at delivering specialist services and theoretically should not be the first point of care for most patients entering the system. TB is included in the district-level package of services along with child health, health promotion and women's health to name a few (Petersen, 2001). TB treatment, although sometimes initiated at secondary or tertiary hospitals, is usually dispensed and collected at clinic level. The exception is the management of drug-resistant TB which is largely dealt with at tertiary level.

The burden of TB in the Eastern Cape Province (EC) and Nelson Mandela Bay Health District (NMBHD) is enormous. This is evident from the fact that TB ranks as the leading cause of admission to hospital and death in the province (Eastern Cape Department of Health (DoH), 2013). NMBHD had the sixth highest total number of TB cases (11 013) and the seventh highest TB incidence in the country (949.3/100 000) (Loveday, Smith & Day, 2014). It was identified as the district most in need of improving TB management. This was based on the burden of TB in the area as well as various programmatic indicators measured.

The NMBHD consists of the geographical area of the Nelson Mandela Bay Municipality (or Metro) (NMBM) and incorporates surrounding areas including

Uitenhage and Despatch (DoH, 2013). Patient-related factors such as poverty and high levels of unemployment (41%) in the Metro as well as the high HIV prevalence (29.3% in 2011) (DoH, 2013) may have contributed to the poor performance of the TB control programme. However, it is likely that the main reason is the lack of intensive case finding and poor management of contacts. The average case finding for new cases of TB per quarter is 3000 in the NMBHD. Ninety percent of these are passively identified at the clinic and contacts are not actively traced. Community surveillance and intensive case finding remains poorly implemented and, if improved, could potentially increase the annual case finding to between 5000 and 7000 new cases per quarter (DoH, 2013).

Estimates suggest that childhood TB accounts for 15-20% of all TB cases reaching up to 40% in some high TB-burden areas (Zar & Pai, 2011). However, childhood TB has been an under-recognised and often under-reported cause of morbidity and mortality worldwide, especially in TB endemic areas (Perez-Velez, 2012). TB control strategies have focussed mainly on adult cases which tend to be more infectious, with childhood cases being neglected. There can be difficulty confirming the diagnosis due to the difficulty in obtaining specimens from small children and the paucibacillary nature of paediatric TB. Under-reporting of culture-negative paediatric cases in national TB programmes results in poor estimates of the extent of disease (Graham, 2011).

Although children do not usually spread TB and thus contribute little to the current epidemic, the burden of childhood TB in a community reflects recent transmission of the disease and the extent of control achieved in the adult population (Marais et al., 2005). In SA, children under the age of 19 years account for 15.3% of the total number of TB cases, with the 0-4 years of age group making up nearly half of the total number of these cases (Smith, Moyo & Day, 2014). The incidence in this age group in 2012 was around 470/100 000. The NMBHD has a similar distribution of childhood TB cases to SA. In the NMBHD 16% of cases are reported in children under 19 years and children under 5 years account for 7.2% of the total case number (Smith, Moyo & Day, 2014).

TB disease progression can be prevented in young children with the use of preventative therapy in the form of single (Isoniazid preventative therapy or IPT) or dual drug regimens (WHO, 2011). However, contact tracing, screening and IPT initiation has been shown to be poorly implemented in areas of South Africa (Van Zyl et al., 2006, Marais et al., 2006; Schaaf et al., 2007; Van Wyk et al., 2010, du Preez et al., 2011, Osman et

al., 2013). Information regarding the IPT services in the Eastern Cape and NMBHD is lacking with no baseline data available.

TB is a disease of poverty. People living in poorer areas are more likely to be exposed to several TB risk factors namely overcrowding, poor access to health, undernutrition, smoking and alcohol and drug abuse (WHO, 2010). In the past it has been shown that TB control can be improved with the improvement of these socioeconomic factors. Tackling these factors requires more than just a functioning national TB programme. It requires unwavering political commitment and nationwide public health efforts.

### **1.3 Problem statement**

It is evident from the numerous studies conducted in the Cape Town area that children who are exposed to infectious TB cases are not receiving the IPT that they require to prevent developing TB disease. The problem lies not only in the initiation of IPT but also in the retention of children who are started on chemoprophylaxis. Although research on this topic in the City of Cape Town is extensive, there is a dearth of information regarding IPT in children in the Nelson Mandela Bay Health District in the Eastern Cape Province. Due to its extremely high TB caseload (949/100 000), the NMBHD has been identified as one of four TB crisis districts in the country. Identifying problem areas and gaps in the IPT programme may help to reduce childhood TB and ultimately assist in curbing the expanding TB epidemic. .

This research project aims to assess whether children <5 years who are in contact with infectious pulmonary TB cases are being managed according to the national TB prevention programme at a single primary health care facility in the Nelson Mandela Bay health district.

The researcher hypothesised that child contacts <5 years are not routinely being identified, screened and initiated on IPT and that there is a large drop-out rate of those that are initiated on IPT.

### **1.4. Study objectives**

The main study objectives are:

1. To determine the number of child TB contacts under 5 years of age noted in index TB patient folders at West End clinic.

2. To assess whether child contacts are screened for TB and if so, how they are screened.
3. To estimate the proportion of child contacts under 5 years of age that are offered TB prevention after being screened for TB as well as the type of drugs prescribed.
4. To estimate the proportion of child contacts <5 years of age that drop out of the system between the screening process and the initiation of IPT
5. To assess the duration of IPT collected by child contacts <5 years of age and the percentage of children who complete the prescribed course
6. To establish if the age, gender, education and employment status of the index case as well as their disease characteristics (HIV status, smear positivity and previous TB) relate to the documentation of child contacts <5 years of age, their screening and initiation of IPT.
7. To assess the programmatic factors that relate to the control of TB in children.

### **1.5. Summary**

Chapter one presented a brief background and introduction to the study. Chapter two is a presentation of the literature review. Chapter three provides details about the research methodology applied in this study. In chapters four and five the findings are presented and discussed. Chapter six summarises the important findings and limitations of the study and provides key recommendations for the future.

## **CHAPTER 2: LITERATURE REVIEW**

### **2.1. Introduction**

The purpose of this chapter is to provide an overview of Tuberculosis and its transmission as well as the risk factors that make children more vulnerable to developing TB disease. It summarises the published literature on the topics of IPT service delivery and the barriers that exist in implementing IPT programmes internationally, in Africa and in South Africa.

This literature review was conducted by using various sources of information. These included government websites (South African and Eastern Cape Departments of Health), peer-reviewed journals accessed via search engines such as PubMed and EBSCOhost on the University of Cape Town database, as well as other websites pertaining to health policies worldwide (World Health Organisation websites). Terms and phrases used in this search included: childhood TB, TB prevention, Isoniazid preventative therapy, IPT, TB contacts, South Africa, missed opportunities, latent TB, TB control.

### **2.2. Overview of Tuberculosis**

Tuberculosis is caused by the bacillus *Mycobacterium tuberculosis* (MTB) which is spread via droplets in the air when a person with active pulmonary TB coughs. TB most commonly affects the lungs (pulmonary TB) but can spread to other organs in the body (extrapulmonary TB) (WHO, 2014). Much attention needs to be paid to the transmission of TB and the development of disease if the principles of effective TB control programmes are to be understood. The importance of early diagnosis and treatment of active and latent cases as well as the prevention of transmission is paramount when considering measures to quell this growing epidemic (Marais et al., 2005). A child's risk of infection relates to the duration and proximity of the exposure to the infectious case as well as the infectiousness of the case (Newton et al., 2008). Examination of the pre-chemotherapy era revealed that after prolonged exposure to a household smear positive case, 60-80% of children became infected with TB compared to 30-40% if the source case was smear negative (Marais et al., 2004).

Not everyone who is infected with MTB develops TB disease. The vast majority of people do not become sick after being infected, with only 10-15% becoming diseased (Narasimhan et al., 2013). The progression from infection to disease depends on the maturity and competence of the immune system. Thus young age and factors causing

immunosuppression carry higher risks of disease progression. For example, an infant has a 40-50% risk of developing TB disease following infection compared to a child between the ages of 5 and 10 years whose risk is only two percent (Marais et al., 2009). HIV infection further increases the risk of developing TB disease. Hessling et al. (2009) estimated that infants who were HIV-infected had a 24.2-fold higher rate of developing any form of TB and a 17.1-fold higher rate of disseminated TB than HIV-uninfected infants. It has also been shown that older HIV-infected children are 3-4 times more at risk of developing TB compared to HIV-uninfected children (Marais et al., 2011). Other risk factors for disease progression include malnutrition, increased host genetic susceptibility to TB (Newton et al., 2008) and active or passive smoking (Marias et al., 2005).

### **2.3. Prevention of TB in children**

Broadly speaking, there are three main strategies that can improve TB control and all of these can directly or indirectly reduce the burden of childhood TB. The strategies include vaccination with Bacille Calmette-Guerin (BCG), case finding with effective treatment of active disease as well as identification and treatment of latent TB infection (Woods et al., 2011).

The protective effect of the BCG vaccine against pulmonary TB in children is variable and there is little evidence to demonstrate the protective role amongst HIV-infected children (Hessling et al., 2009). BCG vaccination of HIV-uninfected infants has been shown to offer some protection against disseminated forms of TB disease, especially miliary TB and TB meningitis (Woods et al., 2011). There is ongoing work being done in the field of TB vaccines to produce a vaccine that is both safer and more effective than BCG and a number have reached the clinical trial phase. However, in a recent large double-blinded, randomised, placebo-controlled phase 2b trial, a new TB vaccine failed to provide any significant protection against tuberculosis (Tameris et al., 2013). Given this outcome, it would seem unlikely that a new vaccine will be available within the next 5-10 years as previously postulated by Hawkridge et al., (2011).

Intensive case-finding and reducing the period of infectiousness are strategies that may reduce transmission rates in high burden settings (Woods et al., 2011). Timely diagnosis and appropriate treatment of index patients with active pulmonary TB can decrease the risk of exposure of those in close contact with the patient (NDoH, 2014). In addition, the burden of childhood TB can be greatly reduced by active contact tracing and the

diligent prescribing of chemoprophylaxis to patients in whom active TB has been excluded (Marais et al., 2005). A 6-9 month course of Isoniazid preventative therapy (IPT) can diminish the risk of developing TB disease by two thirds and this benefit can be increased to almost 90% with good compliance. A recent meta-analysis by Ayieko et al. (2014) confirmed these figures. Randomised controlled trials involving children <15 years of age who were prescribed IPT were included and showed a 59% reduction in the risk of developing TB disease. However, this benefit was not extended to infants less than 4 months of age. IPT in this age group offered no protection. Possible reasons for this are that very young children have immature immune systems and are thus more likely to develop disease and secondly, that Isoniazid (INH) is more likely to effectively treat latent TB infection than provide primary protection against infection.

Shorter courses of combined Rifampicin/Isoniazid therapy can have similar results although the WHO warns that the addition of Rifampicin (Rif) may lead to a greater risk of toxicity (WHO, 2011). A number of studies have compared the efficacy of a 6-9 month course of INH with shorter courses of Rifampicin alone or Rif/INH combinations (van Zyl et al., 2006; Spyridis et al., 2007; Sharma et al., 2013). Although the meta-analysis conducted by Sharma et al. (2013) included studies involving both adults and children, the other two focused only on children. The results are all consistent: compliance to a three or four month course of INH/Rif or Rifampicin is far superior to that of a longer course on INH alone. Contrary to the WHO warning of greater hepatotoxicity, side effects (including hepatotoxicity) were significantly less with the Rifampicin-based courses and the effect of the drugs was the same, if not better than INH alone.

Chemoprophylaxis is particularly important in HIV-infected individuals who have a considerably greater risk of developing TB disease than their HIV-uninfected counterparts. The benefits of IPT in HIV infected children are controversial. Studies published by Zar et al. (2006) and Frigati et al. (2011) show that IPT provided a marked reduction in both overall mortality and incidence of tuberculosis disease in HIV infected children (both on and off anti-retroviral therapy) living in a high-burden TB setting. This is in stark contrast to the results published in a study by Madhi et al. (2011) who showed no benefit of INH in reducing TB disease or death in their study population of HIV-infected and exposed infants.

The comparison of the above studies is difficult for a number of reasons. Firstly, the median age of the patients included in the first two studies mentioned was around 2 years whereas the children included in the study by Madhi et al. (2011) were much younger (median age of 96 days). Also, the children included in the studies by Zar et al. and Frigatti et al. were generally more immunosuppressed and malnourished than the infants in the other study. In addition, the study settings were different with possibly large differences in the background community prevalence of TB. All these are important factors to consider when stratifying the risk that a child has of being infected with TB and developing disease. The conclusions of Zar et al. (2006) and Frigati et al. (2011) cannot be ignored: children who are HIV-infected and markedly immunosuppressed and living in a high burden TB area benefit from the provision of INH.

#### **2.4. South African TB Control Guidelines**

In keeping with the above-mentioned evidence, the NDoH developed clear guidelines for IPT in children. One of the major aims of TB management of children as stated in the 2009 TB control guidelines (p.56) is to identify children who are infected with TB and at risk of developing disease, and to provide them with prophylaxis to prevent disease. These guidelines clearly state that:

*“Any child, under 5 years of age or HIV infected (irrespective of age), with a positive Mantoux skin test, has been infected with TB and should be screened for TB disease. After disease has been excluded, the child should receive INH prophylaxis to prevent the development of TB disease (whether there is known contact with an index case or not).”*

With regard to contact tracing and primary infection prophylaxis the guidelines are just as clear:

*“All children under 5 years of age in close contact with an infectious case of TB, who are asymptomatic for TB, should receive INH prophylaxis (10mg/kg daily for 6 months) to prevent developing TB disease. The likelihood of TB infection in these children is high. A chest x-ray and a Mantoux skin test are not required prior to commencing INH prophylaxis in asymptomatic children. Symptomatic children must have TB disease excluded.”*

Infectious cases include adults or adolescents with either smear or culture positive TB and children with smear positive disease. A close contact is defined as a contact living in the same household or a contact outside of the home with sufficient exposure to the index case to be at high risk of acquiring infection (NDoH, 2009). Prophylaxis needs to be provided after each episode of exposure as it does not offer prolonged protection (NDoH, 2009). In addition to these guidelines there is an easy to follow management algorithm (Figure 1) and prescribing chart related to patient weight (Appendix 2) included in this chapter of the document.

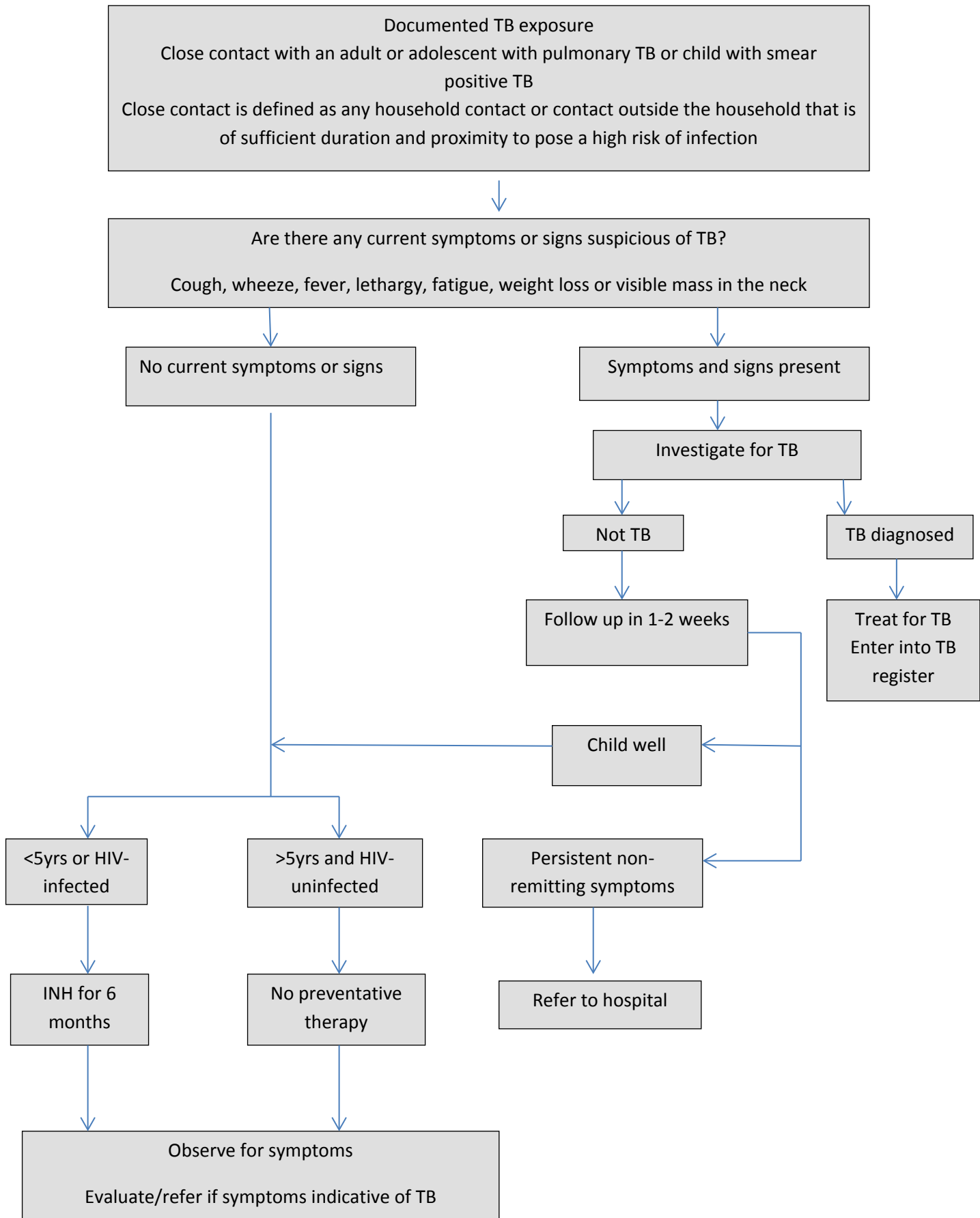
Newer guidelines were released in April 2013 (NDoH, 2013). These recent paediatric guidelines have been published in a separate document rather than combined with the adult management protocol. They have been extended to include the use of GeneXpert to confirm the diagnosis of TB disease in children however there were only minor changes relating to the management of children with TB infection and child contacts of infectious index patients. There have been increases in the recommended doses of INH for some weight bands and a more detailed description of counselling of caregivers at initiation of IPT. More guidance is given for follow-up care including the management of side effects and adherence monitoring. The screening algorithm remains unchanged. The algorithm on page 31 was taken from the 2009 guidelines as this algorithm is currently used in the clinic.

#### **2.4.1. South African Guidelines for IPT in HIV-infected children:**

Given the controversy over the benefit of using IPT in HIV-infected children as mentioned above, (Zar et al., 2006, Frigati et al., 2011, Madhi et al., 2011), country-specific guidelines have been developed by a group of experts in line with WHO guidelines and local practices (Cotton, 2011). The initial guidelines recommended the use of IPT in all HIV-infected children regardless of age after a documented TB exposure and for each subsequent exposure as well as those with a positive tuberculin skin test. They also recommended that in children <3 months of age in whom ART has not been initiated or poor TB exposure screening is anticipated, pre-exposure (or primary) IPT be given for 6 months after active disease has been excluded. In more recent guidelines the latter recommendation has been changed (Schaaf et al., 2013). With ARV's being more easily accessed by infants before 10 weeks of age, the protective effect of ARV's from developing TB is afforded early on in life. Thus pre-exposure IPT is no longer required in these children. The newer guidelines clearly state

that neither pre-exposure nor post-TB disease IPT is recommended in any HIV-infected or –uninfected child.

**Figure 1. Algorithm for screening a child with documented TB exposure** (NDoH, 2009 p57)



## **2.5. IPT Programme implementation**

### **2.5.1 Contact identification**

Despite clear evidence of the benefits of IPT and guidelines published by the NDoH, contact tracing and IPT provision to children appear to be poorly implemented components of the national TB control programme in SA (Du Preez et al., 2011). The SANTCP has largely focussed on the effective management of symptomatic patients with active disease that have presented to healthcare facilities. This passive case finding strategy has, with the help of the DOTS strategy, improved the treatment success rate but has done little to curb the rate of new TB infections (Wood et al., 2011).

This problem is not unique to SA. The literature reveals similar problems in a number of studies done in other developing countries. In a retrospective study conducted in four TB units in India – two in rural settings and the others in urban areas, only 14% of children under 14 years of age with an infective adult household contact were screened for TB, and only 19% of identified child contacts who were eligible for IPT received it (Banu Rekah et al., 2009). No documentation was found in the medical records regarding the medication provided or whether the course was completed.

Malawi, an under-resourced country in Africa with a high HIV and TB burden, has also struggled with the lack of active contact tracing and provision of IPT to children. In a study conducted by Zachariah et al. (2003) in a rural setting in Malawi, active tracing of household contacts yielded nine times more TB disease cases than passive contact tracing. However, the percentage of children who received IPT was not very different between the two groups (17% in passive cohort versus 22% in the active cohort). Even after screening for active TB had been done, 40% of contacts dropped out before initiation of IPT, mostly due to delays in receiving results from the chest x-ray taken during screening.

A mixed-method study conducted in Indonesia found that only one quarter of child contacts completed more than four months of treatment, with the average treatment collection being 2.5 months (Rutherford et al., 2012). Unfortunately the small sample size (n=82) limits the generalizability of the results. Similarly, in a sample of 184 TB contacts in Ethiopia, 33% completed >4 months of IPT and only 12% completed the full six months (Garie, Yassin & Cuevas, 2011).

SA, despite being classified as one of the 22 high burden TB countries by the WHO, has failed to prioritise contact tracing and the provision of IPT to eligible children. Based on

record reviews done at primary health care facilities in Cape Town, several studies confirmed that contact tracing is poorly documented (Van Zyl et al., 2006; Marais et al., 2006; Schaaf et al., 2007; van Wyk et al., 2010; du Preez et al., 2011; Osman et al., 2013). Van Wyk et al. (2011) found that only 1% of children in the study population in the Khayalitsha district who were eligible for IPT were actually initiated on chemoprophylaxis. Information regarding contacts was poorly documented with almost 50% of adult folders having no evidence of any information in this regard.

Similarly, du Preez et al. (2011) studied the extent of missed opportunities for IPT in children with culture-confirmed TB admitted to a tertiary hospital in Cape Town over a 5 year period from 2003-2007. Almost 75% of children <5 years of age in this cohort who were eligible for IPT had not received it, with the vast majority being <3 years of age. A quarter of these children developed TB meningitis or miliary TB and the overall mortality was 5%. Moreover, 41% of HIV infected children >5years of age who were eligible for IPT did not receive it. In both groups the TB source case was commonly the child's parent/s (47% in <5 year group and 60% in HIV infected group). These children represent missed opportunities for the prevention of morbidity and mortality in this vulnerable population, as well as an unnecessary increase in tertiary healthcare service utilisation in an already overburdened setting.

### **2.5.2 IPT compliance and course completion**

The problem lies not only with IPT initiation as described above but also in the retention of children who are started on chemoprophylaxis. Current SANTCP guidelines recommend six months of a daily dose of INH. This regime is largely unsupervised and adherence has been shown to be a major hurdle in preventing TB disease progression in children. Van Zyl et al. (2006), in a retrospective study, showed that there was a significant difference between adherence to a six month course of INH (27% of patients completed the course) and a three month course of a combination of Rifampicin and INH (67% of patients completed the course). Adherence was also significantly better in those who were supervised by a healthcare worker at the clinic (78% adherence) or a community health worker (64%) compared to those who did not have the supervision from a healthcare worker (adherence ranged from 37-45%).

A prospective study conducted in a similar primary care clinic setting aimed to show the difference between previous retrospective studies and a prospective study design (Marais et al., 2006). Despite active contact tracing conducted by study staff, 24% of

eligible contacts were not even offered IPT. In total, 80% of contacts who were eligible for IPT either never received it or completed <2 months of the six month course. The author suggested that it was likely a gross underestimate of the situation in other TB endemic areas, given that the prospective study was conducted in a well-resourced setting with active contact tracing. Little difference was demonstrated between the two study designs reflecting the very real problem of poorly managed child TB contacts.

The crisis is echoed in a recent study conducted in 14 primary healthcare facilities in Cape Town which revealed low numbers of contacts identified (0.7 child contacts <5 years of age per infectious case). Of those identified fewer than half were screened, less than a quarter was initiated on IPT and only 13% of the children who started IPT completed the course (Osman et al., 2013).

These figures reflect the lack of priority placed on contact tracing and TB prevention in developing countries. In contrast, a very large prospective study conducted in Guinea-Bissau, a low income West African country with a high TB incidence (471/100 000) showed encouraging results (Gomes et al., 2011). Of more than 800 children placed on IPT, 76% completed six months of treatment with 80% adherence to the medication. The authors suggest that the reasons for such high adherence levels may be related to the motivation and commitment of the study staff as well as the provision of medication at home rather than in a clinic. This differs from a local study previously mentioned which showed better compliance rates when medication was taken at a health facility (van Zyl et al., 2006).

Successful TB prevention programmes have also been studied in developed countries with low TB burdens. A review of 403 adult subjects started on IPT in a tertiary centre in Western Australia demonstrated remarkable outcomes (Pang et al., 1998). Only 34 patients were lost to follow-up and of the remainder, 90% completed five months or more of INH prophylaxis. This was a nurse-driven service and the treatment was not directly supervised. The author suggests that the success of this programme relates to the attention of healthcare workers to minor details such as the high rate of detection of adverse effects (9% vs 2% in other studies). Although these adverse effects were mostly minor and no different from those reported in previous studies, medication side effects had a significantly negative effect on compliance in the study population and by addressing them, adherence was improved.

A large retrospective Italian study with patients aged between one and 81 years old had similar results (Codecasa & Besozzi, 1998). Reasons for the high levels of initiation and retention on IPT, according to the authors, included extensive patient counselling regarding the reasons for IPT and its relative safety, the provision of information leaflets in the patients' own language and the follow-up of treatment defaulters by telephone and mail. In this study there was a significance difference noted between the adherence of Italians compared to that of immigrants (81% vs 63%). It was suggested that the difference may relate, in part, to cultural and language differences in immigrants resulting in the lack of comprehension of the meaning of IPT.

## **2.6. Side effects and safety of INH and patient adherence**

The use of INH does not come without potential side effects. These can be minor such as headaches, nausea and dizziness or, less commonly, more severe such as hepatotoxicity and fulminant hepatitis (Hawkrigde, 2007). Children are less likely than adults to suffer from side effects of TB medication (Cranswick & Mulholland, 2005). In practice INH was found to be extremely safe and well tolerated even in patients taking HAART (Zar et al., 2006, Le Roux et al., 2012) In the majority of studies mentioned above, no or very few side effects were noted in those patients taking IPT and the presence of side effects had no statistical significance on patient adherence (Gomes et al., 2011; Marais et al., 2006; Rutherford et al., 2012; Banu Rekha et al., 2013).

## **2.7. Barriers to IPT implementation and recommendations from existing studies**

WHO recommended IPT as part of the comprehensive HIV care package since 1998 based on several randomised placebo-controlled trials (Ait Khaled et al., 2009). However, implementation has been slow and by the end of 2009 only 85 000 HIV-infected people worldwide had received INH prophylaxis and the proportion of children is unknown (WHO, 2011). In 2008, under the banner title of 'The Three I's', recommendations and guidelines were released for use by national HIV/TB programmes to address the enormous threat that HIV/TB co-infection poses to HIV-infected people (WHO, 2008). The Three I's include Isoniazid preventative therapy, intensive case finding for active TB and TB infection control.

If the evidence for the use of IPT in children is so compelling, what are the barriers that prevent it from being successfully implemented? Various barriers to contact tracing and IPT have been suggested and some authors have offered recommendations to improve

the management of child TB contacts. Recurring themes throughout the literature include:

### **2.7.1 Health system-related factors**

- 1. Lack of resources in the healthcare sector** (Hawkrigde, 2007; Garie, Yassin & Cuevas, 2011)

#### Recommendation:

Studies have shown that the provision of IPT to HIV-infected patients can save money in medical care and social costs (Getahun et al., 2010). Mandalakas et al. (2012) concluded that screening young children in contact with infectious TB cases without testing them for infection (i.e. without performing a skin test or blood test) was the most cost-effective way of preventing TB in children in high-burden TB areas.

These are important outcomes to note when advocating for the scaling up of IPT programmes as, not only will the government be saving money in the long term by preventing TB disease, the short term staff requirements for the programme should not be excessive if the ‘no-testing’ screening method is adopted. It seems logical for government to redirect financial and human resources into developing a well-functioning screening and IPT programme.

- 2. Lack of awareness of the importance of IPT amongst healthcare workers and poor knowledge of the subject** (Banu Rekha et al., 2013; Van Wyk et al., 2011; Hawkrigde, 2007; Graham, 2011).

#### Recommendation:

Qualitative studies have described healthcare workers’ lack of knowledge regarding IPT and their perceived barriers to its implementation (Banu Rekha et al., 2009; Lester et al., 2010). Staff training is important, but even if guidelines are clear and accurate information is readily available, there is no guarantee that policy will translate into practice (Lester et al., 2010). It is suggested that the influence of peers and leaders is important in determining whether IPT prescription is adopted and “IPT champions” should be identified to promote the use of IPT in the hopes that others will follow. Also, supervision and regular assessment and feedback of the IPT programme may improve implementation.

**3. Difficulty in excluding active TB and the fear of creating INH-resistant strains of TB in patients who have active TB but have been prescribed IPT instead of multi-drug TB treatment (WHO, 2011; Graham, 2011).**

Recommendation:

Excluding active TB in children, both HIV-infected and -uninfected, is not an easy task. There are a number of diagnostic approaches that have been developed for the clinical diagnosis of TB disease using signs and symptoms. However, most have not been standardized making comparisons impossible and few have been validated in HIV-infected children (Shingadia & Novelli, 2003). The SANTCP guidelines have attempted to simplify the diagnostic approach by stratifying the investigations needed according to the resources available, thereby giving guidance to healthcare workers working in resource rich as well as resource poor settings (NDoH, 2009 & 2013). Screening children for TB does not have to be performed at a tertiary hospital provided these guidelines are followed.

Regarding the development of INH-resistant TB after exposure to INH prophylaxis, no clear data is available to prove or disprove the theory. In a meta-analysis done by Balcells et al. (2006) studies conducted in HIV-infected and -uninfected adults from 1951 to 2003 were included. The findings of this analysis highlight the paucity of robust data in this field. Results were limited by small numbers and incomplete culture and sensitivity results indicating the need for further research in this field. Despite these limitations the authors nonetheless recommended the expanded use of INH prophylaxis as a safe, low cost intervention that could reduce the morbidity and mortality burden of TB; but ongoing surveillance of INH resistance should continue in areas where IPT is widely used. This sentiment is reinforced by the results of more recent studies conducted in SA in which no increased risk of INH resistance was found post IPT (van Halsema et al., 2010, Zar et al., 2006). Furthermore, WHO strongly recommends that the fear of the development of INH drug resistance should not be cited as a barrier to the provision of IPT to eligible individuals as there is little evidence to support this (WHO, 2011).

4. **Poor documentation in clinical records and the lack of a standard IPT management and monitoring tool** (Banu Rekha et al., 2013; van Wyk et al., 2011; van Wyk et al., 2010; Osman et al., 2013; Du Preez et al., 2011; Hawkrige, 2007).

Recommendation:

WHO recommends the use of a dedicated IPT register and prophylaxis cards on which to document details of household contacts (WHO, 2006). The positive effects of such a system were demonstrated by a follow-on study in India where IPT completion rates improved from 19% prior to the implementation of the recording systems to 61% once these systems had been implemented (Banu Rekha et al., 2013). A similar pilot study was undertaken in a high-burden clinic in Cape Town. The results were promising with more contacts being identified and initiated on IPT, better documentation of information and improved adherence rates (van Soelen et al., 2013). Although both these studies had small sample sizes, the outcomes are encouraging especially as both were set in high-burden TB areas.

5. **Operational challenges such as the expense and distance of travel (Zachariah et al., 2003; Rutherford et al., 2010), delays in screening chest radiographs being read (Zachariah et al., 2003) and high medication costs (Rutherford et al., 2012).**

Recommendation:

In order to simplify the implementation of INH prophylaxis, the NDoH clearly states that in an asymptomatic child, a chest X-ray and Mantoux test are not required prior to commencing IPT (NDoH, 2009; NDoH 2013). This should allow IPT to be prescribed and dispensed at a primary care facility and reduce the amount of time and money spent by patients getting to the clinic. This simplified screening method was also recommended by Zachariah et al. (2003) after analysing data collected in rural Malawi. As previously mentioned, good adherence rates were seen in Guinea-Bissau where medication was supplied to patients at their homes by healthcare workers (Gomes et al., 2011). Zachariah et al. (2003) went one step further by suggesting that, in order to improve adherence, medication should be given to the index patient at the clinic to pass on to household contacts.

## **2.7.2 Patient-related factors**

### **1. Patient or carer perceptions that a well-child does not require medication**

(Marais et al., 2006; Garie, Yassin & Cuevas, 2011; Rutherford et al., 2010)

#### Recommendation:

The awareness for the need for IPT and the importance of good adherence needs to be addressed amongst parents. Caregivers who had better knowledge of IPT were more likely to give their children medication despite the child being well (Rutherford et al., 2012). Also, caregivers who themselves had positive healthcare experiences were more likely to be compliant in giving their children IPT, thus emphasising the importance of positive relations between parents and healthcare workers. Community education could also improve awareness and perceptions regarding IPT (Garie, Yassin & Cuevas, 2011).

### **2. Population migration resulting in patients being lost to follow-up** (Gomes et al., 2011)

#### Recommendation:

This is a very real problem in SA where much of the population migrate between and within health districts and provinces. The use of a standardised IPT card that is carried with the patients at all times, as suggested by the WHO (2006), may assist with continuity of care between healthcare facilities.

### **3. Difficulty with administration of medication to children** (Rutherford et al., 2012)

#### Recommendation:

Older children are more likely to be compliant with INH therapy (Rutherford et al., 2012, Le Roux et al., 2009). It has been postulated that one of the reasons for this is the difficulty in administering the medication to small children due to its bitter taste and the texture of crushed tablets. Ease of medication administration is especially important where courses are long and for prevention only and child-friendly forms of INH may help to improve compliance in young children.

## **2.8. Patient variables affecting contact reporting**

The above-mentioned studies have described the problems relating to child contact identification and IPT delivery but have not mentioned the demographic characteristics of those index cases more or less likely to report child contacts. This is with the exception of Osman et al. (2013) who reported that smear positive and female index

patients were more likely have child contacts (<5 years) documented whereas older age, HIV positivity and retreatment index cases were associated with poor contact reporting. This may be of importance when devising strategies to improve contact identification.

### **2.9. Programmatic factors relating to childhood TB and IPT**

Delay in the diagnosis of TB results in increased severity and mortality in the index patient and a greater chance of transmission to the community (Sreeramareddy et al., 2009). Total treatment delay is the combination of patient-related and health-system delays (Sreeramareddy et al., 2009) and it has been recommended that it be used as a programmatic indicator at local level (Yimer et al., 2014).

To attain TB control patient delays should not exceed two to three weeks (Sreeramareddy et al., 2009). Reasons for patient delays are complex and include stigma, dissatisfaction with health system and undesirable staff attitudes (Skordis-Worrall, Hanson & Mills, 2010). Delays at health facility level may be attributed to healthcare worker skills, slow laboratory turnaround times or the unavailability of medication. The average health system delays in low to middle income countries assessed in a systematic review was 28.4 days (Sreeramareddy et al., 2009). In SA, the NDoH recommends that 80% of smear results be available within 48 hours and time-to-treatment for patients diagnosed with drug sensitive TB be 2 days. The total time-to-treatment from when a sputum sample is taken should be a mere 4 days (NDoH, 2014).

Although extensive research has been performed regarding the delays in index patients accessing and initiating treatment, no literature could be found regarding time delays pertaining to child contacts being screened or initiated on IPT. It would seem logical that both patient-related and health-system barriers that contribute to delays in initiating index patients on treatment could apply to contact management.

### **2.10. Future research**

Much research has been done regarding the quantitative aspects of eligible children who do not receive IPT, but little has been done to discover the reasons for these missed opportunities at primary care level. Qualitative studies conducted in Indonesia (Rutherford et al., 2012) and India (Banu Rekha et al., 2009) explored the perceptions and difficulties that patients and healthcare workers have experienced regarding IPT, but little has been done in SA. This country's health system has its own set of unique challenges and the population is diverse in its culture, language and health-seeking

behaviour. For these reasons it would be beneficial to study the reasons for the failure of the IPT programme and gain insight into the knowledge, attitudes and behaviours of both the healthcare workers and the caregivers relating to IPT in children in SA. Mixed-methods studies should be performed to assess the lack of caregiver uptake of IPT and their reasons for refusal. These will help to explain attitudes and perceptions of caregivers and assist with developing education and counselling tools to address these barriers.

Although Osman et al. (2013) explored index patient demographic factors that were related to poor reporting of contacts, it would be of value to look at which factors impact on the screening of contacts and on the completion of IPT. This could facilitate the identification of contacts at risk of being lost before screening and those who are more likely to default their medication.

Other areas that could shed light on improving the service would be to study the impact of various interventions put in place at the clinic and in the community. Small pilot studies (Banu Rekha et al., 2013; van Soelen et al., 2013) have already shown the positive impact of the introduction of an IPT register and larger studies could support these findings. Other interventions that could be studied include the impact of healthcare worker training, community awareness campaigns, patient education and decentralization of IPT services by involving community health workers in IPT supervision.

### **2.11. Conclusion**

In conclusion, TB in children causes considerable morbidity and mortality, especially in those under 5 years of age and children who are HIV-infected. Despite this it is often a neglected component of national TB programmes, especially in developing countries with high TB case burdens. It has been shown that IPT is a safe, cost-effective and valuable method of preventing disease progression in children, both those who are infected and uninfected with HIV.

However, it is evident from the literature that IPT has been poorly implemented in developing countries, including SA, due to health system barriers as well as patient-related factors. This study aims to determine current practices in an area with an extremely high TB incidence rate where little background data exists on the topic. With this knowledge it may be possible to put interventions in place and further research the

impact these interventions have on services thus improving the healthcare delivery to children in this area.

## **CHAPTER 3: METHODOLOGY**

This chapter will outline the study design, inclusion and exclusion criteria, data collection and analysis.

### **3.1. Study site**

This study was conducted in West End Primary health care clinic in the Nelson Mandela Bay Metropole, which includes the city of Port Elizabeth, Uitenhage and Despatch. This area is incorporated into the Nelson Mandela Bay Health District (NMBHD), one of eight health districts in the Eastern Cape Province. The NMBHD is made up of 3 sub-districts (DoH, 2013). West End clinic is located within sub-district C. The health district has a total population of 1.2 million people with sub-district C making up 341 635 of the total. Roughly 10% of the population are children under the age of 5 years. Unemployment rates in the district are high with 41% of the population not working. The majority of people in the district speak isiXhosa (57%) and the adult literacy rate is 87%.

West End clinic is one of 53 sites in the district providing primary care TB services to the population. The annual TB case load at the clinic is roughly 300 and there are two nurses dedicated to the management of TB patients, five lay counsellors who are responsible for both HIV-infected and TB patients and a data capturer (Personal communication with Ms Betty Ncanywa, Head of TB Directorate, 30 January 2014). HIV and TB services were integrated into one service within the clinic at the beginning of 2013 (Personal correspondence with Sr Sookdin, Facility Manager, 17 June 2014). At this time the TB services moved into the same room as the HIV service and the lay counsellors from each service were pooled thus sharing the patient load. Some of the major problems facing the management of TB in the primary health care clinics are severe staff shortages (vacancy rate of 48%), inadequate ventilation of clinics due to poor infrastructure and drug-resistant strains of TB (DoH, 2013).

### **3.2. Study design**

A cross-sectional descriptive study design was chosen as it allowed the researcher to observe the adherence to national TB guidelines in a small population group during a defined time period (Carlson and Morrison, 2009). A retrospective record review using

information collected by clinic staff during routine care of patients made the study affordable and manageable with limited time and study funds.

### **3.3. Inclusion & exclusion criteria of sample**

The following criteria were considered for inclusion in the study:

- Patients started on TB treatment up until and including 28 February 2014 were included.
- Only index patients with bacteriologically confirmed pulmonary TB were included. These are patients with smear and/or GeneXpert and/or culture positive sputum results.
- Folders of patients with both drug-sensitive and drug-resistant pulmonary TB were included in the folder review.
- In keeping with studies found in the literature (van Wyk et al., 2011; van Wyk et al., 2010; Banu Rekha et al., 2009), the index patient was defined as a patient over the age of 15 years with infectious TB. National TB Programmes should, according to international standards, record and report TB cases and outcomes of children aged 0-4 years and 5-14 years in separate categories, thus leaving those over the age of 15 to be reported as “adult” cases (Donald, Maher & Quazi, 2007). This is understandable as adolescents are more likely to have adult-type disease as opposed to the paucibacillary disease of childhood TB.
- Child contacts are defined as those children under the age of 5 years who are in close contact with an adult with infectious TB.

Exclusion criteria were as follows:

- Index patients who are younger than 15 years
- Index patients who do not have sputum positive pulmonary TB
- Index patients who have extrapulmonary TB without pulmonary TB
- All child contacts over the age of 5 years regardless of their HIV status.

### **3.4. Sample size calculation**

A similar study in a high TB burden setting established that 20% of eligible child contacts <5 years was initiated on IPT (van Wyk et al., 2010). This figure was used to calculate the sample size of 246 child contacts (<5 years) required to obtain a 95% confidence interval with a 5% precision. This sample size calculation is in line with the point estimation for objectives 3 and 4.

### **3.5. Data collection**

#### **3.5.1. Routine patient care**

All patients who are started on TB treatment at the clinic are entered into the TB treatment register by the TB clinic staff. This information is then entered by the data capturer into the electronic TB register. Index patients should, during the clerking procedure, be asked whether they are in close contact with any children. This information should be recorded at the back of each TB treatment card in the space provided. If child contacts are identified, children who are eligible for IPT owing to their age or HIV status should be screened for TB. Children in whom active TB disease has been excluded should be given a six month course of IPT. Those who are started on IPT should have an IPT card (Appendix 3) created which is not kept in their clinic folder but in a separate file in the TB room of the clinic. This card serves as a record for the duration of the IPT treatment.

Index patients for this study were identified from the drug sensitive TB treatment register and patient folders in the TB filing system. In the study conducted by Osman et al. (2013), there were 0.7 child contacts < 5 years of age identified per index case and it was assumed that it will be similar in this setting. However, the number of child contacts < 5 years of age per index case was less in this study (0.5) therefore 491 index folders were reviewed giving a total of 261 identified contacts < 5 years of age. Index patients were chosen consecutively from 28 February 2014 backwards until the desired sample size was reached. The caseload of the clinic was estimated to be around 300 annually (Personal communication with Ms Betty Ncanywa, Head of TB Directorate, 30 January 2014). By taking a successive sample over more than a year it gave the researcher a clearer picture of how services operate at the clinic throughout the year.

#### **3.5.2. Data collection tool**

Folders of all eligible index patients started on TB treatment at the clinic on or before 28 February 2014 were reviewed using the data collection tool (refer to appendix A) to identify whether there was documentation of contact/s, the number of child contacts identified and their ages. The reason the cut-off date, 28 February 2014, was chosen was to ensure that those contacts who started IPT would have completed the 6-month course by the time the data was collected.

The data collection tool consisted of three sections. Section 1 related to the index patient and was used to collect information relating to the patient's demographics and TB history, both previous and current. This information may be useful to identify patients who are more or less likely to report contacts. The second section related to the recording of the contacts' information and the third section related to the management of these contacts. Data for Section 1 and 2 were collected from the adult folder. All identified contacts under the age of 5 years were cross-referenced with the IPT cards to establish whether the child was screened for TB, initiated on IPT and the child's outcome (Section 3 of the data collection tool).

This data collection tool was based on that used by Osman et al. in 2013 in a number of clinics in Cape Town. It was adapted to meet the needs of the study setting.

### **3.6. Data analysis**

Data was entered into Microsoft Excel version 2010 and analysed using a statistical programme, R (R Core Team, 2013).

Frequency counts and proportions were used to describe categorical variables and means and standard deviations; continuous variables. Initial association between means was analysed using a simple two-sample T-tests to test for statistical significance.

Regression analysis was performed using contingency tables and Chi-square tests on the data set in order to establish the relationships between index patient demographics (age, gender, employment status) and their disease characteristics (HIV status, smear positivity and previous TB) related to the identification of contacts and their management. For the purpose of this analysis, the age of the index patients was dichotomised using the median as a cut-off.

The mean is a measure of central tendency but is particularly susceptible to the influence of outliers. Thus in instances where the mean was skewed by potential outliers giving a large standard deviation (SD), the median was used instead to describe the central tendency. When using the median, the interquartile range (IQR) gives a better idea of the range of values than does the SD (Lund Research Ltd, 2013).

### **3.7. Potential bias**

#### **Incomplete or unavailable clinic records:**

Information in patient folders and on IPT cards was, at times, incompletely captured by the healthcare worker or sometimes the writing was illegible in the clinical records.

Also, due to space constraints, patient folders were filed in more than one place making it difficult to locate all the folders of patients on the register list. Similarly, it is possible that IPT cards of contacts did exist but were not found due to the nature of the clinic's filing system.

Some child contacts <5 years may not have been recorded in the index patient's folders, which may have overestimated screening and/or IPT coverage.

### **Sampling bias:**

As patients were consecutively sampled over a long time frame (> 2 years), it is unlikely that sampling bias would have had a negative impact on the results obtained from this study. Nonetheless, the patients with drug-resistant TB could have inadvertently been excluded due to the sampling procedure. This is discussed further in Chapter 5.

### **3.8. Generalizability**

Due to time and financial constraints only one clinic was investigated, thus the results of this study may not truly reflect the situation in other clinics in the NMBHD.

The population of NMBHD is diverse in culture and language and socioeconomic status. West End clinic serves a predominantly Afrikaans speaking mixed-race community. The culture, health-seeking behaviours and disease profiles may differ to those of a predominantly African, Xhosa speaking or Caucasian, English speaking community and therefore may not be generalizable throughout the Metro.

### **3.9. Reliability and Validity**

Reliability is the extent to which an assessment tool gives the same results on repeated trials (Howell et al., 2012). The data collection tool was piloted on 15 folders to ensure that the data collected was reliable. Problems with the tool were then identified and adjustments made. The data collection tool was validated in a previous study (Osman et al, 2013) and adapted to suit the local setting.

Validity refers to the degree to which the study accurately assesses the concept that the researcher set out to measure (Howell et al., 2012). Due to time and funding constraints it was not feasible to choose a true representative sample of patients as this would have involved collecting data from many clinics across the health district. However, by using a successive sample of patients that incorporated patients presenting to the clinic in both

summer and winter seasons where caseloads might vary as well as holiday times when staffing and patient loads may change, the researcher attempted to attain the most valid results under the circumstances. It is impossible to ensure that the data collected from the IPT cards is a true reflection of how many children received IPT and the amount of medication prescribed. Some nurses may have given the medication but did not record it, similarly with the recording of symptom screens, weight checks and side effect documentation. For this reason, it is likely that the results relating to the aforementioned factors are an underestimation of the actual situation. In the same vein, although medication was prescribed and collected, it cannot be assumed that the child actually took the tablets. Thus the results obtained may be an overestimation of true patient adherence. These factors may affect the validity of the study.

### **3.10. Ethical considerations**

The study design and content was submitted to the University of Cape Town Research Ethics Committee prior to commencement in order to ensure the rights of patients and their families were not in any way violated, in accordance with the principles of good clinical practice contained in the Belmont report (1979) (Cambridge Graduate University, 2015). Approval was obtained from the provincial and local health authority to conduct research in the area. Discussions were held with the clinic manager and staff to explain the reasons for conducting this research, to give them understanding of the research protocol and to gain their support.

The importance of confidentiality is explained in the Declaration of Helsinki: “The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject’s physical and mental integrity and on the personality of the subject.” (WHO, 2001, p374).

In order for the information in patients’ folders to be cross referenced with other sources such as IPT cards, it was necessary for the names of patients to be recorded on the data collection sheets. However, confidentiality of information obtained from medical folders was ensured by using codes instead of names to identify participants

when this information was entered into the Excel spread sheet. A waiver of individual informed consent was applied for since data was anonymised after collection. All data collected was stored safely with limited access by the researcher; data was stored on a password-protected computer. The data sheet was password protected and only the researcher had access to these sources (NDoH, 2006). To ensure safety as well as confidentiality and protection of patient identities, raw data was safely stored in a lockable cupboard to which only the researcher had access.

### **3.11. Risks and benefits of this study**

As this study involved only a review of medical folders, no participants were placed at risk. There are potential benefits to the patients and the community following the dissemination of the outcomes of this research project. Operational benefits include the baseline assessment of this service which can act as a starting point from which further; more in-depth research can be conducted. By assessing the fall-out of contacts at each step in the management process from identification to completion of IPT, this project may be able to identify the major hurdles that prevent children from accessing and completing IPT in the NMBHD context.

## **CHAPTER 4: RESULTS**

This chapter outlines the results obtained from the data collection and analysis. The first section provides an overview of the demographic profile of index patients and their TB disease characteristics, which presents background information on the population which the clinic serves. The second section focuses on the study objectives, namely the identification and management of child contacts <5 years and the relationship between the index patient demographics and the management of these contact.

### **4.1. Index patient**

#### **4.1.1. Index patient demographics**

Index patients who started treatment between 21 October 2011 and 28 February 2014 were included in the study. According to the electronic TB register 690 patients were started on treatment over this time. Of these patients 491 patients were enrolled in the study. 110 patients were excluded based on the fact that their TB was extrapulmonary or sputum negative. There were 65 patients who were excluded based on their age. The remaining 24 folders could not be found.

Table 1 shows the basic population demographics of the index patients who were included in this study. There were more men than women (265(54%) vs 226(46%)) with active TB who presented to the clinic during this time. The mean age was 36.6 years (SD=13.4). Unemployment was high with almost 56% of patients not working. The majority of patients were HIV-uninfected (77.8%). HIV testing was routinely done with only 3% of patients having an unknown HIV status. Education level was not recorded in the folders and was thus removed from the data collection tool after it was piloted.

Table 1. Index patient demographics

	n	%
Male	265	54
Female	226	46
<b>Age:</b>		
Mean = 36.6 years		
SD = 13.4		
<b>Employment status:</b>		
Employed	164	33.4
Unemployed	274	55.8
Pensioner	21	4.3
Student	30	6.1
Unknown	2	0.4
<b>HIV status:</b>		
Infected	94	19.1
Uninfected	382	77.8
Unknown	15	3.1

#### 4.1.2. Index patient TB disease characteristics

The disease characteristics of the index patients are described in Table 2. Most patients (n=347, 70.7%) were diagnosed with TB for the first time and 70% of the patients had drug sensitive TB. For the purposes of this study, no differentiation was made between multidrug resistant (MDR-TB) and mono-drug resistant TB. Drug-resistant TB was recorded in 17 (3.46%) patients, of which 5 were MDR-TB, 2 had unknown drug sensitivities and the remainder were either resistant to Rifampicin or INH.

There was a relatively large portion of patients with unknown drug sensitivities (n=107, 21.8%). This is a reflection of the 2009 SANTCP guidelines. Prior to the introduction of the GeneXpert test in October 2012, TB culture and drug sensitivity testing were not done on patients presenting with TB for the first time. They were presumed to have drug-sensitive TB and treated as such.

Smear positive TB was the most common disease type with 78.2% (n=384) of patients having a positive smear on microscopy. The percentage of smear negative TB cases diagnosed increased after the introduction of the GeneXpert diagnostic test was introduced into the diagnostic protocol in October 2012. Prior to this, less than 10% of cases were smear negative (total smear positive vs smear negative = 93% vs 7%). With the help of the new test, 20% more smear negative cases were diagnosed (total smear positive vs smear negative = 68% vs 28%).

Table 2. Index patient disease characteristics

	n	%
<b>Previous TB:</b>		
Yes	137	27.9
No	347	70.7
Unknown	7	1.43
<b>Sensitivity:</b>		
Drug sensitive	345	70.3
Drug resistant	17	3.46
Not documented	22	4.5
Unknown	107	21.8
<b>Microscopy:</b>		
Smear positive	384	78.2
Smear negative	95	19.4
Not done	5	1
Not documented	7	1.4

#### 4.1.3. Index patient outcomes

Table 3 reflects the treatment outcomes of the index patients. More than half the index patients (54.4% n=267) were cured and 18.9% (93) completed their treatment. The treatment success rate (TSR) is the sum of those cured and those who completed treatment with the total number of patients started on treatment as the denominator (NDoH, 2014). For the period under study, it was 73.3%. Treatment default occurred in 11% (n=54) of index patients and 2% (n=10) failed treatment. Almost 7% of patients were transferred to other facilities to continue their treatment. During the studied period 19 (3.9%) patients died while on TB treatment at the facility.

Table 3. Index patient outcomes

	n	%
Cured	267	54.4
Completed treatment	93	18.9
Defaulted	54	11
Failed	10	2
Died	19	3.9
Still on treatment	1	0.2
Transferred out	34	6.9
Unknown	13	2.7

## **4.2. Contact information**

### **4.2.1. The number of child TB contacts under 5 years noted in index TB patient folders**

Of the 491 index patients, 399 (81.4%) had contacts documented in the folder, in 30 (6.1%) folders it was recorded that the patient was living alone and 61(12.5%) folders had no documentation of contacts. The names of contacts were well documented (100% of folders in which contacts were documented had the actual names of the contacts written).

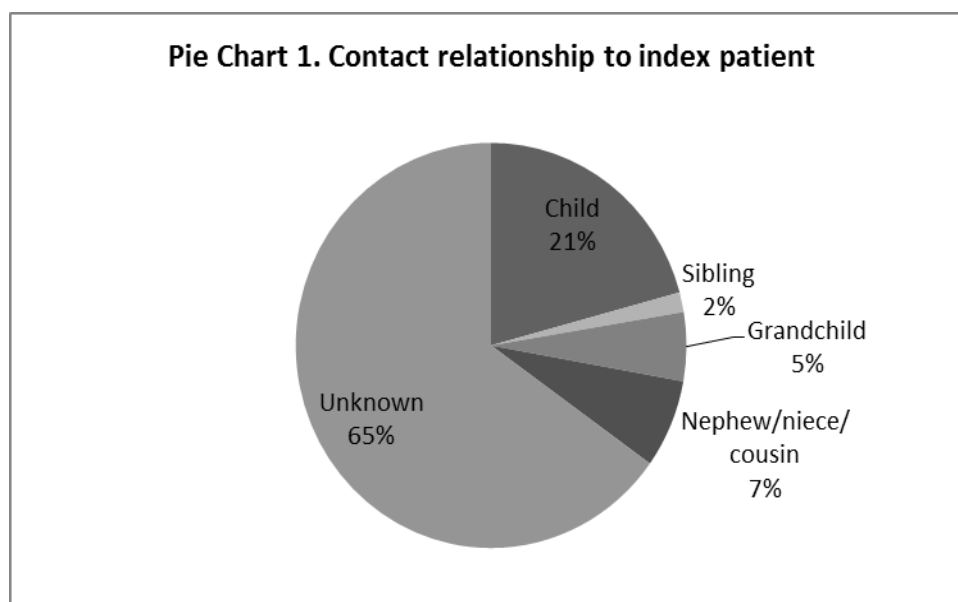
491 index patient folders were used in order to identify 261 child contacts < 5 years for objective 1. Of the 261 child contacts under the age of 5 years, 6 were excluded from the analysis due to missing data. The mean number of contacts of any age identified was 3.6 (SD=2.9) and a mean of 0.53 (SD=0.8) child contacts <5 years were identified per index patient. Table 4 shows the mean number of contacts and child contacts <5 years identified according to TB register year. The total number of contacts identified has remained constant; however, there has been a statistically significant decrease in the number of contacts <5 years identified from 2012 to 2013 ( $t=2.024$   $p=0.02$ ).

Of the 17 DRTB patients that were included in this study, only three had contacts reported (4 contacts in total). Of these contacts, two were initiated on TB prevention therapy. One of these contacts had no documentation of the drugs prescribed for prevention or the number of weeks collected while the other was prescribed 2 weeks of INH and collected no further prescriptions

Table 4. Contacts recorded per index patient

Contacts per index patient	Mean	SD	2011 Mean (SD)	2012 Mean (SD)	2013 Mean (SD)	2014 Mean (SD)
Total number	3.6	2.9	3.8 (2.75)	3.9 (2.86)	3.1 (2.89)	3.9 (2.78)
Child contacts <5 years	0.5	0.8	0.57 (0.88)	0.62 (0.86)	0.45 (0.74)	0.47 (0.76)

More detailed information about the contacts <5 years is seen in Pie Chart 1. As the date of birth of contacts was not routinely recorded in the source documents, the age of contacts was captured in years unless the child was less than a year in which case it was captured in months. The mean age of these contacts was 2.25 years (SD=1.3 years). The youngest child contact identified was one month old. The relationship to the index patient was poorly documented with 65% of contacts not having a documented relationship to the index patient. Of those that were documented, the most common relationship was a child of the index patient (21%).



#### 4.2.2. Child contact screening and methods of screening

Table 5 represents the screening process of the child contacts <5 years who were identified. Of the 261 contacts <5 years identified 70.5% (n=184) were screened using

at least one of the screening methods outlined in Table 6. The most common methods of screening included a symptom screen (n=111, 60.3%) and/or a TST (n=145, 78.7%). Of those who had a TST done, almost half (47.6%) did not have a recorded symptom screen. This is an important point to consider in determining if there was deviation from the screening protocol.

Table 5. Child contact screening methods

Of total screened (N=184)	n	%
Symptom screen	111	60.3
TST	145	78.8
Chest X-ray	16	8.7
Sputum/gastric washing	13	7.1
Referred	3	1.6

#### **4.2.3. IPT initiation and the fall-out of child contacts <5 years between screening and IPT commencement**

Figure 2 illustrates the flow of contacts from identification to treatment completion. Of the 184 contacts who were screened, only 2 patients (1%) were known to have started treatment for TB disease, although in many cases (n=74, 40.2%) there was no documentation of whether TB treatment or IPT was initiated. If taken as a percentage of the total number of contacts identified and analysed (n=255), 56.8% (n=145) of contacts had no documentation of screening or initiation of any therapy – preventative or other. 108 (58.7% CI= ±7.11) contacts were documented to have started TB prevention therapy but only 74 (68.5%) IPT cards were found for patients who had been started on IPT.

There were seven IPT cards found that did not have the index patients' name recorded on them. IPT cards were found for nine contacts who were not eligible for IPT either due to the contacts' age (3 contacts were over 5 years) or due to the index cases' disease characteristics (6 cards were found for contacts of index patients who had sputum negative or extrapulmonary TB). These contacts were excluded from the analysis.

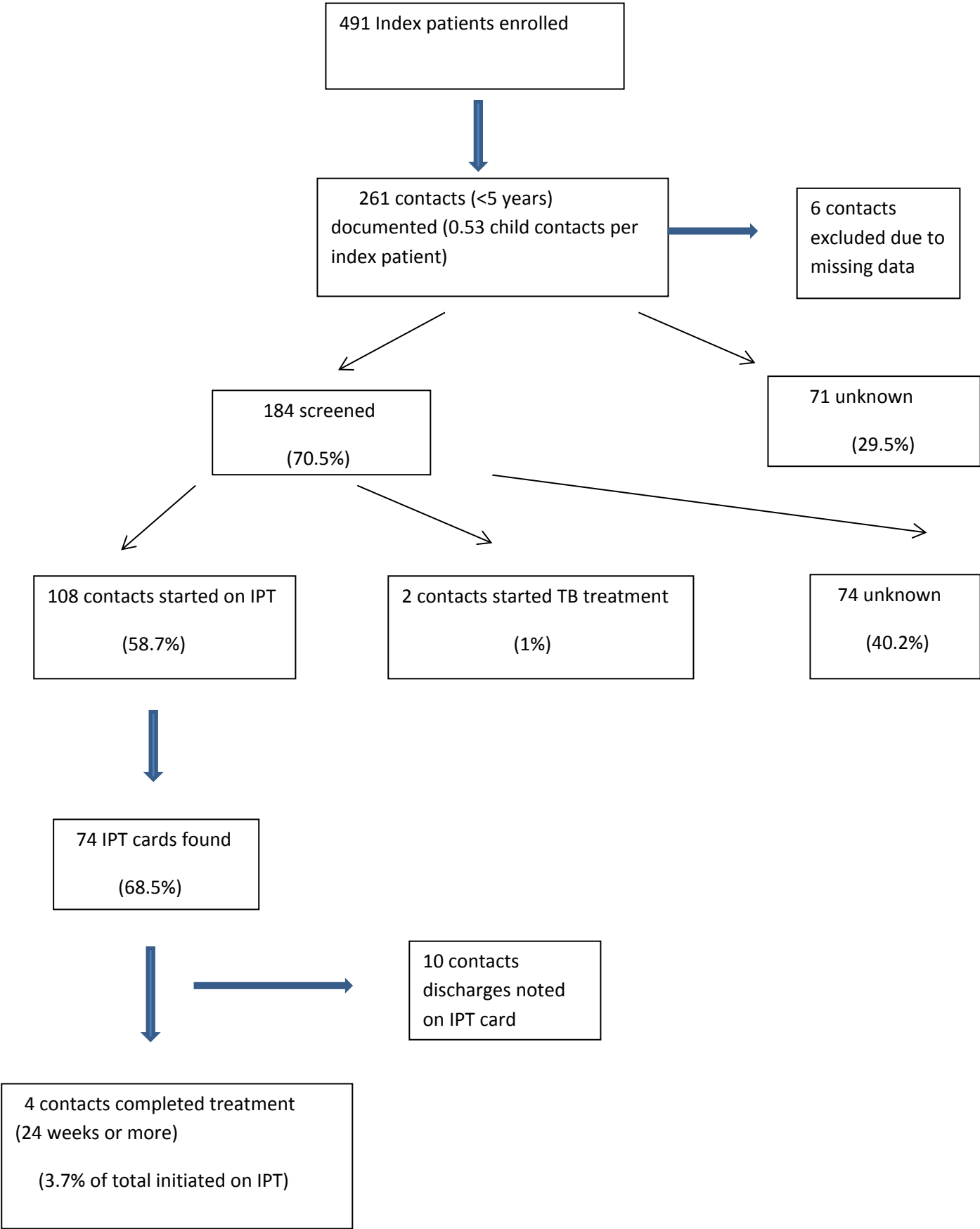
The majority (91.8%) of contacts who were started on TB prevention therapy were given INH. The drugs used for the remaining 8% were not documented. There was no

documentation of side effects (0%) in any folders and routine symptom screens and weight checks, which should be done monthly, were not documented (only recorded on 1 IPT card).

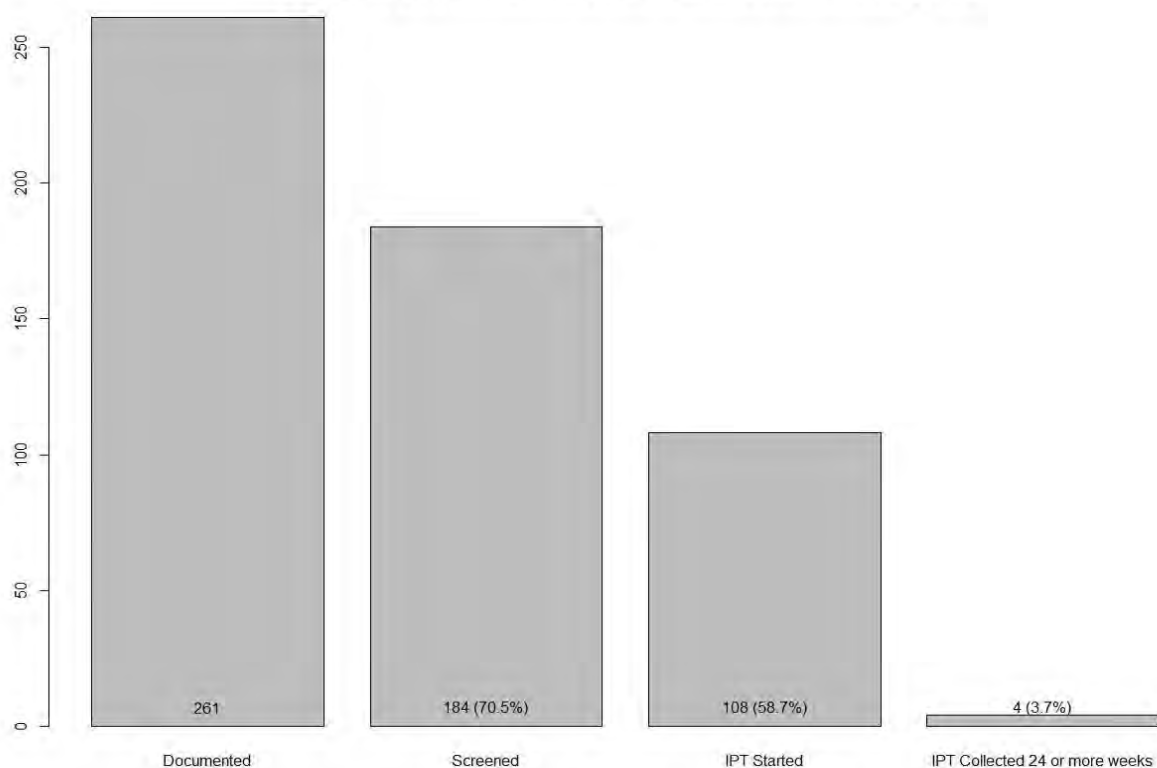
#### **4.2.4. The duration of IPT collected by child contacts <5 years and the treatment completion rates**

The median number of weeks of IPT collected was 8 (IQR=11.25) (Table 6). In 2013 and 2014 the median number of weeks collected was lower than in previous years. The differences between 2012 and 2013 (the two full years included in the study) was statistically significant ( $t = 2.17$  p-value = 0.017). Of those who started IPT, a discharge note was made for 10 children (10%) and 4 children (3.7% CI=  $\pm 3.56$ ) completed the 24 week course. Most children who were discharged had completed 6 months of therapy according to time but had not received treatment for varying lengths of time during these six months making their actual number of weeks of IPT shorter. If they did not collect 24 weeks or more of INH they were not classified as having “completed treatment”. Graph 1 depicts this fall out of children from identification to IPT completion

Figure 2. Flow diagram of contacts from identification to treatment completion



**Graph 1. Fall out of child contacts from identification to treatment completion**



**Table 6. Median number of weeks of IPT collected over study period grouped according to TB register years**

	Median (IQR)	2011 Annual median (IQR)	2012 Annual median (IQR)	2013 Annual median (IQR)	2014 Annual median (IQR)
No. of weeks of IPT collected	8.0 (11.25)	14.0 (12.5)	10.5 (11.0)	5.0 (5.75)	4.0 (7.0)

#### **4.2.5. The relationship between index patient demographics and disease characteristics and the management of child contacts < 5 years**

Chi-square tests were performed on the data set in order to establish whether certain categories of patients were more likely to have contacts < 5 years documented, screened and initiated on IPT. Certain subgroups were excluded from the analysis due to small numbers. These are documented below each table.

Table 7 below shows that males ( $p= 0.007$ ) were less likely to have documentation of child contacts <5 years. The index patients included in the category “child contacts recorded” were those whose folders had documentation of child contacts <5 years as well as those whom had “living alone” or similar documented. The latter group of index patients were included in this category as it implied that the healthcare worker had enquired about child contacts <5 years and had documented that there were none. This is in contrast to those folders that may have had older contacts recorded but no specific documentation of “no contacts <5 years”.

Table 8 shows that male patients ( $p= 0.00$ ) and those with retreatment TB ( $p=0.012$ ) are less likely to bring their contacts for screening.

Table 9 demonstrates that child contacts <5 years of index patients with retreatment TB are less likely to initiate IPT. Age, HIV status, smear status and employment status were not significant predictors of contact documentation or management.

Table 7. Relationship between index patient demographic factors and disease characteristics and child contacts < 5 years documented

	Total in category “child contacts <5 years documented”	No. of records with child contacts <5 years documented (%)	$\chi^2$	Odds Ratio	p-value
<b>§Gender (n=490):</b>					
Male	264	100 (37.9)	7.31	0.60	<b>0.01</b>
Female	226	114 (50.4)		1.0	
<b>§Age (n=490):</b>					
≤35 years	247	117 (47.4)	2.47	1.35	0.12
>35 years	243	97 (39.9)		1.0	
<b>*Employment status (n=437):</b>					
Employed	163	79 (48.5)	1.49	1.30	0.22
Unemployed	274	115 (42.0)		1.0	
<b>**HIV status (n=475):</b>					
Infected	93	40 (43.0)	0.00	0.96	0.96
Uninfected	382	168 (44)		1.0	
<b>**Previous TB (n=483)</b>					
Yes	137	67 (48.9)	1.83	1.34	0.18
No	346	144 (41.6)		1.0	
<b>***Smear status (n=478):</b>					
Positive	383	176 (45.9)	2.78	1.52	0.095
Negative	95	34 (35.8)		1.0	

§ n=490 and not 491 due to missing data required for analysis

\*Employment status excluding pensioners, students and “unknown”

\*\* Excluding “unknown”

\*\*\* Excluding “not done” and “not documented”

Table 8. Relationship between index patient demographic factors and disease characteristics and child contacts < 5 years screened

	Total in category “contact screened”	No. of records with documentation of contact screening (%)	$\chi^2$	Odds Ratio	P value
<b>§Gender (n=255):</b>					
Male	104	64 (61.5)	8.98	0.41	<b>0.0027</b>
Female	151	120 (79.5)		1.0	
<b>§Age (n=255):</b>					
≤35 years	160	118 (73.7)	0.35	1.23	0.55
>35 years	95	66 (69.4)		1.0	
<b>*Employment status (n=232):</b>					
Employed	91	67 (73.6)	0.09	1.14	0.77
Unemployed	141	100 (70.9)		1.0	
<b>**HIV status (n=246):</b>					
Infected	50	36 (72)	0.00	1.02	1.00
Uninfected	196	140 (71.5)		1.0	
<b>**Previous TB (n=251) :</b>					
Yes	73	44 (60.2)	6.37	0.45	<b>0.01</b>
No	178	137 (76.9)		1.0	
<b>***Smear status (n=249):</b>					
Positive	208	152 (73)	0.56	1.40	0.45
Negative	41	27 (65.8)		1.0	

§ n=255 and 261 due to missing data required in analysis

\*Employment status excluding pensioners, students and “unknown”

\*\* Excluding “unknown”

\*\*\* Excluding “not done” and “not documented”

Table 9. Relationship between index patient demographic factors and disease characteristics and child contacts < 5 years initiated on IPT

	Total in category “contacts initiated on IPT”	No. of records with documentation of IPT initiated	$\chi^2$	Odds Ratio	p-value
<b>§Gender (n=253):</b>					
Male	104	42 (40.4)	0.24	0.85	0.62
Female	149	66 (44.3)		1.0	
<b>§Age (n=253):</b>					
≤35 years	159	71 (44.6)	0.48	1.24	0.49
>35 years	94	37 (39.4)		1.0	
<b>*Employment status (n=230):</b>					
Employed	91	46 (50.5)	3.36	1.71	0.07
Unemployed	139	52 (37.4)		1.0	
<b>**HIV status (n=244):</b>					
Infected	50	21 (42)	0.0	0.99	1.0
Uninfected	194	82 (42.2)		1.0	
<b>**Previous TB (n=249):</b>					
Yes	73	24 (32.8)	4.05	0.54	<b>0.04</b>
No	176	84 (47.7)		1.0	
<b>***Smear status (n=247):</b>					
Positive	206	90 (43.7)	0.4453	1.34	0.50
Negative	41	15 (36.6)		1.0	

§ n=253 and not 261 due to missing data required for the analysis

\*Employment status excluding pensioners, students and “unknown”

\*\* Excluding “unknown”

\*\*\* Excluding “not done” and “not documented”

#### 4.2.6. Programmatic factors relating to childhood TB and the IPT programme

Table 10 displays the results relating to operational factors affecting the spread of TB to children. The median time from sputum collection to treatment commencement of the index patient was only 5 days (IQR= 5). This incorporates the transport of specimens to the laboratory, the laboratory work, the processing and checking of results and the notification of the clinic of these results. This median time was consistent over the years studied with a slight decrease in 2014.

The median time taken to screen the contacts after the index patient had been started on treatment was 4 days (IQR= 10). With the exception of 2013 which showed a slightly longer median time (5.0), this variable was also consistent over the years. The large IQR for 2011 (52) reflects the presences of 3 outliers in this category. These three patients were started on IPT 53, 113 and 180 days after the index patient initiated treatment. Reasons for these delays were not reported on the IPT cards. The median time taken to start children on IPT after they were screened was two days (IQR= 3) although in 2013 and 2014, it would appear that screening and IPT initiation often happened on the same day.

Table 10. Programmatic factors relating to IPT

	Median (IQR)	Median 2011 (IQR)	Median 2012 (IQR)	Median 2013 (IQR)	Median 2014 (IQR)
Time (days) from sputum collection to commencement of treatment (index patient)	5 (5)	5.0 (5)	5.0 (5)	5.0 (5)	4.0 (7.75)
Time (days) from index patient treatment start to child screening	4 (10)	4.0 (52)	4.0 (11)	5.0 (15)	3.5 (4)
Time (days) from child screening to IPT start	2 (3)	3.0 (3)	2.0 (3)	0 (2)	0 (0)

## **CHAPTER 5: DISCUSSION:**

This study aimed to assess the IPT programme and the operational components of the TB control programme that relate to the reduction of spread of TB to children. This chapter presents a brief synopsis of key findings and elaborates on how they add to the existing body of knowledge. Where possible, it will attempt to put the results into context within a global, national and local level. Mechanisms and explanations for the findings will be provided where feasible and the strengths and limitations of the study will be examined. Recommendations for future action and further research will be discussed in Chapter 6.

### **5.1. Index patient**

#### **5.1.1 Index patient demographics**

Globally the prevalence of TB is higher in men than in women with higher TB-related morbidity being reported in males (WHO, 2014). Similar to national and global TB infection rates, the ratio of male to female patients with TB disease in this study was 1.2:1 (n=265:226). This trend could be attributed to a real difference in epidemiology or reflect differential access to health care facilities or the use of healthcare services (WHO, 2014). In general, men tend to delay seeking care for longer but women experience greater difficulty accessing *appropriate* medical attention (van den Hof et al., 2010). The diagnosis of TB in women is often hindered owing to their presentation with non-TB specific symptoms. The mean age of index patients in this cohort was 36.6 years (SD = 13.4), similar to global trends of young patients in their economically active years being most affected by TB (WHO, 2014).

Unemployment rates in SA are high with 25% of adults between the ages of 15 and 65 years being unemployed in the country between 2011 and 2013 (Health Systems Trust, 2015). The Eastern Cape provincial figures are even higher (28% and 31% for 2011 and 2013 respectively). According to the 2011 population census unemployment in NMBM was 36.6%. (Statistics South Africa, 2015). However, at West End clinic more than half the study population (n=274, 56%) was without work. This discrepancy could relate to the fact that this clinic is located in a low-income area where employment rates are far below those of the high income areas also located within NMBM. Socioeconomic status is important as TB is a disease of poverty which commonly occurs in overcrowded

settings (Yammer, June & Holm-Hansen, 2014). Education levels of the index patient could not be assessed as it is not routinely recorded in the TB clinic folders.

It is of clinical importance to know the HIV status of patients investigated for TB as those who are HIV positive have a greater chance of being smear negative, having poorer outcomes and higher mortality rates (WHO, 2014). The African region has the highest HIV/TB burden in the world. In SA HIV prevalence in newly diagnosed TB cases was 65% in 2012. This is vastly different to the results obtained in this study. Only 19% of patients diagnosed with TB were HIV-infected. This is a true reflection of the situation as 97% of patients were tested for HIV – a figure that matches the Eastern Cape provincial testing coverage but far exceeds both the district (74%) and sub district (80%) test coverage (DoH, 2013). The relatively low HIV-positive rate of the index patients is unlikely to have affected the study results as HIV status was not a significant predictor of child contact documentation, screening or IPT initiation as shown in Tables 7, 8 and 9.

#### **5.1.2. Disease characteristics of index patients:**

##### a) Drug sensitivities:

The global rate of MDR-TB is 3.5% (WHO, 2014). In SA this percentage is not much higher (4.1%) but because of the enormous total number of TB cases, this percentage equates to a significant burden (14 161 MDR-TB cases in 2012) (Njeka, 2014). The situation in the EC is dismal. Of the 2205 cases of MDR-TB diagnosed in the laboratory in 2012, less than half (1062) were initiated on appropriate treatment. The province also had some of the worst outcomes with a mortality rate of 27.7% and a treatment success rate of only 27.8% (Njeka, 2014).

In this study 17 (3.46%) index patients had DR-TB with five being MDR-TB. The number of DR-TB cases included in this study was likely to be an underestimation of the true situation in this area. The reason for this is that those patients who were included in this patient cohort were only those patients who initiated standard treatment at the clinic before being transferred to the local TB specialist hospital to initiate treatment specific to their drug-sensitivity pattern once the results became available. The majority of patients are referred prior to starting treatment at the local clinic and are then only registered on the DR-TB register, which is a separate register. Once patients have been initiated on treatment and are stable, they are transferred back to the clinic to

continue treatment with regular visits to the outpatient services at the TB hospital. It is the responsibility of the clinic, however, to manage the contacts of these patients.

Although the number of DR-TB index cases was small in this sample, the management of the contacts was not optimal. There were missed opportunities for initiating and completing IPT. Moreover, the contacts of these patients were not given higher priority regarding adherence to preventative therapy. Examination of the DR-TB register could give a more accurate assessment of these patients and the management of their contacts.

The relatively high number of cases with unknown drug sensitivity (n=107, 21.8%) was a result of compliance to the previous national TB programme guidelines. Prior to the GeneXpert being rolled out in the clinics (October 2012), the routine management of patients with no previous history of TB involved only microscopy as a baseline diagnostic test (NDoH, 2009). Only those who had previous TB routinely had a sputum culture as well as a smear done prior to commencement of treatment.

This posed two major problems. The first related to the lack of known drug-sensitivities in those patients presenting with TB for the first time. Drug-resistant TB could have been missed at baseline and only diagnosed later because of poor response to routine TB treatment resulting in a delay of initiation of effective treatment. During this time the index patient could have infected many contacts including children. Secondly, the lack of a baseline culture resulted in some patients who may have been smear negative but culture positive not having treatment initiated. Although not as infectious as smear positive patients, smear negative patients still pose a risk of transmission of the disease (Marais et al., 2004). With the introduction of GeneXpert testing more smear negative cases are being picked up as shown by the results in this study. This is especially important in HIV positive patients who are more likely to have smear negative disease (WHO, 2014).

b). Transmission risk:

Providing effective treatment and reducing mortality are important components of a TB control programme. However, in areas with high TB incidence, reducing transmission from infectious TB cases also needs to be a priority (Narasimhan et al., 2013). The risk of infection following exposure is largely governed by a combination of the infectiousness of the source case, the duration of and proximity to the contact and a

range of social and behavioural factors including overcrowding, tobacco smoke and internal air pollution.

The infectiousness of the source case correlates with the bacillary load in the sputum (Narasimhan et al., 2013). Thus smear positive cases are more infectious than smear negative cases (Marais et al., 2004; Narasimhan et al., 2013) and an untreated smear positive case can infect up to 10 individuals per year (Narasimhan et al., 2013).

Adherence to national protocols was excellent with 98% of patients having a documented smear result. The results obtained from this study showed an extremely high smear positive rate of 78.2% (n=384) far greater than that of South Africa (39%) and the Eastern Cape (42%) in 2012 (Health Systems Trust, 2015). This high rate of infectiousness is concerning when considering measures to reduce transmission of TB to vulnerable populations such as children. The above-average smear positivity rate may reflect late presentation of index patients to the clinic resulting in contacts being exposed to TB for longer durations.

#### c). Retreatment TB:

Nearly 30% of patients included in this study had previous TB. The details of these cases including the time between the previous and current episodes and the outcome of the previous episode(s) was not part of the data collection tool, so definite extrapolations could not be made. This figure is in keeping with the previously reported range of 10-30% of recurrent TB within some weaker tuberculosis control programmes (Chaisson & Churchyard, 2010). Reasons for this high rate could be two-fold. Firstly, it has been shown that in HIV-negative patients (such as the majority of cases at the West End Clinic), retreatment TB is predominantly associated with reactivation of disease after poor initial treatment outcome. This contrasts with HIV-infected individuals who are predominantly re-infected (Middelkoop et al., 2012). Secondly, it could be related to the factors mentioned previously, namely the high burden of infectious TB cases in the community who present late in the disease, making the risk of reinfection extremely high in both the HIV-infected and uninfected population.

Relating the above figures to the index patient treatment outcomes supports the argument that suboptimal initial treatment outcomes in this setting may contribute to the high rate of retreatment cases. The global treatment success rate in 2012 estimated by WHO (2014) was 86% but South Africa is well below this with numbers ranging

between 76-79% (WHO, 2014; Health Systems Trust, 2015; Massyn et al., 2014). More concerning are the statistics found in the Nelson Mandela Bay Health district Health Plan 2013/2014. Treatment success rates (TSR) for the district and specifically for sub district C were 68% and 58% respectively. Compared to these, West End clinic performed well with a treatment success rate of 73% (n=350). It is worth noting that almost 10% of patients were either transferred to another facility or had unknown outcomes, however the defaulter rates compared to the national average were high (national = 6%, study =11%). There is much work to be done to reach provincial targets of an 80% TSR and a 7% defaulter rate for 2013/2014 (DoH, 2014).

There were 110 patients excluded from the analysis who had either extrapulmonary or no microbiological confirmation of TB. Those without a documented microbiological diagnosis were most likely empiric diagnoses which by definition would be bacteriologically negative and more likely to be HIV positive (Lawn et al, 2011). This may explain some of the differences between the documented rates of HIV positive patients in the clinic compared to national records (19% vs 65%) and in the smear positive percentages (78,2% vs 39%). However the high rates of patients who are HIV negative, smear positive and are TB retreatment cases are all concerning in that they reflect high risk cases for community transmission. Together with the high defaulter rates and poor treatment outcomes the results reflect the TB control programmes inability, as implemented in this clinic, to sufficiently impact on community based transmission through the lack of intensive case finding and defaulter tracing.

## **5.2. Contact information**

### **5.2.1. Contact documentation**

Contact identification was well reported in index patient folders. Only 12.5% of patient folders had no documentation of contacts. A total of 261 child contacts < 5 years were identified from 491 adult folders giving a mean of 0.53 (SD=0.8) child contacts < 5 years per index case. Earlier studies in Cape Town have documented 0.7-1.3 child contacts < 5 years per infectious TB case (Osman, et al., 2013 and Marais, et al., 2006). The lower number was observed in a retrospective study of routinely collected data in primary healthcare clinics across Cape Town, a study with similar design to this one (Osman, et al., 2013); whereas the higher number was obtained in a prospective study using home visits and active contact tracing (Marais et al., 2006). West End clinic relies

on passive contact tracing. Index patients are requested to bring their contacts to the clinic for screening; they are not actively traced by a healthcare worker.

The NDoH TB guidelines (2014) make a clear distinction between a contact and a household contact with definitions below:

**Contact** - Any person who has been exposed to an index patient

**Household contact** - A person who shared the same enclosed living space for at least eight continuous hours or for frequent prolonged periods with the index case during the 3 months before commencement of the current treatment episode.

The importance of this relates to the risk of transmission of disease from the index case with household contacts being at greater risk. In child contacts <5 years of age this is especially important as contact between a caregiver and child is usually close and prolonged, placing the child at high risk of acquiring TB. Up to 75% of the total annual risk of infection of pre-school children results from infectious household residents (Wood et al., 2010) highlighting the need to identify these high risk children.

The results of this study show that documentation of the relationship of the index patient to the child was poor making risk stratification for the child difficult. 65% of child contacts <5 years of age identified did not have any documentation of this. This could be partly explained by the lack of space for such information on the index patient folder and on the IPT card.

Looking at the mean number of contacts identified over time it is evident that although the mean value of the total number of contacts (those <5years and >5years) remained constant at around 3.6, the number of child contacts <5 years of age per index patient decreased significantly from a high of 0.62 in 2012 to 0.45 and 0.47 in 2013 and 2014 ( $p=0.02$ ) respectively. It may be of relevance to note that TB and HIV services were merged in the clinic at the beginning of 2013 (Personal correspondence with Sr. Sookdin, Facility manager, 17 June 2014). Prior to this there was a dedicated TB room with staff who dealt solely with TB and patient clinical records that related to TB only. After integration the location of the TB services was physically moved to the other side of the clinic and the staff complement was amalgamated with the HIV staff into one service. This resulted in fragmentation in the storage of patient folders and, according to an informal interview with one of the lay counsellors, less time to focus on TB cases as

her time was now divided between HIV and TB (Personal correspondence with Sharon Warmington, Lay counsellor, 17 September 2014).

It is important to view the issues surrounding documentation and patient management in light of the difficulties faced by the clinic staff. Although there was no change in the actual number of staff over the study period, the merge of HIV/TB services has led to these staff members also managing HIV in those who are dually infected. Initially, this could have negatively impacted on recordkeeping and defaulter and contact tracing while staff adjusted to the logistics and work load of the new system. WHO calls for national programmes to implement and scale-up integrated TB/HIV services to provide better care for those patients that are dually infected and to achieve more favourable treatment outcomes (WHO, 2012). Integration of HIV and TB services has been shown to be beneficial to both patient outcome and health delivery costs (Schultz, Draper & Naidoo, 2013; Uyei et al., 2011). This dip in the mean number of contacts <5 years documented could be explained by initial “teething problems” experienced during the change in services.

### **5.2.2. Screening of child contacts <5 years**

The next step in the IPT process, following the identification of contacts, is the screening of contacts to exclude active disease prior to starting IPT. Of the 255 contacts included in the analysis, 72% (n=184) was screened using one or more of the following: symptom screen, TST, chest X-ray, gastric washing or sputum and referral for further management. This compares favourably with results from studies conducted in Cape Town. Osman et al. (2013) showed 46% of identified contacts were screened and van Wyk et al., 2010 and 2011 demonstrated even more shocking results - 21% (n=5/24) and 2%(n= 4/149) respectively. Although this clinic performed better than previous studies, the opportunity to screen young children was missed in more than a quarter of child contacts < 5 years identified. This relates to the problem of passive case finding. The responsibility rests on the index patient to bring the child to the clinic or to convince the child’s caregiver to take the child for screening.

#### **a). Screening methods:**

Of those contacts < 5 years who were screened, the majority (79%) were screened using a TST. Of those screened using a TST, almost half (48%) had no documentation of a symptom screen. This practice does not follow the SANTCP screening protocol in

either the 2009 or 2013 guidelines. These guidelines state that a symptom screen should be done first and only if positive, should further investigations be performed. There are many reasons that TST's may negatively impact the screening process. These include: the extra time required to perform the test and read the result, it could place an unnecessary burden on an already over-extended workforce, the delay in screening if the tuberculin protein is out of stock, the possibility of incorrect administration of the tuberculin protein or the risk of inaccurate interpretation of the results, unnecessary pain for the child and increased time delay as the test should be read 48-72 hours after administration. This time delay between administration and reading the result is a possible point of default as it requires parents' time and money to return to the clinic. All these are important factors to consider when exploring barriers or perceived barriers to screening child contacts <5 years.

WHO (2006) recommended that the lack of available resources to perform a TST and chest X-ray should not preclude contact screening and management as a simple clinical assessment is adequate. The symptom-based approach was evaluated by Triasih et al, (2015) in a large study in Indonesia. They concluded that this approach is an effective strategy in the screening and management of child contacts and that the lack of TST and chest X-ray should not be a barrier to child contact screening and management. Although flawed in some respects, especially in the lack of comparison between the microbiological evaluation and symptom-based screening approach of all subjects to get a better sense of the extent of TB disease at baseline, the study came to a useful conclusion (Jeena, 2015). Jeena (2015) proposed that screening using sputum GeneXpert may have a major impact on the tuberculosis control programme and would be cost-effective. In the EC, as in many other primary care clinics across the country, it is unlikely that the current staff complement could successfully screen children using this method due to lack of time and facilities.

In keeping with WHO (2006) recommendations, the NDoH (2013) included a symptom screening tool in the latest version of the childhood TB treatment guidelines. If implemented and used correctly, it will be most useful to streamline contact screening and could possibly be used in research projects to evaluate its usefulness in the South African context. In the current system, there is very little space on the index patient folder to record contact symptom screening.

### 5.2.3. IPT initiation

Of the 184 children who were screened 59% (n=108) were documented as having started prevention therapy, two started full TB treatment and for the remaining 40% (n=74) of children there was no documentation of further management or follow-up. These 74 children represent missed opportunities for providing TB preventative therapy in a community where TB is rife. From the existing study design it was not possible to determine whether the caregivers of these children were offered IPT and declined or whether IPT was never prescribed. Caregiver perception that a well-child does not need medication interfered with IPT provision in previous studies (Marais et al., 2006; Garie, Yassin & Cuevas, 2011; Rutherford et al., 2010).

Furthermore, the fall-out of contacts <5 years could relate to the screening methods used. A TST was used for screening in the majority of screened contacts. This requires that the child returns to the clinic 48-72 hours later for the result to be read (NDoH, 2013). Other authors have described the negative impact of high transport costs on IPT initiation (Zachariah et al., 2003; Rutherford et al., 2010) and this may be applicable in this setting due to extra clinic appointments. Other possible explanations for missing documentation in these contacts include: IPT was not prescribed due to poor staff knowledge, the contacts may have been started on TB treatment but record of them was not found during the search procedure or they might have been started on IPT without documentation on an IPT card or the IPT card was not located.

There were 74 IPT cards that were found for children starting preventative therapy. This represents 69% of those who were started on preventative therapy and 40% of the total number who were screened. IPT cards were found for nine children who were started on IPT that were either older than 5 years of age or who were contacts of non-bacteriologically confirmed pulmonary or extrapulmonary TB index cases. This showed a deviation from protocol which states that only contacts of index patients with **bacteriologically confirmed pulmonary** TB who are **under** 5 years of age are eligible for IPT. Children older than 5 years of age are eligible if they are HIV infected (NDoH 2009; NDoH, 2013). There was no documentation of the HIV status for the children over 5 years of age mentioned above. Also, there were seven cards which had poor or no documentation of the index patient's name precluding the assessment of these contacts.

The number of IPT cards found may be an under-representation of the actual number of existing cards as there were a number of issues experienced during the data collection from the IPT cards. Firstly, the filing system was inefficient and not user-friendly mostly due to a lack of accessible filing space in the clinic. Cards from contacts that were started on IPT prior to 2013 were either filed in the index patients folders which were kept in the archive room or put into an unlabelled pile on a shelf in a room which was also a store room for broken furniture which made it extremely difficult to search for files. Cards of contacts that were started on IPT in 2013 were filed in a single, poorly labelled folder in a cupboard close to the TB room. Those who started IPT in 2014 had cards that were in the paediatric file inside the TB room. It is very likely that some contacts may have had cards but that these could not be located during the search.

Secondly, it was sometimes difficult to link the IPT card with the index patient. Seven cards were found that did not have index patient names and could not be matched to any contact that was recorded in the index patient folders. Thus these contacts were excluded from the analysis. The cards do not have a specific space for the index patient TB register number which also would have been a useful way of linking the two patients.

Other concerns relating to these cards include the lack of dedicated space for documentation of the index patients' drug sensitivities. This is important information to know as it may change the drugs required for prevention. For example, the SANTCP 2013 guidelines recommend that if the index patient is resistant to INH then Rifampicin should be used for four months instead of INH for six months for preventative therapy. The management of contacts of MDR-TB patients is controversial. Young children and those with HIV infection are at especially high risk of developing disease after exposure (Schaaf & Marais, 2011). WHO does not recommend the use of second-line drugs in child contacts of MDR-TB patients (WHO, 2006) and this is reiterated in the South African guidelines (2013). However, in other settings, successful treatment of latent TB infection has been documented with the use of a tailored drug regime using two or three drugs based on the sensitivities of the index patient (Schaaf & Marais, 2011). Given the discrepancies in evidence, it may be better for child contacts < 5 years of age of MDR-TB index patients to be referred for expert assessment and initial management. The clinic could then continue management and liaise with the specialist should any queries arise.

Of great concern is the lack of dedicated space to record the HIV status of the child contacts. All HIV-infected children regardless of age should be given IPT after exposure to a known bacteriologically confirmed pulmonary TB case (Cotton, 2011, Schaaf et al., 2013, NDoH, 2013). Given that HIV-infected children are at extremely high risk of developing TB disease (Hessling et al., 2009), a higher level of suspicion is required when managing these children, especially those who have a known TB exposure. A positive HIV status should alert the clinician to pay extra attention to signs and symptoms at follow-up visits. HIV status was not recorded on any IPT card examined.

Additionally, there was no routine documentation of symptom checks or repeat weight checks at subsequent visits to collect IPT. The importance of this is two-fold. Firstly to pick up any child who may have developed TB disease (Triasih et al., 2015; NDoH, 2013) and secondly to increase the dose of INH according to the increasing weight of the child so that an effective dose is maintained throughout the course. Side effects of IPT were never documented on the IPT cards that were examined. Although many studies have shown very few side effects in patients taking INH and little significant impact of side effects on patient adherence (Gomes et al., 2011, Marais et al., 2006, Rutherford et al., 2012, Banu Rekha et al., 2013), Pang et al. (1998) attributed the success of the IPT programme in Australia to the identification and management of side effects to INH even if they were minor. Addressing side effects, regardless of how minor they may be, and re-assuring caregivers may improve retention of contacts taking IPT in this setting too.

#### **5.2.4. Retention of child contacts on IPT and course completion**

It is recommended by WHO that a 6-month course of INH be used to prevent TB in child contacts <5 years of age (WHO, 2006) and this is also the NDoH guideline (2009 & 2013). However, practically, this has been shown to be difficult to translate into practice with adherence rates being extremely poor (Van Zyl et al., 2006; Marais et al., 2006; Osman et al., 2013). Results of this study are similar. The median number of weeks of IPT collected by contacts was 8 (IQR=11.25).

The number of weeks of IPT collected by contacts over the years follows a similar pattern to the number of child contacts <5 years identified over the years with a statistically significant drop in the median from a high of 14 weeks in 2011 to 5.0 and 4 weeks in 2013 and 2014 respectively. This study only included the first two months of

2014 so this may not be a true representation of the year as a whole. A possible explanation for this may, once again relate to the merge of TB and HIV services and the initial “teething problems” that might have been experienced.

Discharge notes were recorded on only 10% of cards and a mere 4 (3.7%) contacts completed the course (defined as 24 weeks or more). The discrepancy between the above figures relates to the definition of “course completion” used in this study. Some contacts completed 6 months of treatment according to time but had fewer than 24 weeks of INH collected due to periods of missed doses during the 6 months that were never “caught up”. These missing doses may have resulted from poor patient compliance or from INH being out of stock (personal communication, Sr Geswint, TB nurse, 3 February 2015). The reasons were not recorded in the contacts’ notes.

The literature identifies many possible reasons for poor IPT compliance. These include health system-related factors such as resource constraints (Hawkridge, 2007; Garie, Yassin & Cuevas, 2011), poor healthcare worker knowledge of the subject and lack of importance placed on IPT (Banu Rekha et al., 2013; Van Wyk et al., 2011; Hawkridge, 2007; Graham, 2011) and the absence of a standardised IPT monitoring tool (Banu Rekha et al., 2013; Van Wyk et al., 2011; Van Wyk et al., 2010; Osman et al., 2013; Du Preez et al., 2011; Hawkridge, 2007).

All of these could contribute to the poor outcome of child contacts <5 years in this setting. The high number of vacant posts in NMBHM indicates a lack of human resources (DoH, 2013) while occasional stock-out of INH and purified protein derivative (PPD) used for TST’s have hindered contact screening and IPT prescriptions in the past (personal communication with Sr Geswint, TB nurse, 3 February 2015). The evidence of deviation from national protocols suggests that more training of health care workers is needed and the need for a monitoring tool is clear from the poor documentation of investigations and the high number of contacts that are lost to follow-up.

Patient-related factors that also might play a role include the time and money required for caregivers to bring their children to the clinic (Zachariah et al., 2003; Rutherford et al., 2010), community perceptions that well children do not require medication (Marais et al., 2006, Garie, Yassin & Cuevas , 2011; Rutherford et al., 2010) and population migration within and between health districts resulting in children discontinuing therapy (Gomes et al., 2011).

Compliance to shorter courses of TB prevention therapy has been studied with consistent outcomes (van Zyl et al., 2006; Spyridis et al., 2007; Sharma et al 2013). Adherence to 3 or 4 month courses of INH/RIF or Rifampicin alone is significantly better. Correlating this study's results with the literature shows that had the TB prevention course been 12 weeks rather than 24, 40% (n=43) of contacts would have completed it compared with 4% (n=4). This is important information when contemplating strategies to improve the TB prevention programme outcomes.

#### **5.2.5. Index patient demographics and disease characteristics associated with child contact management:**

Literature relating index patient demographics and child contact management is lacking. Osman et al. (2013) found that younger, female, HIV-negative and new smear positive patients were more likely to have contacts documented but the associations between these factors and contact screening and IPT initiation have not been explored. In this study there was no statistical association between HIV status, smear status and employment status and contact documentation and management. Smear status is the important variable here as smear positive index patients have a higher chance of transmission of the disease (Marais et al., 2004) and thus contacts of these patients should be more urgently sought and diligently managed.

In keeping with the above finding, female index patients in this study were also more likely to report child contacts < 5 years and were more compliant at bringing them for screening. This may relate to the differences in gender help-seeking behaviours between men and women. Women take longer to access appropriate care but once on treatment; are more likely to complete it, whereas men tend to default treatment more often and have worse treatment outcomes (van den Hof et al., 2010). Relating this to contact management may mean that women are more prone to comply with health provider advice and follow the instructions to bring their child for screening. Unfortunately, the number of children completing the IPT course was too small to assess whether this relationship extended to the completion of IPT as well.

Previous TB was a significant risk factor for contacts <5 years not being screened and not being initiated on IPT. Caregivers' experience of the healthcare system and their knowledge regarding TB has been shown to affect child contact adherence to IPT (Rutherford et al., 2012). The more positive their experience and the better their knowledge, the more compliant their contacts were to IPT. Patients with previous

episodes of TB may have defaulted their medication due to unpleasant experiences of the healthcare system which could translate in their child contacts <5 years of age being adversely affected. It has been shown that TB treatment defaulters have poor knowledge of *their* disease (Tachfouti et al., 2012) and this may equate to little understanding of the need for medication in their well-child which is a well-described barrier to providing IPT to children (Marais et al., 2006; Garie, Yassin & Cuevas, 2011; Rutherford et al., 2010).

### **5.3. Programmatic factors relating to the control of childhood TB and IPT**

Reducing the time period of infectiousness of the index patient has a direct impact on the prevalence of infectious TB (Wood et al., 2011). An increase in this period is a result of delays in health seeking behaviour, availability of laboratory results and initiation of effective treatment for those with active TB (Wood et al., 2011) and may cause severe illness in the individual and high transmission rates in the community (Yimer, Bjune & Holm-Hansen, 2014). The mean time taken for an index case to be started on TB treatment from the time of the first sputum collection at this clinic was almost 8 days. However, there was a large standard deviation (14.5) due to a small number of outliers who had unique reasons for the delay. These reasons included patients that were investigated and initiated treatment elsewhere; some patients were smear negative and culture positive and thus had to wait for the culture result prior to initiating therapy, which can take up to 6 weeks. One patient refused to come to the clinic to start treatment despite numerous home visits. Thus the median value (5 days) may be of more use when reporting on this particular variable.

Comparing this figure with similar figures in the literature was a challenge as each study or review article had different definitions that were used to define patient factor delays, health system delays and total delays (Sreeramareddy et al., 2014; Yimer, Bjune & Holm-Hansen, 2014; Storla, Yimer & Bjune, 2008). Although relevant to the transmission of TB to child contacts, patient delays were not studied in this research project. It is evident from a previous study that longer delays are associated with higher bacillary load on sputum smear (Storla, Yimer & Bjune, 2008). This study population demonstrated a high percentage of smear positive index patients indicating significant delay somewhere along the cascade. The median time from sputum collection to treatment initiation was only 5 days making it more likely that it is patient-related

factors causing the delay or repeated health facility visits prior to the diagnosis of TB being made.

What is of interest was the consistency in this time to treatment across the years included in the study. There was very little change in the mean despite the introduction of the GeneXpert (in October 2012) and its rapid turnaround time compared to culture. An explanation for this could be that most patients are positive on smear microscopy which is a quick test with a turnaround time of less than 2 days (NDoH, 2014). Thus the addition of the GeneXpert has made less of an impact than it would have in a setting with more smear negative, culture positive patients such as a clinic with a high HIV infection rate where patients wait weeks for culture results.

The time from the index patients' treatment start date to the contact being screened showed great variability because of a number of outliers (mean=16.53, SD=37.3 days). These contacts were screened many months after the index patient was started on treatment but no explanations were recorded in the clinic notes. The median of four days (IQR=10) is a better reflection of the actual situation. While the median time from screening to start of IPT was a mere two days (IQR=3), almost 80 contacts were lost at this stage. Improvement may be possible if the screening protocol is followed closely and a symptom screen is done instead of a TST as a baseline test. In doing so, contacts could start IPT on the same day that they are screened thereby improving IPT initiation rates. It would seem that protocols were followed better in 2013 and 2014 as the median time to IPT start from screening was 0 days compared to two and three days in 2012 and 2011 respectively.

#### **5.4. Strengths of this study**

One of the major strengths of this study was the relatively long time frame that it spanned. Programmatically there were several changes, both in the functioning of the clinic as well as in national protocol. This allowed a comparison in outcomes from before the GeneXpert was used and after it was introduced into the diagnostic guidelines. Also, the HIV/TB services in the clinic were amalgamated at the beginning of 2013 which made data analysis before and after the merge possible.

The data collected in this study focused not only on the child contact information, but also on the index patient disease characteristics and the programmatic issues that relate to the management of the index patients and contacts. These are important factors as

they are all interdependent and play pivotal roles in understanding the strengths and pitfalls of the TB control programme in this area.

This retrospective descriptive, cross-sectional study was able to give a good representation of routinely collected data. By plotting these results on a graph (Graph 1), a visual account of the fall out of contacts along each step of the management algorithm was produced. This information can be used to tackle specific areas of need and further investigate the difficulties in providing an efficient IPT service at this clinic.

#### **5.5. Limitations of this study:**

- The study relied on data collected from patient files. As with all record reviews, a major limitation is missing information (Gearing et al., 2006). Due to the nature of medical notes it cannot be assumed that because something was not documented, it was not done. Thus, in this study if there was no record of it, it was recorded as “unknown”. This may have affected the results as information may have been collected but not recorded in clinical notes and was thus recorded as “unknown” for study purposes. Data may also have been under-recorded due to the inability to find index patient records and IPT cards during the search procedure.
- The study only took into account those patients who were started on TB treatment. It did not account for those patients who were diagnosed with TB but never returned to the clinic for treatment initiation or those who were diagnosed in hospital and transferred to the clinic but defaulted. Contacts of these patients are at particular risk as they have never been identified by the health system and are thus unaware of their risk of acquiring TB.
- The cohort of DR-TB index patients was small and, as previously mentioned, probably not a true representation of the actual situation in the clinic. Results relating to the management of contacts of these patients should be treated with caution and further investigation is required.
- This study was conducted at a single primary care clinic in NMBHD with a specific socioeconomic profile. Results cannot be generalised to other clinics in the NMBHD.
- The study design did not allow for the assessment of the uptake of IPT by caregivers. Caregivers’ refusal of medication may pose a difficult barrier to overcome. A longitudinal study design would have allowed for this assessment.

In addition, it would have given a more accurate account of the outcome of contacts.

## **CHAPTER 6: CONCLUSION AND RECOMMENDATIONS**

### **6.1 Conclusion:**

In conclusion, this study highlights the failure of certain aspects of the IPT programme at West End clinic. The tracing of child contacts <5 years in this setting was suboptimal with fewer child contacts being identified per adult index case than in previously published studies. Although still inadequate, compared to previous studies, this clinic's contact *screening* and IPT initiation rates are better than expected. However, retention of child contacts <5 years on IPT is inadequate with a significant fallout of children at various time points from identification to treatment completion and very few contacts completing the course. The findings emphasise the fact that documentation is poor and protocols are not always closely followed. Operational challenges such as a poorly designed IPT card and a disorganised filing system may contribute to these downfalls, although staff and patient-related factors are also likely to play a role. Child contacts <5 years of index patients who are male or retreatment cases are at higher risk of poor management and should be targeted for more attentive management.

Programmatic data reveal that time to treatment and time to IPT initiation is short. However, of particular concern, is the high proportion of smear positive cases, the high rate of retreatment TB and the relatively elevated defaulter rate. These imply late presentation, high transmission rates and poor treatment adherence all of which can negatively impact on the control of childhood TB.

### **6.2. Recommendations:**

#### **National level:**

- The index patient TB cards should be remodelled to allow for adequate space to record information regarding contacts, their relationship to the index patient, symptom screening results and whether further investigations are required. Tick box systems are quick and easy to use and offer a reminder of what needs to be done.
- Shorter courses of TB preventative therapy have been shown to be as effective and have better adherence (van Zyl, et al., 2006; Spyridis, et al., 2007; Sharma et al., 2013). The possibility of using a three month course should be further explored.

- A standardised IPT register should be instituted. This will improve the filing system for contacts on IPT and assist with routinely recorded information. The limitations on the current IPT cards mentioned previously could be remedied and once again, tick boxes could be used to improve data recording thereby saving time.
- The use of IPT patient cards that are given to the child similar to the HAART cards used in HIV-infected patients has been suggested by WHO. These may be useful in this setting because they could facilitate good continuity of care and the easy transfer of contacts from one healthcare centre to another, if necessary. It may be possible for community health workers to use these cards in conjunction with the IPT register to assist in monitoring child contacts in the community and delivering medication to their homes. This may have positive impacts on compliance rates as it would reduce time and money spent by the caregivers to bring their children to the clinic each month.

**Provincial and community level:**

- By reducing the infectious period between onset of symptoms and start of treatment, the risk of transmission to contacts could be reduced. Thus, the community should be made aware of the benefits to themselves and the community of early presentation to healthcare facilities. This education can be done in the form of posters and fliers, local radio adverts and the use of any contact with the health services to educate and screen adults and children.
- To address the pitfalls of passive contact tracing, a community healthcare worker should be assigned to actively trace contacts and provide caregiver education. This may increase the number of contacts identified and the number of children brought for screening.
- Staff training and regular refresher courses should be organised for all clinic staff, not only those working in the TB room. Protocols should be clearly visible in the TB room as a reminder to staff. Supervision by senior trained staff is important to support junior staff members.
- Routine audits of a few pertinent indicators should occur at regular intervals to assess progress. These audits could coincide with quarterly reports (such as number of new cases, cure rates, defaulters) already requested by the DoH. Indicators relating to IPT could include total number of child contacts screened

and the proportion started on IPT. These figures could be included in annual reports as well as the proportion of child contacts that was initiated on IPT and completed the course. By requesting staff to present a formal report on these indicators, more focus may be placed on contact tracing during routine patient management and record-keeping.

- Index patient categories that have been shown to be of greater risk of poor contact documentation or follow-up should be earmarked for more attentive consultations and in-depth counselling regarding their disease and the risk it poses to their contacts.
- The development and distribution of a caregiver information sheet in their home language and using simple, lay terms may be helpful. This would give the caregiver written information regarding the need for IPT, the common side effects and how to react and how best to administer the medication. By addressing caregivers' concerns at the time of screening and initiation of IPT, retention of children on IPT may be enhanced. This counselling could be done by a trained lay counsellor.
- It might be useful to appoint one person to take charge of child contacts. This could even be a lay counsellor who can be trained and tasked with the job of monitoring contacts' visits, tracing defaulters and reducing fallout along from identification to treatment completion.
- The auditing of a wider range of indicators is required in order to assess the impact of the merge of HIV/TB services in the EC setting. The dip in IPT-related outcomes may be due to initial 'teething problems' relating to the change in services and it would be of interest to examine the data from 2014 to see if these indicators are on the rise again
- A study into the management of contacts of DR-TB should be undertaken.
- More in-depth qualitative research should be conducted to understand the barriers or perceived barriers relating to patient, healthcare worker and operational challenges that hinder the delivery of IPT to children.

## **REFERENCES:**

1. Ait-Khaled, N., Alarcon, E., Bissell, K., Boillot, F., et al. 2009. Isoniazid preventive therapy for people living with HIV: public health challenges and implementation issues. *International Journal of Tuberculosis and Lung Disease*, 13(8), pp. 927–935.
2. Ayieko, J., Abuogi, L., Simchowitz, B., Bukusi, E.A., Smith, A.H., Reingold, A. 2014. Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: a meta-analysis. *BMC Infectious Diseases*, 14 (91), pp.1-10.
3. Balcells, M.E., Thomas, S., Godfrey-Faussett, P., Grant, A., 2006. Isoniazid Preventive Therapy and Risk for Resistant Tuberculosis. *Emerging Infectious Diseases*, 12 (5), pp. 744-751.
4. Banu Rekha, V.V., Jagarajamma, K., Wares,F., Chandrasekaran, V., Swaminathan, S., 2009. Contact screening and chemoprophylaxis in India's Revised Tuberculosis Control Programme: a situational analysis. *International Journal of Tuberculosis and Lung Disease*, 13 (12), pp. 1507-1512.
5. Banu Rekha,V.V., Jagarajamma, K., Chandrasekaran, V., Wares, F., Sivanandham, R., Swaminathan, S., 2013. Improving screening and chemoprophylaxis among child contacts in India's RNTCP: a pilot study. *International Journal of Tuberculosis and Lung Disease*, 17(2), pp. 163–168.
6. Carlson, M.D. A. , Morrison, R.S., 2009. Study Design, Precision, and Validity in Observational Studies. *Journal of Palliative Medicine*, 12(1), pp. 77-82.
7. Chaisson, R.E. and Churchyard, G.J., 2010. Recurrent Tuberculosis: Relapse, Reinfection, and HIV. *Journal of Infectious Diseases*, 201, pp.653–655.
8. Claremont Graduate University. 2015. *History of Ethics* [online]. Available at: <<http://www.cgu.edu/pages/1722.asp>> [Accessed on 10 February 2015].
9. Codecasa, L.R., Besozzi, G., 1998. Acceptance of Isoniazid Preventative treatment by close contacts of tuberculosis patients – a 692-subject Italian

- study. *International Journal of Tuberculosis and Lung Disease*, 2(3), pp.208-212.
10. Cotton, M., 2011. INH preventive therapy (IPT) in HIV-infected South African Children. *The South African Journal of HIV Medicine*, June 2011, pp. 27-30.
  11. Cranswick, N., Mulholland, K., 2005. Isoniazid treatment of children: can genetics help guide treatment? *Archives in Childhood Disease*, 90, pp. 551-553.
  12. Department of Health, Eastern Cape (DoH). 2013. Nelson Mandela Bay Metro District Health Plan 2013/14-2015/16. Personal correspondence with Ms Betty Ncanywa, TB Directorate, Nelson Mandela Bay health district, 01 February 2014.
  13. Department of Health, Republic of South Africa (NDoH). 2006. Guidelines for Good Clinical Practice in the Conduct of Clinical Trials with Human Participants in South Africa. Department of Health: Pretoria, South Africa.
  14. Department of Health, Republic of South Africa. 2009. National Tuberculosis Management Guidelines 2009. Department of Health: Pretoria, South Africa.
  15. Department of Health, Republic of South Africa. 2013. Guidelines for the Management of Tuberculosis in children 2013. Department of Health: Pretoria, South Africa.
  16. Department of Health, Republic of South Africa. 2014. National Tuberculosis Management Guidelines 2014. Department of Health: Pretoria, South Africa.
  17. Donald, P.R., Maher, D., Qazi, S., 2007. A research agenda to promote the management of childhood tuberculosis within national tuberculosis programmes. *International Journal of Tuberculosis and Lung Disease*, 11(4), pp. 370–380.
  18. Dookie, S., Singh, S., 2012. Primary health services at district level in South Africa: a critique of the primary health care approach [online]. *BMC Family Practice*, 13(67). Available at: <http://www.biomedcentral.com/1471-2296/13/67> [Accessed 3 February 2015].

19. Du Preez, K., Hessling, A., Mandalakas, A., Marais, B., Schaaf, H., 2011. Opportunities for chemo-prophylaxis in children with culture-confirmed tuberculosis. *Annals of Tropical Paediatrics*, 31, pp.301-310.
20. Frigati, L.J., Kranzer, K., Cotton, M.F., Schaaf, H.S., Lombard, C.J., Zar, H.J. 2011. The impact of isoniazid preventive therapy and antiretroviral therapy on tuberculosis in children infected with HIV in a high tuberculosis incidence setting. *Thorax*, 66, pp. 496-501.
21. Garie K.T., Yassin M.A., Cuevas L.E., 2011. Lack of Adherence to Isoniazid Chemoprophylaxis in Children in Contact with Adults with Tuberculosis in Southern Ethiopia. *PLoS ONE*, 6(11): e26452.  
doi:10.1371/journal.pone.0026452
22. Gearing, R.E., Mian, I.A., Barber, J., Ickowicz, A., 2006. A Methodology for Conducting Retrospective Chart Review Research in Child and Adolescent Psychiatry. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, Aug (15), pp.126-134.
23. Getahun, H., Granich, R., Sculier, D., Gunneberga, C., Blanca, L., Nunna, P., Raviglione, M., 2010. Implementation of isoniazid preventive therapy for people living with HIV worldwide: barriers and solutions. *AIDS*, 24(suppl 5), pp. S57–S65.
24. Gomes, V.F., Wejse, C., Oliveira, I., Andersen, A., Vieira, F. J., Carlos, L.J., Vieira, C.S., Aaby, P., Gustafson, P., 2011. Adherence to isoniazid preventive therapy in children exposed to tuberculosis: a prospective study from Guinea-Bissau. *International Journal of Tuberculosis and Lung Disease*, 15(12), pp.1637-1642.
25. Graham, S., 2011. Missed opportunities for prevention of tuberculosis in children. *Annals of Tropical Paediatrics*, 31, pp.297-299.
26. Graham S.M., Triasih, R., 2013. More Evidence to Support Screening of Child Contacts of Tuberculosis Cases: If Not Now, Then When?. *Clinical Infectious Diseases*, 57 (12), pp.1693–1694.
27. Graham, S.M., Sismanidis, C., Menzies, H.J., Marais, B.J., Detjen, A.K., Black, R.E., 2014. Importance of tuberculosis control to address child

- survival. *Lancet*, 383, pp.1605–1607.
28. Harrison, D., 2009. *An Overview of Health and Health care in South Africa 1994 – 2010: Priorities, Progress and Prospects for New Gains*. [online] Available at: <<ftp.bhfglobal.com/files/bhf/overview1994-2010.pdf>> [Accessed 20 January 2015].
29. Hawkrigde, T., 2007. Tuberculosis contacts and prophylaxis. *South African Medical Journal*, 97(10), pp.998-1000.
30. Hesseling, A.C., Cotton, M.F., Jennings, T., Whitelaw, A., Johnson, L.F., Eley, B., Roux, P., Godfrey-Faussett, P. and Schaaf, H.S., 2009. High Incidence of Tuberculosis among HIV-Infected Infants: Evidence from a South African Population-Based Study Highlights the Need for Improved Tuberculosis Control Strategies. *Clinical Infectious Diseases*, 48, pp. 108-114.
31. Health systems Trust, 2015, Health Indicators. [online] Available at: <<http://indicators.hst.org.za/healthstats/25/data>> [Accessed 4 January 2015].
32. Hill, PC., Rutherford, ME., Audas, R., van Crevel, R. & Graham, SM. 2011, Closing the Policy-Practice Gap in the Management of Child Contacts of Tuberculosis Cases in Developing Countries', *PLoS Med*, 8(10), pp. e1001105. doi:10.1371/journal.pmed.1001105
33. Howell, J., Miller, P., Park, H.H., Sattler, D., et al. 2012. Reliability and Validity [online]. *Writing@CSU. Colorado State University*. Available at <<http://writing.colostate.edu/guides/guide.cfm?guideid=66>> [Accessed 1 February 2015].
34. Jaganath, D., Zalwango, S., Okware, B., Nsereko, M. et al., 2013, Contact Investigation for Active Tuberculosis Among Child Contacts in Uganda. *Clinical Infectious Diseases*, 57(12), pp.1685–1692.
35. Jeena, P.M., 2015. Editorial Commentary: Contact Tracing in Children Exposed to an Index Case of Tuberculosis: The Need, the Challenge, and the Impact. *Clinical Infectious Diseases*, 60 (1), pp.19-20.
36. Karim, S.S., Churchyard, G.J., Karim, Q.A., Lawn, S.D., 2009. *Lancet*, 374(9693), pp. 921–933.

37. Lawn, S.D., Harries, A.D., Williams, B.G, Chaisson, R.E., Losina, E., De Cock, K.M., Wood, R. 2011, Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? *International Journal of Tuberculosis and Lung Disease*, 15(5), pp.571–581.
38. Leard Statistics, 2013. Measures of Central Tendency [online]. Laerd Research Ltd. Available at: <<http://www.statistics.leard.com>> [Accessed 2 February 2015].
39. Le Roux, S.M., Cotton, M.F., Golub, J.E., le Roux, D., Workman, L., Zar., H.J., 2009. Adherence to isoniazid prophylaxis among HIV-infected children: a randomized controlled trial comparing two dosing schedules [online].*BMC Medicine*, 7(67). Available at [www.biomedcentral.com/1741-7015/7/67](http://www.biomedcentral.com/1741-7015/7/67) [Accessed 8 May 2015].
40. Le Roux, S.M., Cotton, M.F., Myer, L., le Roux, D.M., Schaaf, H.S. 2012. Safety of long-term isoniazid preventative therapy in children with HIV: a comparison of two dosing schedules. *International Journal of Tuberculosis and Lung Disease*, 17(1), pp.26-31.
41. Lester, R., Hamilton, R., Charalambous, S., Dwadwab, T., Chandler, C., Churchyard, G., Grant, A., 2010. Barriers to implementation of isoniazid preventive therapy in HIV clinics: a qualitative study. *AIDS*, 24 (suppl 5), pp. S45–S48.
42. Loveday, M., Smith, J., Day, C., 2014. Knowing our epidemic: key challenges facing the TB programme in South Africa. In: A. Padarath and R. English eds. 2014. *South African Health Review*. Health Systems Trust, pp. 139-153.
43. Madhi, S.A., Nachman, S., Violari, A., Kim, S, Cotton, M.F., et al. 2011. Primary Isoniazid Prophylaxis against Tuberculosis in HIV-Exposed Children. *New England Journal of Medicine*, 365, pp.21-31.
44. Makanjuola, T., Taddese, H.B., Booth, A., 2014. Factors Associated with Adherence to Treatment with Isoniazid for the Prevention of Tuberculosis amongst People Living with HIV/AIDS: A Systematic Review of Qualitative Data. *PLoS ONE*, 9(2): e87166. doi:10.1371/journal.pone.0087166

45. Mandalakas, A.M., Hesselning, A.C., Gie, R.P., Schaaf, H.S., Marais, B.J., Sinanovic, E., 2013. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. *Thorax*, 68, pp. 247–255.
46. Massyn N, Day C, Dombo M, Barron P, English R, Padarath A, editors. *District Health Barometer 2012/13*. Durban: Health Systems Trust; October 2013.
47. Massyn, N., Day, C., Peer, N., Padarath, A., Barron, P., English, R. 2014. District Health Barometer 2013/14. Health Systems Trust: Durban, South Africa.
48. Marais, B.J., Gie, P.R., Schaaf, H.S., Hesselning, A.C., Obigara, C.C., Nelson, L.J., Enarson, D.A., Donald, P.R., Beyers, N. 2004. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. *International Journal of Tuberculosis and Lung Disease*, 8(3), pp.278-285.
49. Marais, B.J, Obihara, C.C., Warren, R.M., Schaaf, H.S., Gie, R.P. and Donald, P.R., 2005. The burden of Childhood tuberculosis: a public health perspective. *International Journal of Tuberculosis and Lung Disease*, 9 (12), pp. 1305-1313.
50. Marais, B.J., van Zyl, S., Schaaf, H.S., van Aardt, M., Gie, R.P., Beyers, N., 2006. Adherence to isoniazid preventive chemotherapy: a prospective community based study. *Archives of Diseases in Childhood*, 91, pp.762-765.
51. Marais B.J., Ayles H., Graham S.M., Godfrey-Faussett P. 2009. Screening and preventative therapy for tuberculosis. *Clinical Chest Medicine*, 30, pp. 827-846.
52. Marais, B.J., Rabie, H., Cotton, M.F., 2011. TB and HIV in children – advances in prevention and management. *Paediatric Respiratory Reviews*, 12, pp. 39–45
53. Marais, B.J., 2014. Quantifying the tuberculosis disease burden in children. *The Lancet*, 383, pp. 1530-1531.

54. Middelkoop, K., Bekker L-G., Shashkina, E., Kreiswirth, B., Wood, R. 2012. Retreatment tuberculosis in a South African community: the role of re-infection, HIV and antiretroviral treatment. *International Journal of Tuberculosis and Lung Disease*, 16(11), pp.1510–1516.
55. Naidoo, S., Taylor, M., Jinabhai, C.C. 2007. Critical Risk Factors Driving the Tuberculosis Epidemic in KwaZulu-Natal, South Africa. *The Southern African Journal of Epidemiology and Infections*, 22(2,3), pp. 45-49.
56. Narasimhan, P., Wood, J., MacIntyre, C., Mathai, D. 2013. Risk Factors for Tuberculosis. *Pulmonary Medicine*, [online]. Available at: <http://dx.doi.org/10.1155/2013/828939> [Accessed 21 January 2015].
57. Newton, S.M., Brent, A.J., Anderson S., Whittaker, E., Kampmann, B. 2008. Paediatric Tuberculosis. *The Lancet*, 8, pp.498-510.
58. Njeka, N., 2014. Multi-Drug Resistant Tuberculosis Strategic Overview of MDR-TB Care in South Africa. [online] Available at: <[http://www.health-e.org.za/wp-content/uploads/2014/03/Strategic\\_overview\\_of\\_MDR\\_TB\\_RSA.pdf](http://www.health-e.org.za/wp-content/uploads/2014/03/Strategic_overview_of_MDR_TB_RSA.pdf)> [Accessed 1 February 2015].
59. Osman, M., Hesselning, A., Beyers, N., Enarson, D., Rusen, I., Lombard, C., van Wyk, S. 2013. Routine programmatic delivery of isoniazid preventive therapy to children in Cape Town, South Africa. *Public Health Action*, 3 (3), pp. 199-203.
60. Pang, S.C., Harrison,R.H., Brearley, J., Jegathesan, V., Clayton, A.S., 1998. Preventive therapy for tuberculosis in Western Australia. *International Journal of Tuberculosis and Lung Disease*, 2(12), pp. 984-988.
61. Perez-Velez, C., 2012. Pediatric Tuberculosis - new guidelines and recommendations. *Current Opinion in Pediatrics*, 24 (3), pp. 319-328.
62. Petersen, K. 2001. *A comprehensive primary care service package for South Africa* [online]. Western Cape Government. Available at <http://www.westerncape.gov.za/sites/www.westerncape.gov.za/files/document>

[s/2003/comprehensive\\_health\\_care\\_services\\_1.pdf](#) [Accessed 10 February 2015].

63. R Core Team, 2013. R: *A language and environment for statistical computing* [online]. R Foundation for Statistical Computing, Vienna, Austria. Available at: <<http://www.R-project.org/>>.
64. Rutherford, M.E., Ruslami, R., Maharani, W., Yulita, I., Lovell, S., Van Creveld, R., Alisjahbana, B., Hill, P.C., 2012. Adherence to isoniazid preventive therapy in Indonesian children: A quantitative and qualitative investigation. *BMC Research Notes*, 5 (7), pp.1-7.
65. Schaaf, H.S., Marais, B.J., Whitelaw, A., Hesselning, A.C., Eley, B., Hussey, G.D., Donald, P.R., 2007. Culture-confirmed childhood tuberculosis in Cape Town, South Africa: a review of 596 cases. *BMC Infectious Diseases*, 7, pp.140 doi:10.1186/1471-2334-7-140.
66. Schaaf, H.S., Marais, B.J., 2011. Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians. *Paediatric Respiratory Reviews*, 12, pp. 31–38.
67. Schaaf, H.S., Cotton, M.F., Boon, G.P., Jeena, P.M., 2013. Isoniazid preventive therapy in HIV-infected and –uninfected children (0-14 years). *South African Medical Journal*, 103 (10), pp. 714-715.
68. Schulz, S.A., Draper, H.R., Naidoo, P., 2013. A comparative study of tuberculosis patients initiated on ART and receiving different models of TB-HIV care. *International Journal of Tuberculosis and Lung Disease*, 17(12), pp.1558-63.
69. Shingadia, D., Novelli, V., 2003. Diagnosis and treatment of tuberculosis in children. *Lancet Infectious Diseases*, 3, pp. 624-633.
70. Skordis-Worrall, J., Hanson, K., Mills, A., 2010. Confusion, caring and tuberculosis diagnostic delay in Cape Town, South Africa. *International Journal of Tuberculosis and Lung Disease*, 14(2), pp.171–180.
71. Smith, J., Moyo, S., Day, C., 2014. A review of TB in children and adolescents in South Africa 2008-2012. In: A. Padarath and R. English eds.

2014. *South African Health Review*. Health Systems Trust. pp. 155-171.
72. Sreeramareddy, C.T., Panduru K.V., Menten, J., Van den Ende, J., 2009. Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. *BMC Infectious Diseases*, 9(91), doi:10.1186/1471-2334-9-91.
73. Sreeramareddy, C.T., Qin, Z.Z., Satyanarayana, S., Subbaraman, R., Pai, M., 2014. Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. *International Journal of Tuberculosis and Lung Disease*, 18(3), pp.255–266.
74. Statistics South Africa, 2015. *Nelson Mandela Bay* [online]. Available at: <[http://beta2.statssa.gov.za/?page\\_id=1021&id=nelson-mandela-bay-municipality](http://beta2.statssa.gov.za/?page_id=1021&id=nelson-mandela-bay-municipality)> [Accessed on 1 February 2015].
75. Storla, D.G., Yimer, S., Bjune, G.A., 2008. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health*, 8(15), doi:10.1186/1471-2458-8-15.
76. Tachfouti, N., Slama, K., Berraho, M., Nejjari, C., 2012. The impact of knowledge and attitudes on adherence to tuberculosis treatment: a case-control study in a Moroccan region. *Pan African Medical Journal*, 12(52), pp. 1-8.
77. Tameris, M. D., Hatherill, M., Landry, B.S., Scriba, T.J., Snowden, M.A., et al. 2013. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. *The Lancet*, 381, pp. 1021-1028.
78. Triasih, R., Robertson, C.F., Duke, T., Graham, S.M., 2015. A prospective evaluation of the symptom-based screening approach to the management of children who are contacts of tuberculosis cases. *Clinical Infectious Diseases*, 60(1), pp. 12-18.
79. Van den Hof, S., Najlis, C.A., Bloss, E., Straetemans, M., 2010. *A systematic review on the role of gender in tuberculosis control* [online]. Available at: [http://www.tbcare1.org/publications/toolbox/tools/access/Role\\_of\\_Gender\\_in\\_TB\\_Control.pdf](http://www.tbcare1.org/publications/toolbox/tools/access/Role_of_Gender_in_TB_Control.pdf)> [Accessed 2 February 2015].

80. Van Halsema, C.L., Fielding, K.L., Chihota, V.N., Russell, E.C., Lewis, J.J., Churchyard, G.J., Grant, A.D., 2010. Tuberculosis outcomes and drug susceptibility in individuals exposed to isoniazid therapy in a high HIV prevalence setting. *AIDS*, 24(7), pp. 1051-1055.
81. Van Soelen, N., du Preez, K., van Wyk, S.S, Mandalakas A.M., Enarson, D.A., Reid, A.J., Hesselning, A.C., Does an Isoniazid Prophylaxis Register Improve Tuberculosis Contact Management in South African Children? *PLoS ONE* 8(12): e80803. doi:10.1371/journal.pone.0080803.
82. Van Well, G.T., Paes, B., Terwee, C.B., Springer, P., Roord, J.J., Donald, P.R., van Furth, A.M., Schoeman, J., 2009. Twenty Years of Pediatric Tuberculous Meningitis: A Retrospective Cohort Study in the Western Cape of South Africa. *Pediatrics*, 123 (1), pp.e1-e8.
83. Van Wyk, S., Hamade, H., Hessling, A., Beyers, N., Enarson, D. and Mandalakas, A. 2010. Recording isoniazid preventative therapy delivery to children: operational challenges. *International Journal of Tuberculosis and Lung Disease*, 14 (5), pp.650-653.
84. Van Wyk, S., Reid, A., Mandalakas, A., Enarson, D., Beyers, N., Morrison, J. and Hessling, A. 2011. Operational challenges in managing Isoniazid Preventative Therapy in child contacts: A high-burden setting perspective. *BMC Public Health*, 11 (544), pp.1-6.
85. Van Zyl, S., Marais, B., Hessling, A., Gie, R., Beyers, N. and Schaaf, H. 2006. Adherence to anti-tuberculosis chemoprophylaxis and treatment in children. *International Journal of Tuberculosis and Lung Disease*, 10 (1), pp.13-18.
86. Villarino, E.M., Scott, N.A., Weis, S.E., Weiner, M, et al. 2015. Treatment for Preventing Tuberculosis in Children and Adolescents A Randomized Clinical Trial of a 3-Month, 12-Dose Regimen of a Combination of Rifapentine and Isoniazid. *The Journal of the American Medical Association Pediatrics*, doi:10.1001/jamapediatrics.2014.3158.
87. Wood, R., Johnstone-Robertson, S., Uys, P., Hargrove, J., Kiddelkoop, K., Lawn, S., Bekker, L-G., 2010. Tuberculosis Transmission to Young Children in a South African Community: Modelling Household and Community

- Infection Risk. *Clinical Infectious Diseases*, 51(4), pp.410-408.
88. Wood, R., Lawn, S., Johnstone-Robertson, S., Bekker, L., 2011. Tuberculosis control has failed in South Africa – time to reappraise strategy. *South African Medical Journal*, 101 (2), pp. 111-114.
89. World Health Organization, 2001. Declaration of Helsinki. [online] *Bulletin of the World Health Organization*, 79(4), pp. 373-374. Available at: [http://www.who.int/bulletin/archives/79\(4\)373.pdf](http://www.who.int/bulletin/archives/79(4)373.pdf) [Accessed 10 February 2015]
90. World Health Organization. 2006. *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. [online] Geneva: World Health Organization. Available at: <[http://www.who.int/hq/2006/WHO\\_HTM\\_TB\\_2006.371\\_eng.pdf](http://www.who.int/hq/2006/WHO_HTM_TB_2006.371_eng.pdf)> [Accessed: 12 August 2012].
91. World Health Organization. 2008. *WHO Three 'T's meeting: intensified case finding, isoniazid preventive therapy and TB infection control for people living with HIV*. [online] Geneva: World Health Organization. Available at: <[http://www.who.int/hiv/pub/tb/3is\\_mreport/en/](http://www.who.int/hiv/pub/tb/3is_mreport/en/)> [Accessed: 25 May 2014].
92. World Health Organization. 2010. *WHO | The Global Plan to Stop TB 2011-2015*. [online] Geneva: World Health Organization. Available at: <<http://www.stoptb.org/global/plan/>> [Accessed: 16 May 2014].
93. World Health Organization. 2010. *WHO | Tuberculosis and HIV*. [online] Geneva: World Health Organization. Available at: <<http://www.who.int/hiv/topics/tb/en/index.html>> [Accessed: 11 November 2011].
94. World Health Organization. 2011. *Global tuberculosis control: WHO report 2011*. [online] Geneva: World Health Organization. Available at: <[http://www.who.int/tb/publications/global\\_report/en/index.html](http://www.who.int/tb/publications/global_report/en/index.html)> [Accessed 8 October 2012]
95. World Health Organization, 2011. *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings*. [online] Geneva: World Health Organization.

Available at: <[www.who.int/tb/challenges/hiv/en/index.html](http://www.who.int/tb/challenges/hiv/en/index.html)> [Accessed 7 November 2011].

96. World Health Organization. 2013. *WHO | Tuberculosis*. [online] Available at: <<http://www.who.int/mediacentre/factsheets/fs104/en/index.html>> [Accessed: 5 February 2013].
97. World Health Organization, 2014. Global tuberculosis report 2014. [online] Available at: <[http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf?ua=1)> [Accessed 3 January 2015]
98. Yimer, S.A., Bjune, G.A., Holm-Hansen, C., 2014. Time to first consultation, diagnosis and treatment of TB among patients attending a referral hospital in Northwest, Ethiopia. *BMC Infectious Diseases*, 14:19  
<http://www.biomedcentral.com/1471-2334/14/19>.
99. Zachariah, R., Spielmann, M-P., Harries, A.D., Gomani, P., Graham, S.M., Bakali, E., Humblet, P., 2003. Passive versus active tuberculosis case finding and isoniazid preventive therapy among household contacts in a rural district of Malawi. *International Journal of Tuberculosis and Lung Disease*, 7 (11), pp. 1033-1039.
100. Zar, H.J., Cotton, M.F., Strauss, S., Karpakis, J., Hussey, G., Schaaf, H.S., Rabie, H., Lombard, C.J., 2007. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. *British Medical Journal*, doi:10.1136/bmj.39000.486400.55.
101. Zar, H, Pai, M., 2011. Childhood Tuberculosis - a new era. *Paediatric Respiratory Reviews*, 12 (Editorial), pp 1-2.
102. Personal correspondence with Ms Betty Ncanywa, TB Directorate, Nelson Mandela Bay Health District , 30 January 2014.
103. Personal correspondence with Sharon Warmington, lay counsellor, West End Clinic, 17 September 2014.
104. Personal correspondence with Sr Sookdin, Facility manager, West End Clinic, 17 June 2014.

105. Personal correspondence with Sr Geswint, TB nursing sister, West End Clinic, 3 February 2015.

## Appendix 1. Data collection tool

### Section 1.

Date	
Study number	
Adult TB register number	

1. Patient Name: \_\_\_\_\_

2. Age/DOB: \_\_\_\_\_

3. 

M	F
---	---

4. 

Employed	Unemployed	Pensioner	Student
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5. RVD status 

Positive	Negative	Not documented
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6. **TB history:**

6.1. Previous TB 

Y	N	unknown
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6.2. Date first sputum sent (relating to most recent diagnosis of TB): \_\_\_\_\_

6.3. Date positive sputum result printed: \_\_\_\_\_

6.4. Date treatment started: \_\_\_\_\_

7. **Current TB**

7.1 Sputum results:

<b>Smear</b>	Positive	Negative	Not done	Not documented
<b>Xpert</b>	Positive	Negative	Not done	Not documented
<b>Culture</b>	Positive	Negative	Not done	Not documented

Study no. \_\_\_\_\_

7.2.  Drug sensitive  Drug resistant

7.2.1. If resistant, to what drugs?

\_\_\_\_\_

7.3. Outcome

Cured  Completed  Defaulted  Failed  Died  Still on treatment

Transferred out  Not documented

## **Section 2.**

### **8. Contact information:**

8.1	Are contacts documented on the history sheet or in clinical notes	Y/N
8.2	Is there documentation of “no contacts <5years” in the adults TB folder	Y/N
8.3	Are the names of the TB contacts documented in the adult TB folder	Y/N
8.4	Were IPT cards found for these contacts?	Y/N
8.5	Total number of contacts documented	
8.6	Number of contacts <5 years (as identified by DOB or age)	
8.7	Number of contacts >5 years (as identified by DOB or age)	
8.8	Number of contacts with age unknown	

**Section 3.**

Study no. \_\_\_\_

<b>Contacts &lt;5 years</b>	Contact 1	Contact 2	Contact 3	Contact 4	Contact 5
Name					
Age/DOB					
Folder number					
Relationship to index case					
Screened: Y/N/U					
Date:					
Symptom screen Y/N/U					
TST: Y/N/U					
CXR: Y/N/U					
Sputum/Gastric Washing: Y/N/U					
Referred for further management: Y/N/U					
TB treatment started: Y/N/U					
Drugs used					
Date initiated					
IPT started Y/N/U					
Drugs used					
Date initiated					
Number of weeks completed					
Drug side effects: Y/N/U					
If yes, describe					
Discharge noted: Y/N					

**Appendix 2:** Daily dosage recommendations for INH preventive therapy in children (Guidelines for the management of Tuberculosis in children, NDoH, 2013, p11)

Weight band (kg)	Daily INH (100mg tablet)
2-3.4	¼ tablet
3.5-4.9	½ tablet
5-7.4	¾ tablet
7.5-9.9	1 tablet
10-14.9	1 ½ tablets
15-19.9	2 tablets
20-29.9	3 tablets
30-40	4 tablets

Appendix 3: IPT card

NELSON MANDELA BAY MUNICIPALITY BUSINESS UNIT: HEALTH <b>TB - PROPHYLACTIC TREATMENT</b>									
MOTHER / GUARDIAN			FIRST NAME				SURNAME		
ADDRESS					REASON FOR TREATMENT: Contact of: ..... Tuberculin Reactor .....				
RACE	A	B	C	D	SEX	M	F	DATE OF BIRTH	
PREVIOUS B.C.G.		DATE .....			SCAN .....				
IMMUNISATION:		UP TO DATE : YES ..... NO .....							
MONTHLY CHECK: MASS AND SYMPTOMS									
DATE		RESULTS							
.....		.....							
.....		.....							
.....		.....							
.....		.....							
PRESCRIPTION (Date, Drugs, Signature, Qualification)									
.....									
.....									
.....									
AMOUNT OF TREATMENT ADMINISTERED:									
MONTH		AMOUNT							
.....		.....							
.....		.....							
.....		.....							
GAINED:		DATE	NEW		TRANSFER FROM OTHER CLINIC		RECOVERED FROM LOST		
.....		.....	.....		.....		.....		
LOST		DATE	COURSE COMPLETE		TRANSFER TO OTHER CLINIC		VANISHED DIED PATIENT		
.....		.....	.....		.....		.....		

PEM 4147 (1/2007)

## Appendix 4: Eastern Cape Letter of approval



### Eastern Cape Department of Health

Enquiries: Zonwabele Merile

Tel No: 040 608 0830

Date: 21<sup>st</sup> July 2014

Fax No: 043 642 1409

e-mail address: zonwabele.merile@impilo.ecprov.gov.za

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Dear Dr F Tucker

**Re: An assessment of the Isoniazid Prevention Therapy programme for children in a busy primary healthcare clinic in Nelson Mandela Bay, Eastern Cape**

The Department of Health would like to inform you that your application for conducting a research on the abovementioned topic has been approved based on the following conditions:

1. During your study, you will follow the submitted protocol with ethical approval and can only deviate from it after having a written approval from the Department of Health in writing.
2. You are advised to ensure, observe and respect the rights and culture of your research participants and maintain confidentiality of their identities and shall remove or not collect any information which can be used to link the participants.
3. The Department of Health expects you to provide a progress on your study every 3 months (from date you received this letter) in writing.
4. At the end of your study, you will be expected to send a full written report with your findings and implementable recommendations to the Epidemiological Research & Surveillance Management. You may be invited to the department to come and present your research findings with your implementable recommendations.
5. Your results on the Eastern Cape will not be presented anywhere unless you have shared them with the Department of Health as indicated above.

Your compliance in this regard will be highly appreciated.

signature removed

**DEPUTY DIRECTOR: EPIDEMIOLOGICAL RESEARCH & SURVEILLANCE MANAGEMENT**





**UNIVERSITY OF CAPE TOWN**  
**Faculty of Health Sciences**  
**Human Research Ethics Committee**



Room E52-24 Old Main Building  
Groota Schuur Hospital  
Observatory 7925  
Telephone [021] 404 7682 • Facsimile [021] 406 6411  
Email: [nosi.tsama@uct.ac.za](mailto:nosi.tsama@uct.ac.za)  
Website: [www.health.uct.ac.za/research/humanethics/forms](http://www.health.uct.ac.za/research/humanethics/forms)

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24 June 2014

**HREC REF: 345/2014**

**Ms J Shea**  
SCAH  
Room 3.16 3<sup>rd</sup> Floor  
ICH Building  
Red Cross Children's Hospital

Dear Ms Shea

**PROJECT TITLE: AN ASSESSMENT OF THE ISONIAZID PREVENTION THERAPY PROGRAMME FOR CHILDREN IN A BUSY PRIMARY HEALTH CARE CLINIC IN NELSON MANDELA BAY, EASTERN CAPE (MPhil candidate- Faye Tucker)**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**Approval is granted for one year until the 30<sup>th</sup> June 2015.**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: [www.health.uct.ac.za/research/humanethics/forms](http://www.health.uct.ac.za/research/humanethics/forms))

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

***We acknowledge that the MPhil student, Faye Tucker is also involved in this study.***

Please quote the HREC reference no in all your correspondence.

Yours sincerely

signature removed

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN ETHICS**

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

