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UNIVERSITY OF THE WITWATERSRAND

FACULTY OF HEALTH SCIENCES



HOUSEHOLD TUBERCULOSIS CONTACT TRACING AMONG CHILDREN UNDER FIVE IN THE RURAL KWENENG DISTRICT – BOTSWANA.

Frank Ngoy Mpoyo Lusaya (MD)

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfilment of the requirements for the degree of Master of Public Health in the field of Health Systems and Policy.

Johannesburg / RSA, 2015

***HOUSEHOLD TUBERCULOSIS CONTACT TRACING AMONG CHILDREN UNDER FIVE IN THE RURAL KWENENG DISTRICT - BOTSWANA*.**

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DECLARATION

I, Frank Ngoy Mpoyo Lusaya declare that this research is my own work. It is being submitted for the degree of Master of Public Health in the field of Health Systems and Policy at the Faculty of Health Sciences of the University of the Witwatersrand, Johannesburg. No part of it has been nor will be submitted for a degree at this or any other University. All the quotations have been acknowledged and distinguished. This research project received a clearance certificate for protocol number MO51021 from the Ethics committee for Research on Human Subjects.



Frank Ngoy Mpoyo Lusaya (MD)

10 September, 2015

DEDICATION

I dedicate this study to my wife Francine K. Ilunga and my son Mike Mpoyo Lusaya. I thank them for their lovely encouragement, endless support, and enthusiasm during the many days and nights spent working on this research.

ABSTRACT

Study topic: Household tuberculosis contact tracing among children under five in the rural Kweneng District - Botswana.

Purpose: Screening of young children exposed to tuberculosis (TB) in a household setting is widely recommended, but rarely implemented in some endemic countries. The aim of this study was to screen household under five children who have been exposed to smear-positive pulmonary tuberculosis (PTB) of adult cases; to explore and describe the initial follow-up of these children by the Kweneng district health care system; and to determine clinical outcomes (occurrence of TB disease and latent tuberculosis infection) among those children.

Methods and procedures: In a nested case-control type study design, under 5 years child contacts of 200 randomly selected adult smear positive pulmonary TB patients, were enrolled and evaluated for TB infection and disease. Risk factors were compared between those with TB and those without TB. Data was collected during the study period (December 2005 through November 2006) through face-to-face interviews using a pre-designed data collection tool. Child contacts were then investigated at their respective nearest health facility using Tuberculin Skin Test (TST), clinical examination, and chest x-ray (CXR). Finally child contacts were diagnosed as follow: No TB, Latent Tuberculosis Infection (LTBI), or TB disease. We defined LTBI as having a TST ≥10 mm at 48–72 hours.

Major results: A total of 497 child contacts were recruited, of which 278 (55.9% [95%CI: 51.4% - 60.3%]) and 219 (44.1% [95%CI: 39.7% - 48.6%]) were respectively girls and boys both in age group: 0-24 months: 51 (10.3% [95% CI: 7.8% - 13.4%]) and 25-59 months: 446 (89.7% [95% CI: 86.6% - 92.2%]).

Among all children 19 (3.8% [95% CI: 2.4% - 6.0%]) were found not vaccinated. The duration of exposure to TB case ranged from 1 to 4 months; and the social proximity of child contact to TB case was as follow: 185 (37.2% [95%CI: 33.0% - 41.7%]) were first degree relatives, 304 (61.2% [95%CI:56.7% - 65.4%]) distant relatives, and 8 (1.6% [95%CI: 0.8% - 3.3%]) child contacts were not related to the cases. The respondent dissatisfaction rate about TB screening (follow-up) by the health care system was 163 (81.50%).

Of 497 child contacts, 104 (20.9% [95%CI: 17.5% - 24.8%]) were initially screened for TB at the time the TB index cases were diagnosed. 163 (81.5% [95%CI: 75.4% - 86.6%]) respondents were dissatisfied about the initial follow-up and screening of child contacts by the health care system. Among all 497 child contacts evaluated at the time of this study, LTBI prevalence rate was 35.0% [95%CI: 30.8% - 39.4%], and the prevalence of TB disease was 3.4% [95% CI: 2.1% - 5.5%].

Under five children who had been screened initially were less likely to have TB infection or disease identified during the evaluation by this study, than those who had not been screened (OR=0.296, $X2 = 20.202$, $p < 0.001$) by Kweneng health care system.

Main Conclusions: This is the first comprehensive household TB contact tracing in under five children exposed to smear positive TB from adult cases in the rural Botswana. The study found that health care services in Kweneng were not adequately implementing TB contact tracing of household under five children. When children were followed up during this study, we documented a high prevalence rate of TB infection and disease among child contacts who had not

been followed up and screened for TB by the health system. This not only suggests that under five child living in the same household with an adult TB case in rural Botswana is at high risk of LTBI and active TB disease; but it also evidently supports the benefice and importance of household contact tracing in enhancing case finding and prevention of tuberculosis disease (Triasih, 2015).

Recommendations: A scale-up of targeted household contacts tracing for under five children followed by appropriate management can enhance early case detection and lower the risk of TB transmission among under five children.

A targeted tuberculosis contact tracing with an emphasis on younger children should be made a priority by the Botswana National TB Programme (BNTP). The policy needs to clarify who is responsible and accountable for TB contact tracing services. The gap between guidelines and practice, and the human resource capacity should be addressed. An improved training of TB care providers on guidelines in Kweneng district will be important in strengthening TB contact tracing.

Key words: Contact tracing, household, tuberculosis, latent tuberculosis infection, index case, child contact, under five child, follow-up, preventive therapy, TST, CXR.

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LIST OF ACRONYMS

AFB:	Acid- Fast Bacilli
AIDS:	Acquired Immune Deficiency Syndrome
ANC:	Antenatal Care
ATS:	American Thoracic Society
ATT:	Anti-Tuberculosis Therapy
ASHM:	Australasian Society for HIV Medicine
BCG:	Bacille Calmette–Guérin
BCC:	Behaviour Change Communication
BNTP:	Botswana National Tuberculosis Programme
BOTUSA:	Botswana - United States of America Partnership
CDC:	US Centres for Disease Control and Prevention
CKGR:	Central Kgalagadi Game Reserve
CMS:	Central Medical Store
C.S.O:	Central Statistics Office
CWC:	Child's Welfare Clinic
DHTMT:	District Health Team Management
DNA:	Deoxyribonucleic Acid
DOTS:	Direct Observed Treatment, Short-course
EPI:	Expanded Programme on Immunization
EPTB:	Extra Pulmonary Tuberculosis
FWE:	Family Welfare Educator
ICF:	Intensified Case Finding
IEC:	Information, Education and Communication
IMCI:	Integrated Management of Childhood Illness
IPT:	Isoniazid Preventive Therapy
IPTT:	Isoniazid Preventive Therapy Trial
HIV:	Human Immunodeficiency virus
IGRAs:	Interferon–Gamma Release Assays
INH:	Izoniazid
IUATLD:	International Union against Tuberculosis and Lung Disease
LIP:	Lymphoid interstitial pneumonitis
LSTM:	Liverpool School of Tropical Medicine

LTBI:	Latent Tuberculosis Infection
MD:	Doctor of Medicine
MDR TB:	Multidrug-resistant Tuberculosis
NACA:	National AIDS Coordinating Agency
NSW:	New South Wales
NTCA:	National Tuberculosis Controllers Association
NTCP:	National TB Control Programme
OAG:	Office of the Auditor General
PMH:	Princess Marina hospital
PPD:	Purified Protein Derivative
PTB:	Pulmonary Tuberculosis
RFLP:	Restriction Fragment Length Polymorphism
RNTCP:	Revised National Tuberculosis Control Programme
RPT:	Rifapentine
RSA:	Republic of South Africa
LIP:	Interstitial pneumonitis
SLH:	Scottish Livingstone Hospital
SSKB:	Sir Seretse Khama Barracks
TB:	Tuberculosis
TBTC:	Tuberculosis Trial Consortium
TST:	Tuberculin Skin Test
UNDP:	United Nations Development Programme
WHO:	World Health Organization
WLMA:	Wildlife Management Areas.

CHAPTER 1: INTRODUCTION

This chapter discusses the background and rationale of the study. It then provides an overview of the situation of Kweneng district where the study was conducted. A complete statement of the problem and the justification of the study are also discussed in this chapter. The concepts and terms used in this study are then clearly defined. Lastly this chapter presents the aim, and specific objectives of the study. It is important to note that the context and content throughout this research report refer to the state of the situation at the time this study was conducted: from December 2005 through November 2006. This was before the current updated Botswana National Tuberculosis Program (BNTP) guidelines recommending symptom-based TB screening.

1.1. Background and rationale

Tuberculosis (TB) in children is a global public health concern, especially in sub-Saharan Africa. In Botswana the incidence of tuberculosis is extremely high with over 500 per 100,000 (Lockman & Sheppard, et al. 2001), and 536 per 100,000 in 2008 (Ministry of Health of Botswana, 2011b). TB infection in children is usually transmitted by an adult (often a family member) having sputum-positive pulmonary tuberculosis (PTB). While TB in children is often missed or overlooked due to non-specific symptoms and difficulties in diagnosis (WHO 13b); young children who live in close contact with a smear-positive PTB case are at particular risk of TB infection and disease. In other words, the likelihood of the child being infected with TB could be increased in a child who has history of close contact (family member, person living in the same household, friend, caretakers) with a smear-positive TB patient (South African National Department of Health, 2000).

Children under five years and infants are mostly at risk of developing TB disease after infection (WHO, 1998). This means that children under-five are especially at risk of TB if their mother, father or relative in the same household is sick or dies from tuberculosis.

The first priority of TB prevention and control programs is to identify and correctly treat all active TB cases; and the South African National TB Control Programme (NTCP) (South African National Department of Health, 2000) considers the cure of infectious cases as the highest priority of TB control. However, the second priority is contact investigation to identify persons who had exposure to TB, to evaluate and treat them for latent TB infection (LTBI) and active TB disease (Marks & Taylor et al. 2000). Numerous studies have found that contact investigations are a valuable means of identifying new TB cases, and they are recommended by WHO and the International Union Against Tuberculosis and Lung Disease (WHO, 2006a) The Prevention of new TB cases is an essential component of The Botswana national tuberculosis control program, which outlines the intensified case finding (ICF) in high-risk groups, infection control and contact tracing as some of the examples of primary prevention (Ministry of Health of Botswana, 2011a). Child tuberculosis contact screening and management can enhance case finding and prevent tuberculosis disease. It is universally recommended but rarely implemented in tuberculosis-endemic settings (Triasih & Robertson, et al. 2015)

The World Health Organization (WHO) and most national tuberculosis programs (NTPs) advise that all children under five years of age who are in close contact

with a sputum smear-positive source case should be screened for tuberculosis (WHO, 2006a)

Botswana national TB programme (BNTP) recognises that young children living in close contact with an index case of smear positive PTB are at high risk of TB infection, Hence tracing of children who are household contacts of infectious adults is part of the national TB control policy (Ministry of health of Botswana, 2007).

BNTP recommends that all close contacts including household contacts should be evaluated for TB; and children under five years must be given special attention during contact tracing (Ministry of health of Botswana, 2011a). However such contact tracing is not necessary for smear-negative PTB unless the index case is a child. In contrast to previous BNTP and World Health Organization (WHO) guidelines on contact tracing in under-five that had recommended clinical examination, tuberculin skin test (TST) and chest radiography as part of contact investigation in addition to history of exposure to infectious TB, current BNTP guidelines of 2011 consider that clinical assessment alone is sufficient to decide whether a paediatric contact is well or symptomatic; hence routine assessment of child contacts does not require any more chest x-ray (CXR) and/or a TST (Ministry of health of Botswana, 2011a).These guidelines have adopted the current WHO recommendations that outline the use of clinical assessment alone as a sufficient approach to decide whether the contact is well or symptomatic in low- and middle-income settings where CXR and TST have limitations because these tests are often not readily available or possible. Therefore these tests should not be considered a requirement for routine assessment of exposed

contacts in low- and middle-income settings (WHO, 2014). Hence the lack of radiology or tuberculin skin testing should not be an impediment to contact screening and management (Triasih et al. 2015).

The purpose of contact screening and management mainly are twofold: firstly, to identify contacts with undiagnosed TB disease among the contacts of an index case; and secondly, to provide preventive therapy for contacts without TB disease.

Hence contact screening strategy may help increased TB diagnosis in earlier stages, prevent the spread of tuberculosis, and therefore have an impact on morbidity and mortality, especially among younger children. Despite this overall benefit from TB contact tracing envisaged by the Botswana National Tuberculosis Programme (BNTP); from our personal observation, yet this well-established intervention is seldom implemented in Botswana as it would be rarely implemented in any other TB endemic setting (Triasih & Rutherford et al. 2012).

1.1.1. Approach to contact tracing in under five child in Botswana.

At the time of this study in December 2005 - November 2006, the Botswana National Tuberculosis Control Programme (BNTP) was still using the previous guidelines stipulated in the 1995, 5th edition of the Botswana National tuberculosis programme manual recommending TST, CXR and clinical examination of under-five child contacts. These three investigations were also regarded as a prerequisite for an adequate screening of household contacts by previous WHO guidelines (Marais & Pai, 2007). Therefore our study investigations were carried out according to the approach of 1995 National tuberculosis guidelines and policy. But at the time (2015) we are submitting this final research

report new developments have already occurred in the field of TB control worldwide and the Botswana Ministry of Health (MOH) has adopted new strategies and already revised both the 1995 national TB guidelines and its revised 6th edition of 2007. At least now the current 7th edition of the national tuberculosis programme manual published in 2011 emphasises on both the importance of paediatric TB in general and TB contact tracing and examination in particular. This 7th edition guidelines represents the international standards and recommendations from the WHO and the International Union against TB and Lung Disease (IUATLD), combined with local knowledge and expertise to ensure their relevance to Botswana (Ministry of Health of Botswana, 2011a).

This current national TB policy and guidelines consider the new approach of TB contact tracing as stipulated in the currently used 2011 Botswana national tuberculosis programme manual. These are aligned with the recent advances that have improved the ability to diagnose LTBI and active disease in children (Marais et al. 2007) and adapted to the most recent WHO guidelines. Thus currently in Botswana, clinical assessment (simple symptom based screening) alone of child contacts is sufficient to decide whether the contact is well or has symptoms of tuberculosis, and routine assessment of exposed contacts does not require a CXR or TST(Ministry of health of Botswana, 2007) and (Ministry of health of Botswana, 2011a). In addition to that, isoniazid (10 mg/kg daily for six months) preventive treatment (IPT) is now recommended for all children under five household contacts of sputum smear-positive PTB patients in whom TB disease has been excluded.

The success of this new approach will depend on its rapid implementation at both district and health facility level; if effectively implemented, it would be the most relevant to the Botswana context; where sometimes TST seems unavailable in some health facilities, and radiography facility and radiologists for the provision of CXR services are not immediately available at primary health care level such as clinics and health posts where TB screening services of child contacts and evaluation other TB contacts should be happening.

Nevertheless contact tracing for smear-negative PTB or EPTB in Botswana is unnecessary unless the index case is a child (Ministry of health of Botswana, 2007).

While we are presenting this final research report this year 2015, attempts have been made to adopt and integrate the Botswana new (2011) policy approach related to the evaluation or routine assessment of exposed TB contacts in our study discussions

1.2. Study context

Botswana is an upper-middle income country (World Bank, 2014) in Southern Africa. The public health system in Botswana comprises 24 health districts. The management of TB is fully integrated into the primary health care system, TB services are provided in each of the 24 health districts through hospitals, clinics and health posts (Ministry of Health of Botswana, 2011a). This study was conducted in Kweneng district which is a rural landlocked district located in the south-eastern part of Botswana. It shares boundaries with other districts: Southern district in the south, Gantsi in the north, Kgatleng, in the east, Central Northeast, Kgalagadi and Central Kgalagadi Game Reserve (CKGR) in the west.

Administratively the district is split into two parts: Kweneng East and Kweneng West which represent the health district 5 and 20 respectively (Appendix A). The western part of Kweneng is a remote area and less developed than the eastern side of this district. Wildlife is concentrated in Kweneng West and the rest of the district supports more livestock. Most inhabitants of Kweneng are subsistence farmers engaged in animal rearing (mainly cattle) and crop production.

The physical geography is generally that of an undulating plateau. The terrain is flat covered by shrub trees and thick mantle of unbroken sand veldt. The harsh geographical, cultural and socio-economic status have a strong bearing on the health care system. More specifically the follow-up of TB cases and contact tracing that are challenged by the high mobility of nomadic ethnic groups such as the Basarwa: Bushmen (found in the western and north-western parts of the district), people living in remote settlements and scattered cattle posts which are difficult to reach by the health care system. In addition, alcohol abuse, passivity and socio-cultural aspects among these groups constrain their ability to participate in sustainable health care services in general and in the TB control programme in particular.

1.2.1. Demography:

According to the demographic data at the time of this study, as indicated in Table 1, the total population of Kweneng in 2001 was 230,335 (111,519 males and 118,816 females) of which approximately 32,247 (14.0%) were children aged 0 - 5 years (Central Statistics Office, 2001).

Table 1: District total population estimates (2001)

District	Number	Male	Female
Kweneng East	189,773	91,045	98,728
Kweneng West	40,562	20,474	20,088
Total	230,335	111,519	118,816

* Source: 2001 Botswana population and housing census

The average household size is 5.1 people and the mean number of children per household is 2.54 in the rural areas compared to 1.31 and 2.20 in urban towns and urban villages respectively (Central Statistics Office, 1994).

1.2.2. Health status and health care system:

The primary health care services in Kweneng are well established and functioning throughout the district. The health care network consists of two referral hospitals (both located in Kweneng East), one military hospital (Sir Seretse Khama Barracks hospital), 23 public clinics (15 in Kweneng East and 8 in Kweneng West); 36 health posts (22 in Kweneng East, 14 in Kweneng west); and mobile stops. There were no private practice/clinic in Kweneng West when this study was conducted. The few private clinics in the district were based in Kweneng East. About 75% of the population is within 15 km of a health facility, 25% within 8 km (Kweneng District Health Team Management, 2002). However, only 46.1% of the population are within 8 km (4.97 miles) of a maternity facility.

The HIV/AIDS pandemic is a great challenge for health care services in Botswana in general and in Kweneng in particular (see Table 2). Based on several sentinel surveys in the country, the trend in the national HIV prevalence among women aged 15-49 years in Antenatal Care (ANC) was 36.2% in 2001, 35.4% in 2002 and reached 37.4% in 2003 (NACA, BOTUSA et al. 2003).

Table 2: Botswana second generation HIV/AIDS surveillance trends in Kweneng District

	HIV Prevalence % [95% CI]		
District	**2001**	**2002**	**2003**
Kweneng East	29.5% [25.3- 33.7]	29.2% [25.0-33.3]	32.1% [26.8-37.5]
Kweneng West	24.3% [15.8- 32.7]	28.7% [21.2- 36.1]	27.0% [19.8-34.3]

* Source: NACA (National Aids Coordinating Agency)

95%CI: 95% Confidence interval.

Botswana has one of the highest TB notification rates in the world and has consistently reported in excess of 590 cases per 100,000 population annually since 2000 (Ministry of Health of Botswana, 2007). Since 1975 when Botswana National Tuberculosis Control Programme (BNTP) was launched by ministry of health, appreciable progress had been achieved over the years and Botswana experienced a major decline in TB notification rates from 506/100,000 in 1975 to 199/100,000 in 1989. But during the early 1990s,TB rates began to rise again, and reached for example a peak in 2002 with a notification rate of 623/100 000, while the total number of cases increased from 5655 in 1995 to 10228 in 2005 (Ministry of Health of Botswana, 2007).

The increase of TB is largely due to the advent of HIV infection in Botswana (BOTUSA et al. 1999). It is well known that without HIV co-infection, only about 5% of people infected with TB bacilli develop active TB disease during their lifetime. While 50% may become ill with TB among people co-infected with HIV and TB (South Africa National Department of Health, 2000).

As shown in Table 3 below, during the period 2002-2003 Kweneng district had a total of 1060 pulmonary TB (PTB) patients representing 89.8% of the overall total of 1180 TB cases registered in the district. Of the 1060 pulmonary TB, 443 (41.8%) were smear-positive pulmonary tuberculosis cases. Smear positive new cases were 402 (41.3%). In 50.5% (535) of all pulmonary TB cases, no sputum was collected for AFB (Acid- Fast Bacilli). This is an indication that although the Botswana National TB Programme (BNTP) guidelines emphasize sputum examination as the most valuable method for passive TB case diagnosis in Botswana; it appears like the Kweneng health care system relied more on CXR in the investigation of suspected pulmonary TB patients. Chest radiography diagnosis of TB in adult persons is difficult and unreliable because abnormalities identified on a CXR are sometimes not specific to TB (Ministry of Health of Botswana, 1995). However a CXR remains a valid procedure for diagnosis of primary TB in children.

TB data is captured at health facility level using two tools: The TB register and TB patient card; at TB district coordination level data is entered in a manual and electronic TB registers which are regularly maintained.

Table 3: Kweneng District TB Case finding report 2002-2003

	Pulmonary TB				Extra Pulmonary TB	Total
TB Case	**Smear+**	**Smear–**	**No Smear**	**Total**		
New cases	402 (41.3%)	73 (7.5%)	499 (51.2%)	974 (89.4%)	115 (10.6%)	1089 (100.0%)
Relapses	35 (48.6%)	6 (8.3%)	31 (43.1%)	72 (94.7%)	4 (5.3%)	76 (100.0%)
After Default	5 (71.4%)	1 (14.3%)	1 (14.3%)	7 (87.5%)	1 (12.5%)	8 (100.0%)
After Failure	1 (14.3%)	2 (28.6%)	4 (57.1%)	7 (100.0%)	0 (0.0%)	7 (100.0%)
Total	443 (41.8%)	82 (7.7%)	535 (50.5%)	1060 (89.8%)	120 (10.2%)	1180 (100.0%)

Source: Kweneng district electronic TB register

1.3. Statement of problem

Tuberculosis is one of the challenging public health issues affecting Kweneng district as well as the rest of Botswana. TB burden in Kweneng might be a result of the general increased TB in Botswana due to increasing prevalence of HIV in Botswana (Ministry of Health of Botswana, 2011a).

Kweneng district was one of two districts with the highest reported TB cases load in 2002 (NACA et al. 2003). The 1999 evaluation of the Botswana National Tuberculosis Programme (BNTP) showed that the Botswana Ministry of health is fully aware of the magnitude of tuberculosis problem (BOTUSA et al. 1999), and the government is highly committed to and engaged in the provision of financial and logistic support as well as other resources such as skilled manpower for the

tuberculosis programme. But in spite of these commitment and engagement, BNTP performance indicators remain low.

Although procedures on how to conduct tuberculosis contact tracing and evaluate TB contacts are clearly stated in the national programme manual, the 1999 evaluation identified a number of weaknesses (BOTUSA et al. 1999):

- Contact tracing is often not done or done to a limited extent.
- Tuberculosis contact forms are often not available or not filled out.
- There is no specific attention to children under five years of age.
- It is not always clear who is the responsible person for contact tracing.

The results of interviews with patients during the Botswana programme review in May 1999 also indicated that only 20% of household members were checked for tuberculosis within the past 6 months. And 66% of interviewed patients felt that families were not sufficiently informed by health care workers about tuberculosis in family members of contacts of tuberculosis patients currently under treatment in districts (BOTUSA et al. 1999).

In Kweneng district, at the operational level, there is no information on whether or not routine tuberculosis contact tracing is adequately undertaken. And where it is done there is no clear emphasis on children under five. Most health facilities in Kweneng might be aware of the policies and strategies on tuberculosis contact tracing but the proportion of child contacts under five screened for TB by health workers needs to be verified and their clinical outcomes established. For example, tuberculosis contact examination forms and tuberculin skin test (TST) might be available in health facilities but may not be used. If they are used, the evaluation of children contacts under five years may be incomplete. This study sought to

investigate how well tuberculosis contact tracing of children under five years is done in Kweneng district; to determine the outcome (prevalence of active TB and LTBI) of contact tracing in under five children; and to find the demographic risk factors risk factors (screening status) associated with TST positivity among children under five who were household contacts of diagnosed sputum smear-positive pulmonary tuberculosis cases.

1.4. Justification for the study

The Botswana TB rate was reported the sixth highest in the world at 536 per 100,000 in 2008 (Ministry of Health of Botswana, 2011b).Thus in a rural district of a country with such high incidence of tuberculosis, children living in contact with a person with smear positive disease are at higher risk of TB infection and disease. Therefore, they need special consideration including tuberculosis contact screening and management; which can further enhance case finding and prevent tuberculosis disease (Triasih et al. 2015) in Kweneng district.

Generally missed opportunities for tuberculosis contact tracing constitute a major impediment to improving tuberculosis control programme in the community. In Kweneng district, tuberculosis outpatients' cards reveal that little contact tracing is done and that few contacts are given appropriate Isoniazid Preventive Therapy (IPT). TB screening is universally recommended but rarely implemented in tuberculosis-endemic settings (Triasih et al. 2015). While the Botswana National Although the TB Control Program guidelines recommend TB screening in children (Ministry of health of Botswana, 2011a), from our observation on the field/ practice, it seems child TB contact efforts including household TB screening of under-five have been given less attention in Kweneng district. The TB programme

in this district mostly focuses on adult TB case finding and management, but offer little priority to contact tracing of young children. Generally an adult subject might take initiative and walk by him/herself to a health facility to demand TB services including screening services when a family member in the same household is diagnosed with TB; but a young children is enable to do so. Hopefully with the current Botswana National TB program guidelines which recommends now an effective and simple approach to child tuberculosis contact management (Ministry of Health of Botswana, 2011a); the Kweneng health care system should be able to effectively implement at least child contact tracing at its primary healthcare level because this approach sounds more feasible in resources-limited settings as it does not require any more TST or CXR.

However, it is important and relevant that this study of a representative rural sample firstly, finds out whether or not children under five in a household contact with adult confirmed sputum-positive pulmonary tuberculosis cases are followed up; and secondly, measures the occurrence of infection (latent tuberculosis infection or disease) in these contacts. A number of studies on tuberculosis have been conducted in Botswana, but at the time of this research there was still very limited data on household tuberculosis contact tracing in childhood especially in rural areas. Thus this study will yield important baseline data on household tuberculosis contact tracing in rural settings in Botswana, that can be utilised in the near future by the TB control programme, district heath team management (DHTMT), and policy makers for informed decision making to plan contact tracing activities or review contact tracing guidelines particularly for children under five. The information generated in this study will also add to the knowledge, the value of contact tracing of children under five in rural settings in sub-Saharan Africa.

1.5. Concepts and definition of terms

1.5.1. Tuberculosis index case:

The first case or initial active case from which the process of contact investigation

Begins (Public Health Agency of Canada, 2014). In other words, it is the initially identified case of new or recurrent TB in a person of any age in a specific household or other comparable setting in which others may have been exposed (WHO, 2012). An index case is the case around which a contact investigation is centred; in this study the working definition is any diagnosed smear-positive pulmonary tuberculosis patient registered by Kweneng district health facilities between March 2003 and February 2005.

1.5.2. Tuberculosis contact:

Any person who has been exposed to an index case (WHO, 2012). In this study TB contact refers to an under five years child individual who lives in the same household and had close, regular or prolonged contact with a diagnosed sputum smear-positive TB patient; especially in small, poorly ventilated places for a certain exposure. The term “close contact” refers to contact within the prior 24 months either within the household (Graham & Ahmed et al. 2012). Based on the definition used by the Tuberculosis Trial Consortium (TBTC) from Center for Diseases Control and Prevention (CDC) for the study 26 protocol; all contacts of TB index cases who shared an enclosed space for ≥ 4 hours a week, are close contacts and are most likely to be infected with TB. However, the different definitions utilized for the term “close contact of TB” can make the yield of contact tracing irregular among different settings (Loredo & Cailleaux–Cezar et al. 2014). Therefore the definition should be tailored to the local epidemiological context; the

bottom line is that no safe exposure time to airborne M. tuberculosis has been established. If a single bacterium can initiate an infection leading to disease, then even the briefest exposure entails a theoretic risk (Paul & Al-Maani et al. 2013). Nevertheless Triasih et al. (2015) in a study conducted in Yogyakarta, Indonesia, they defined "close contact" as living in the same house with the index case within the last 3 months, or having had frequent contact with the index case for a minimum of 8 hours per day, within the last 3 months if not living in the same house.

Hence in the context of Botswana as a country with high TB incidence rates, and a population highly mobile, moving frequently and mostly between villages, towns, and farms/ cattle posts (Lockman et al. 2001); especially during weekends and holydays), a tailored definition is more appropriate and applies to any person who shared a house or room regardless of the duration whether he sleeps there a single night/day or each weekend with a TB patient or spent time with the patient frequently during the period of infectiousness. Thus in Botswana close contacts would include household members, co-workers and schoolmates with close and frequent interaction with the index case (Ministry of health of Botswana, 2011a) Therefore regardless of the duration a family member who lives in the same home as the TB patient is a close contact. A family member or friend who lives elsewhere but visits for a few hours every other week is another-than-close contact both should be given high priority especially in these settings.

This study focused only on TB contacts who were under five years of age children who have been exposed to tuberculosis by living into close contact or other-than-close contact in the same household with an infectious smear-positive pulmonary tuberculosis case registered by the Kweneng district TB programme. Thus any other TB case who was family member or friend who lived elsewhere but visited for either a few hours every other week, slept there each weekend or lived in a household with children for ≥ 4 hours a week was neither part of this study nor the definition of tuberculosis contact.

1.5.3. Household contact:

A person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before initiation of the treatment (WHO, 2012).

This definition varies considerably and must be adapted to the local context. The determination of the amount of exposure, estimated as the time spent with the index case, is likely subjective. Therefore the three months period is a general guideline; the actual period of infectiousness may be longer or shorter (WHO, 2012).

In this study household contacts were children under five living in the same household with the index case during the infectious period of a duration relying on recall by the index case of the time symptoms began.

1.5.4. Tuberculosis contact tracing:

This is one of the methods applied for active case-finding. When a new case of TB is found, a search must be made around the case as soon as possible to

identify others who may contact the disease. The patient home visit may be useful to establish a supportive relationship with the patient and his family, identify children at risk of TB and/or any other person exposed. Close contacts (e.g. households) need to be checked giving particular attention to children. For the purpose of this study contact tracing refers to the identification and investigation (by TST with or without clinical examination or chest radiography) of all children under five years who have been contact of a known household sputum-positive TB case. This involves the systematic evaluation of these children contacts for disease or latent TB infection (LTBI).

1.5.5. Tuberculin Skin Test (TST) or Mantoux test:

The Tuberculin Skin Test (TST) is the primary tool used for diagnosis of LTBI in worldwide. It determine whether the person is infected with mycobacterium tuberculosis. An infected person presents a hypersensitivity reaction detectable two to eight weeks after infection.

TST is the most commonly utilised tool for diagnosing latent tuberculosis infection in children under-five contacts in Botswana and elsewhere in TB high burden countries. Mantoux test is the unique tuberculin testing used in Botswana. It consists of an intradermal injection of 0.1 ml of 5 TU (tuberculin units) purified protein derivative (PPD) solution. The reading, interpretation and recording of TST reactions (in millimetres of induration) is done within 48 to 72 hours after the injection.

It is important to know that beside the TST, the Interferon–Gamma Release Assay (IGRA) are also used to determine whether a person is infected with M. tuberculosis through measuring the immune system response to TB proteins in

blood. So far there are limited evidence to guide the use of IGRA in young children under five years (Australasian Society for HIV Medicine, 2010). And it is not yet used in Botswana and in most low- and middle-income countries.

1.5.6. Tuberculosis chemoprophylaxis:

It refers to preventive tuberculosis treatment and consists of Isoniazid for at least 6 months. It is called “Isoniazid prophylaxis” It can greatly reduce the likelihood that the exposed child will develop tuberculosis during current exposure Latent tuberculosis Infection (LTBI).

1.5.7. Latent tuberculosis Infection (LTBI):

It is a mycobacterium tuberculosis infection which has been contained by the immune system of infected person (host). This means a person is infected by tuberculosis, but s/he is not (yet) ill or does not present any symptom of TB disease and often cannot transmit the TB disease. In this study we defined LTBI as having a TST reaction of ≥10 mm at 48–72 hours.

The HIV and nutritional status of children were not part of the study objectives, Hence this study did not read TST's any differently in HIV positive children and severely malnourished children, meaning that WHO and others would regard as positive TST of 6 mm in a child who was HIV positive or malnourished would have been misread in this study as a negative TST.

1.5.8. Active TB /TB disease:

A disease caused by mycobacterium tuberculosis germ. Generally the chief symptoms of active TB (disease) are: cough, fever, night sweats, weight loss etc. The diagnosis of active TB can be done through:

1. A smear or culture taken from any source in the person's body tests positive for tuberculosis and the person has not completed the appropriate prescribed course of medication for active tuberculosis disease.
2. Radiographic, clinical and/or laboratory which are sufficient evidences to support medical diagnosis of TB disease and justify instigated treatment.

The diagnosis of tuberculosis in children is difficult and poses problems that are not present in adults due to the fact that children are less likely to have obvious symptoms of tuberculosis. In addition, sputum samples are difficult to collect from children (American Thoracic Society & CDC 2003). Recent research criteria to diagnose TB in children have been published by Graham et al. (2012) which outline: - An acceptable definition of a positive TST as ≥10 mm skin induration in an HIV-uninfected child or a ≥5-mm induration in an HIV-infected or severely malnourished child, regardless of BCG vaccination. - A history of exposure to M. tuberculosis defined as a reported close contact to a person with active tuberculosis. Where the term "close contact" refers to contact within the prior 24 months either within the household or outside the household. - CXRs Definitions for diagnostic research purposed an approach that requires a "yes" or "no" response to the presence of cardinal radiological features.

However it is important to emphasize that a recommendation for CXRs evaluation by 2 independent readers experienced in reviewing paediatric CXRs and blinded to clinical categorization, and the use of standardized forms a proposed approach to CXR assessment might not be a realistic and implementable recommendation in resources challenged setting especially in rural area with high burden of TB. This recommendation might significantly discourage or limit the research effort in

those settings. - Definition of clinical symptoms and signs suggestive of tuberculosis in younger children was also recommended.

According to Graham et al. (2012) the above definitions are intended for use in clinical research to evaluate diagnostic assays and not for individual patient diagnosis or treatment decisions or reporting of childhood tuberculosis.

Although these criteria were not fully used in our study particularly the review of CXRs by two independent blinded readers and use of standardized forms; at least the diagnosis of TB (and LTBI as well) in this study closely lined up with the above criteria proposed by Graham et al. (2012).

1.6. Study objectives

The overall aim of the study was to describe the screening and clinical outcomes of children under five years of age living in close household contact with the adult smear-positive pulmonary TB index cases registered in the rural Kweneng district between March 2003 and February 2005.

The specific research objectives were:

1. To estimate the proportion of child caregivers satisfied with the household TB screening by the district health care system.
2. To determine the proportion of child contacts initially screened for TB by the district health care system at the time the TB index case was diagnosed.

3. To determine the occurrence of tuberculosis infection and disease in children under five years who were household contacts of adults with pulmonary tuberculosis.

4. To compare the prevalence of tuberculosis disease and latent tuberculosis infection (LTBI) between those child contacts initially screened for tuberculosis and those that were not.

CHAPTER 2: LITERATURE REVIEW

Tuberculosis is a serious threat to public health, especially in sub-Saharan Africa (Guwatudde & Nakakeeto et al. 2003), it remains one of the leading cause of death in children especially in developing countries (Zaman, 2010) including Botswana. The 2013 WHO Global TB report reveals an estimated 530 000 new TB cases and 74 000 deaths among children in 2012 (WHO, 2013a). Although awareness is growing, childhood tuberculosis (TB) remains a neglected disease in many resource-limited settings. TB in children is often missed or overlooked due to non-specific symptoms and difficulties in diagnosis. This has made it difficult to assess the actual magnitude of the childhood TB epidemic, which may be higher than currently estimated (WHO, 2013b). In part this reflects operational difficulties, lack of visibility in official reports, as well as perceptions that children tend to develop mild disease, contribute little to disease transmission, and do not affect epidemic control (Marais & Schaaf et al. 2010). At an international level there is greater appreciation that children contribute significantly to the global TB disease burden and suffer severe TB-related morbidity and mortality, particularly in TB-endemic areas. However, this is not always the case at the national or local level in resource-challenged settings and there remains an urgent need for both feasible and implementable and updated TB policies to guide clinical practice including contact tracing of under five children control (Marais et al. 2010)**.** Young children are the most at risk for three main reasons: firstly, they are more prone to develop severe extra pulmonary TB (such as TB meningitis and others); secondly, they easily develop severe pulmonary disease with bronchial obstruction; and thirdly, young children are more likely to progress into TB disease after being infected. The risk of developing disease after TB infection for instance was

estimated to 24% in children aged one to five years old, and 43% in infants below one year old compared to 15% in adolescents and 5–10% in adults (Miller & Seal et al. 1963).

Botswana had one of the highest TB notification rates among high TB burden countries; its downward TB trend reversed in 1990 and increased to a peak incidence of 623 per 100,000 in 2002, one of the highest worldwide. In 2008 the rate of TB in Botswana was the sixth highest in the world at 536 per 100,000 (Ministry of Health of Botswana, 2011b); this increase in TB notification could be attributable to the high HIV prevalence (23%) in Botswana (ranked 2nd highest in the world) (UNAIDS, 2012).

Younger children who live in poor socioeconomic conditions are at highest risk of TB infection and disease. They particularly form an important epidemiological cluster that accounts for a notable proportion of TB morbidity. Efforts to improve TB control must therefore not only target adults (through case detection and the cure of infectious cases), but should also be geared toward younger children through screening children who have been in contacts with adults TB cases (Van Rie & Beyer et al. 1999).

Thus the identification of case of active or latent tuberculosis infection in a younger child could be an indicator suggesting that transmission of tuberculosis has occurred recently (American Thoracic Society et al. 2003), and search around this child of should be initiated to find the source case. In other words, when the diagnosis of active tuberculosis is confirmed in a younger child, it means that someone close to that child, almost always an adult, must have active tuberculosis and is possibly transmitting the disease to other contacts as well. For

example, a review and analysis of 95 studies from low- and middle-income settings by Fox et al. (2013), shows active TB prevalence of 3.1% in all contacts, and 51.5% latent TB infection. The prevalence of TB among household contacts and children 0-5 years contacts was respectively 3.1% and 10%. These findings are an evidence suggesting that children living in household contact with an adult active tuberculosis case are at higher risk for tuberculosis infection and disease. Among those that get infected, youngest children (under five years of age) are at increased risk of developing TB disease. For these reasons, improved contact investigations will have a great impact in reducing the number of TB in children under five years of age. Therefore, the World Health Organization (WHO), International Union against Tuberculosis and Lung Disease (IUATLD), and the International Standards for Tuberculosis Care all recommend that children who have been exposed to infectious cases of TB, need to be evaluated for active TB and considered for treatment of latent tuberculosis infection (LTBI) once active TB has been excluded (WHO, 2012). While the WHO guidelines advise that all children under five contacts of sputum smear-positive cases should be actively investigated for tuberculosis and provided with preventive chemotherapy after active TB has been excluded (WHO, 2006a); The implementation of these recommendations faces challenges since at the global level there is no clear guidance on epidemiological and programme conditions under which contact investigation is indicated. The following are some of these challenges:

- Selecting the TB index patients for which contact investigation should be prioritised
- The difficulty in making a differential diagnosis of LTBI in a highly BCG-vaccinated population

- Ruling out incipient active disease
- Shortage of skilled human resources
- The lack of procedures for documentation and follow-up of contact screening and chemoprophylaxis in national programs
- The lack of accurate and age specific segregated data on contact screening activities etc.
- Limited capacity building

Due to challenges, the screening of children household contacts of tuberculosis (TB) cases is rarely implemented in most TB endemic settings in resource-limited countries such as Botswana (Soumya & Banu, 2010).

Infants and young children under five years are at particular risk for the infection and disease (WHO, 2004). Thus efforts to improve TB control must also concentrate on screening children contacts in addition to targeting case detection and treatment of adult cases.

According to Van Rie et al. (1999), historically, the highest TB mortality ever reported (600 deaths/100 000) was in children aged 0- 4 years in Wales in the middle of the 19th century. It means youngest children carry the biggest burden for the disease and the morbidity and mortality is higher in young children than in older children or adult contacts. For example findings in a retrospective descriptive study conducted in two urban communities of Cape Town, South Africa by Van Rie et al. (1999), showed that of the total case load, 36% (1383 cases) were in children 0-4 years old against 9% (361 cases) in children 5-14 years old. More remarkably the age specific TB case notification rate in children 0- 5 years in the same study was 3.5 times the case notification rate in

adults. Although these could be notification rates with the inevitable problem of inaccuracies, a high TB case notification rate of 3588/100 000/year in young children 0–5 years old is one of the evidence based justification for targeted (children under five) TB screening.

Since the source of infection in every child with TB is an infectious adult, treating smear positive infectious adults is the priority as this is the key to interrupt transmission of TB; however a TB epidemic cannot be controlled by only treating cases using ant tuberculous drugs (DOT). In addition to the treatment of cases, national tuberculosis control programmes should extend effort pay to contact tracing and provision chemoprophylaxis of infected children. According to Murray & Stylbo et al. (1990) because of its lower cost effectiveness active contact tracing of children (smear negative) only intervene at a later stage in TB control programme; this is in contrast to the International Union Against Tuberculosis and Lung Disease and the American Academy of Paediatrics guidelines that recommends active contact tracing, chemoprophylaxis for asymptomatic children and the treatment of symptomatic children is an integral part of TB control programme (Van Rie et al.1999). In developing countries young children account for higher (39%) proportion of total TB cases, compared to 2 –7% in high-income countries which was much less than the 15% for developing countries (Murray et al. 1990). Such high proportion of TB in young children, if not treated, constitutes a reservoir from which new adults cases of TB will arise in the next years (Van Rie et al. 1999). Therefore in high TB burden countries, leaders and program planners need to allocate sufficient resources including funds to TB contact tracing activities targeting young children. Since 80% of children with active TB were between 0–5 years, Van Rie et al. (1999) argued in their study that treatment

costs can be minimised by focusing active contact tracing to this age group. This sound argument aligns with both the WHO recommendations and the Botswana national TB programme that support TB contact racing in young children. In addition to Van Rie et al. study, Fox et al (2013) reviewed 203 published studies and their results support also for the existing priority given in WHO recommendations for screening children contacts aged under 5 years. However in this last study, it is difficult to make strong recommendations for the implementation of specific interventions (Guyatt & Oxman et al. 2008), since all reviewed studies were observational studies.

In conclusion, young children under 5 years are vulnerable and an age group at risk of TB. This risk is increased among those children living in household proximity with an infectious adult TB case (Van Rie et al. 1999)**.** Thus contact tracing of this group of children should be given high priority in the national TB control programme and policy. This strategy (contact tracing) not only intends to diagnose asymptomatic cases of primary TB and prevent complications of active disease, but it is an opportunity to offer chemoprophylaxis to infected children who have no active disease after evaluation. A systematic review of household contact studies in low–middle-income countries by Janina & Madhukar et al. (2008) found aggregate rates of 4.5% for active TB and 51.4% for LTBI. This indicates that contact investigation is extremely useful and deserves great consideration in the improvement of early case detection and decrease of transmission in high-incidence areas. A number of others studies suggest that contact tracing contributes to tuberculosis control effort (Müller & Kretzschmar et al. 2000); (Aparicio & Hernández, 2006) and (Ziv & Daley et al. 2001). When effectively

implemented, it can have an impact on morbidity and mortality, especially among children (Nair, 2001).

In Botswana when a new case of smear-positive pulmonary tuberculosis is diagnosed, a search around this case must be done within 72 hours (3 days) after case registration, to find others persons who might have contracted the disease. Targeted persons are usually close contacts such as family members, in particular children under five years of age (Ministry of Health of Botswana, 2007).

The discussion in the following sections review the literature on the transmission of TB to children exposed to an infectious case in the same household, the screening of child contacts of smear-positive TB cases as an important and worthwhile part of a TB control programme, and the appropriate investigation and treatment of latent tuberculosis infection (LTBI).

2.1. Household transmission of TB to child contacts

As discussed above, person living with TB patients are at risk of infection and disease, and children under five are at greatest risk (Jonathan & Megan, et al. 2014), since they have a higher risk of progressing into tuberculosis disease (Hoskyn, 2003). It is assumed that if a child develops tuberculosis, the source was an adult infectious case, usually living in the same house. However the presence of an adult infectious tuberculosis case in the same household as a child with tuberculosis does not necessarily imply adult-to-child transmission. Young children may have been infected either in the community or in the household as it was demonstrated in a study by Schaaf et al. (2003). As mentioned earlier, in developing countries a big number of children per family, increases the probability of at least one child getting infected by an infectious household TB case (Van Rie

et al. 1999). Meanwhile the transmission of TB from a child to another seems to be rare. Though there are very few and conflicting views on this subject, contact tracing for sputum smear-positive children should be also given priority in TB control program. For e.g. transmission from a seven year old child in a Sydney school was found in a study conducted by (Cardona & Alperstein et al. 1999). These findings prove that transmission of TB from young child to another may occurred. While we generally admit that the source of childhood TB is an adult infectious TB case, usually living in the same house with the child, this may not always be correct in all situations. A young child with an infectious TB could be him/herself the source case of infection among his/her contacts across the age spectrum (adults and children). For example Puryear & Seropola, et al. (2013) found 2.2% (12/548) new TB cases whom median age was 31 years (IQR 23–38) among contacts of pediatric TB index cases in Botswana. Although Puryear et al. did not explore the possibility of the primary index cases (sources case from which children initially got TB) being included in the 2.2%; but at least their study concluded that the yield of household contact tracing using pediatric index cases was similar to the traditional adult index case approach. However considering a similar study tracing adult tuberculous contacts (source) through children TB cases by Somu & Vijayasekaran et al. (1997) which detected 13 new adult tuberculosis cases (9.3%) among adult contacts of children with tuberculosis, and outlined an overall 61% children who had tuberculous adult contact may simply suggest that both Puryear et al. and Somu et al. could be simply a reverse of contact tracing (case finding) evaluation of a smear positive index adult case rather than a traditional adult index case approach as stipulated by Puryear et al. (2013). Hence both the yield of 2.2% and 9.3% adult new TB cases contacts of

children with TB respectively in Puryear et al. and Somu et al. studies, more likely suggests adult source cases who were undiagnosed rather than adult contacts infected by children index cases. This corroborative approach (finding adult tuberculous contact source) is as important as tracing the contacts of a smear positive index adult case, such as household contacts, it could help to detect adult source cases especially in communities where the denial of tuberculosis by adults is obvious due to the social stigma attached to TB because of the HIV/TB relationship.

Furthermore, a household contact study by Fuimaono & Vince (1997) found the occurrence of transmission from child index cases to child contacts. 32 (39%) out of 83 children contacts had TB and were started on TB treatment, and 2 children 6 months old had LTBI and put on INH prophylaxis. Furthermore the yield of 2.2% (12 cases out of 548) of new TB cases in a household contacts tracing study of pediatric TB index cases in Botswana by Puryear et al. (2013) indicates the occurrence of transmission from child index case to a household contact. But since the median age of contacts was 31 years in this last study and due to data limitations on outcomes disaggregated by age group, it would be somehow difficult to argue in favour of a household transmission from child index case to younger children contacts. Whether the household TB transmission from child index to child contact is high or not, in our study children cases were not part of the study approach or investigation.

The transmission of TB from an adult to a child is influenced by certain underlying factors including socio-economic characteristics, such as crowded household conditions (more than one person per room), nutritional status of the child, and

proximity to the index case (Van Rie et al. 1999). Also the intensity of exposure to tuberculosis cases and severity of disease in the index case are key risk factors in in tuberculosis transmission. For example, if a mother who coughs and has sputum smear-positive pulmonary tuberculosis, her infant has great chance to be infected, because of close contact and the higher risk of inhaling a significant amount of infectious droplets. Thus beside the susceptibility, vulnerability and circumstances of exposure elements, the assessment of priority in TB contact investigation should also consider the characteristics of disease in index. For example in the Australasian contact tracing manual, all household contacts and children under five, are given high priority (Australasian Society for HIV Medicine, 2010).

Child contacts under five years are assigned high priority for investigation because also the peak incidence of TB among young children occurs been one and four years of age, as demonstrated in a Bacille Calmette-Guérin (BCG) trial in Puerto Rico study by Comstock & Cauthen (1993). Nevertheless, Begun & Newall et al. (2013) suggested in their study that contact tracing could involve targeted investigations of intimate or close contacts.

The household TB transmission to contacts has been evaluated by previously studies such as the case-control study carried by Claessens & Gausi (2002a) in Malawi that revealed that there was a higher frequency of TB in households of index TB patients than in control (households with no TB index case).This could be supported by Lienhardt & Sillah et al. (2003) study in child contacts in Gambia, West Africa, which study showed that the risk of being TST-positive (10 mm or more) was higher in children who were in households contact with individuals

with infectious TB than in those who were in contact with community controls. Lienhardt et al. findings meant the risk of being TST positive was higher in contacts of cases than in contacts of control subjects.

The high risk of household tuberculosis transmission has also been verified in several studies. For example in New York City by Munoz & Starke et al. (2000), in Malawi by Topley & Maher et al. (1996) where 180 (63,8%) had evidence of tuberculosis, in South Africa by Beyers et al. (1997) and in Botswana by Kenyon & Copeland et al. (2000). Furthermore Gessner & Weiss et al. (1998) have documented that tuberculosis infection developed in 25% of child contacts and that 9.6% of them progressed to active disease. Last but not least Marks et al. (2000) found that contacts who had active TB were more likely to be household contacts and children younger than 6 years of age than non-household contacts.

In all these studies, contact with an individual tuberculosis case in a household setting emerged as the strongest risk factor for tuberculosis infection. This was also substantiated by a study conducted in the Gambia, West Africa, where 135 (35%) children presented a palpable TST induration, which demonstrated that tuberculosis was directly related to the intensity of exposure of the child to the individual with tuberculosis (Lienhardt. et al. 2003).

Data from a study on tuberculosis transmission in the family show a relatively high risk of intra-family tuberculosis transmission (Wang & Turner et al. 2002). In this study 66.3% of contacts had minimal disease, 27.8% had moderately advanced disease, but only 5.9% had advanced disease. Findings from this study supports early diagnosis approach through family contact investigations which can

contribute .to the reduction new tuberculosis cases and eradication of the disease (Wang et al. 2002).

Thus, the literature clearly demonstrates that the source of infection in a child is usually an adult TB case infectious living in same household and that young children under five years of age are at higher risk of infection and disease. However transmission of tuberculosis may also occur in the community. To this end Schaaf et al. (2003) have tried to establish epidemiological links and confirm household transmission in a restriction fragment length polymorphism (RFLP) study. In this study they showed that of 35 children, 19 (54%) children had household members identified with tuberculosis, 12 with the same strain as the child. However 29 (83.0%) of strains in the children were part of community clusters, but definite contact with source cases was established in only 15. Although this result suggests that the higher proportion (83.0%) of strains were from the community than the household, the research did not indicate whether or not the difference was statistically significant. Furthermore due to problems in recovering specimens or extracting DNA in this research, RFLP analysis was done in only 832 adults and 35 children of the 1139 adults and 65 children with confirmed TB. The possible bias of this smaller sample may limit drawing meaningful conclusions on whether tuberculosis transmission mostly occurred in households or generally in the community. Since most other studies found a high rate of infection and disease in children household contacts of cases, TB control programmes should continue to recommend targeted (household) TB contact screening. Thus the best way to prevent tuberculosis in younger children should be an effective identification and treatment of infectious cases coupled with contact tracing of children household contacts of index cases**.**

2.2. Screening of children under-five household contacts of smear-positive tuberculosis cases

Investigation of contacts may enhance the early detection of TB and reduce the risk of transmission (Fox et al. 2012). The evaluation and TB prophylaxis treatment of infection in children contacts of adults who suffer from pulmonary tuberculosis is a worthwhile approach (Beyers et al. 1997) especially in a high endemic area. According to Graham (2007). Any child who has been exposed to smear-positive TB must be screened for TB. In Botswana contact tracing of children who are household contacts of infectious TB cases is part and parcel of the national TB control programme. The Botswana National Tuberculosis programme manual indicates that when a new case of tuberculosis is discovered a search must be immediately made to identify the source of infection and also others who may have contracted the disease. Usually only close contacts (e.g. family members) need to be checked, paying particular attention to children under five (Ministry of Health of Botswana, 1995). Thus contact investigations of adult pulmonary cases should identify children with previously undiagnosed TB or latent tuberculosis infection (LTBI). For example a contact study investigation of adult TB cases from eight health jurisdictions in California, evaluated 202 contacts under five years and 122 aged 5-14 years (Lobato & Royce et al. 2003). They found that a high percentage (41%) of contacts had a positive tuberculin reaction, especially among close household contacts. Also fourteen previously undiagnosed active TB cases were found, including seven children under five years of age. Such studies therefore justify the need for screening child TB contacts.

The likelihood of a child becoming infected with TB, increases among children who have a medical history of close contact (family member or any other person living in the same household, relative etc.) with a smear positive TB patient (South African National Department of Health, 2000). This can be substantiated by the finding of high transmission rate among children under five years in a study in Harare, Zimbabwe (Mtombeni & Mahomva et al. 2002). Also a documented 78% of children infected or developed TB disease in a study that evaluated 125 under five children household contact of 73 MDR (Multidrug-resistant) pulmonary TB in the Western Cape Province of South Africa (Seddon & Hesseling et al. 2013).

Basically when a child is infected with tuberculosis he may not present any symptoms, but the infection can silently progress leading to later development of severe illness. Children under five years with LTBI have been only recently infected

are at a higher risk of progressing to active TB disease. The literature suggests that 40% of untreated infants will develop active TB disease although the risk of progression decreases throughout childhood (Paediatric Tuberculosis Collaborative Group, 2004). These children are also more likely than older children and adults to develop life-threatening forms of TB disease in particular meningeal and disseminated disease.

Hence, in order to detect the problem earlier before the child becomes ill, we perform a tuberculosis skin test using the intermediate PPD (Mantoux) skin test (Ministry of Health of Botswana, 1995). However new developments that have occurred in the field of TB control worldwide prompted the Botswana national guidelines on the management of tuberculosis to shift and adopt new strategies.

Hence currently the Botswana National TB Guidelines consider that clinical assessment alone is sufficient to decide whether a paediatric contact is well or symptomatic, and routine assessment of child contacts does not require a chest x-ray (CXR) or a TST (Ministry of health of Botswana, 2011a). This new approach focusing more on symptom-based screening is a bit different from the previous Botswana national TB guidelines (emphasising on TST), which we used during this research.

Screening for tuberculosis in child contacts of tuberculosis index cases is an essential procedure and part of case management strategy, for both close and more occasional contacts (Olivier, 2003) and it should be an essential function of primary health care for all high risk groups of children, such as children under five and household contacts of smear-positive TB cases. Contact tracing is extremely important to identify cases and latent tuberculosis (TB) especially among children under the age of 5 years in household contact with smear positive adult index case. For instance the study in a socio-economically deprived area in the United Kingdom, out of 263 contacts the highest yield proportion of contacts requiring full treatment or chemoprophylaxis were contacts of smear-positive index cases 33 (12.5%) as compared to contacts of those with smear-negative pulmonary tuberculosis (12 out of 156; 7.7%) and non-pulmonary disease (14 out of 277; 6.2 %) and it was demonstrated in this study that the contact-tracing strategy was more effective than new entrant screening (Underwood & White et al. 2003). Also a study in Malawi found much higher transmission rates than reported elsewhere with 63.8% of child household contacts of sputum positive adults cases testing positive (Topley et al. 1996).

The aims of screening contact children are essentially to identify those infected by the index case and appropriately offer preventive therapy to those infected or Direct Observed Treatment Short-course (DOTS) for those with TB disease. This proposal is supported by Marks et al. (2000) who argued that the second priority of TB prevention and control programmes is contact investigation. The first priority being the diagnosis and treatment of all TB diseased persons.

Active contact tracing is promoted in a number of countries albeit with minor variations. For example, the New South Wales (NSW) Health Department (2001) suggested that high-risk contacts of highly infectious cases including all children under five living in the same household or dwelling with index case should be screened for TB within seven days of diagnosis. The Botswana guidelines on contact tracing and examination recommend that a search around the new case of smear-positive pulmonary TB should be made within 3 working days from the date of registration (Ministry of Health of Botswana, 2007).

The findings of 14% of children with infection (LTBI) and 34% with TB in a South African household contact tracing study of 155 children under five in contact with 80 index cases by Beyers & Gie et al. (1997) is further evidence supporting the necessity of tracing for an early detection and prevention of tuberculosis disease in children under five years of age. In the same study the authors also found that children under two years of age had more severe disease than those aged 2-5 years. Similar results were observed in the documented high transmission rate (49% with probable TB and 28% with suspected TB) among under-five contacts in a study conducted in Harare, Zimbabwe by Mtombeni et al. (2002).

The British Thoracic Association has recommended the follow-up for at least two years of close contacts of smear-positive cases of tuberculosis after an initial screening visit (Teale & Cundall et al.1991). But Selby *et al* cited by Teale et al. (1991) have suggested a reduction in the duration of follow up although not specifying exactly how much it could be reduced. But in a review of results of contact procedures in Leeds, Teale et al. (1991) tried to determine whether their study could support the reduction the duration of follow-up of contacts. They found that of the 42 TB cases diagnosed through contact procedures the majority (71%) was identified at the first visit but subsequent TB cases were still diagnosed during late follow-up: 19% at 6 months and 10% TB at 16 – 24 months. Although there was a progressive decrease in case detection over time, a number of cases would have been missed if follow-up was terminated early. The usefulness of ongoing follow-up have also been documented by Marks et al. (2000) who identified an additional 213 positive TSTs positive during subsequent follow-up in addition to the 1512 positive cases diagnosed on initial TST screening. These findings were quite relevant to the Botswana context, where tuberculosis guidelines were silent about the time for follow-up of contacts at the time we conducted this study. But now at least this is less of an issue in contact tracing since the current Botswana National Tuberculosis guidelines published in 2011 adopted symptom-based screening approach which does not necessary need the use of TST, this approach is also proposed by Marais & Gie et al. (2006b) and strongly recommended by WHO (2012). In addition, the guidelines put emphasis on the contact investigations that must be started as soon as possible and at least within one week of the TB registration date for the index case (Ministry of Health of Botswana, 2011a). Therefore since the risk of developing TB disease after

infection is much greater for children under 5 years (and all HIV-infected individuals).

Based on the above guidelines and recommendations After close contact to a smear positive PTB index case, the Botswana National TB recommends to give IPT to all children < 5 years (and HIV positive children ≥ 5 years) if there is no evidence of active TB disease (Ministry of Health of Botswana, 2011a). Hence in this context all children exposed to a smear positive adult and who are asymptomatic regardless of TST status would be treated for latent TB. This an approach which may be more feasible especially in many resource- limited settings such as Botswana. However, exceptionally this approach may still be unsuitable for some rural areas in resource-challenged settings especially in high HIV prevalence areas, as symptom-based approaches offered little diagnostic value in HIV-infected children (Marais et al. 2006b). Most of these settings are challenged by limited access to a medical doctor or trained TB nurse, who can timely and efficiently offer child contact screen services using a simple symptom-based approach with reasonable degree of accuracy; and be able to exclude active TB prior to offering IPT in addition to making clinical follow-up for additional diagnostic value especially in high risk children.

Therefore, while the symptom based screening offers the exciting prospect of improving treatment access for children especially in resource limited settings, caution is required, because very young children (under 3 years old) have an increased risk of rapid disease progression, yet the approach performed less well in this group (children under 3 years) as indicated by Marais et al. (2006b).

The importance of screening TB contacts cannot be overemphasized. For example, in the same study by Marks et al. (2000), a large number of contacts of drug-resistant and cavitary tuberculosis index cases was identified during follow up by TB contact workers who spent much effort and time in tracing contacts of these cases. Their effort in identifying secondary cases greatly contributed in the reduction of undiagnosed drug-resistant cases and prevention future transmission of this form of tuberculosis in the family and the community at large. Thus an effective contacts screening is essential for preventing secondary TB cases and is especially important for child contacts (Hortoneda & Saiz et al. 1996). Contact tracing should be followed by the provision of an appropriate preventive therapy or treatment of positive contacts.

2.3. Evaluation and treatment of latent tuberculosis infection (LTBI) in children under five during contact tracing.

The evaluation for TB infection and disease, in children usually follows the diagnosis of a case in an adult, and relies on tuberculin skin testing, chest radiograph and clinical symptoms TB diagnosis in children usually follows discovery of a case in an adult, and relies on tuberculin skin testing, chest radiograph, and clinical signs and symptoms (Khan & Starke, 1995). All National TB Programs (NTPs) should screen household contacts for symptoms of disease and provide isoniazid preventive therapy (IPT) to children under five years who are household contacts. Some programmes screen and provide isoniazid preventive therapy to all children (WHO, 2006a) as recommended by current the 2011 guidelines from Botswana national TB control programme. Also the WHO recommends the provision of IPT to all under five child TB contacts, regardless of their TST results and after active TB has been excluded (WHO, 2006a).

In 1995 the Botswana National TB program (BNPT) published a manual for TB with a section on TB contacts in children but does not give a clear indication of the TB investigations required. Although the investigation and treatment of infected contacts is an important strategy of the BNPT, its priority is secondary to the treatment of TB cases. During the period of this study, the Botswana TB guidelines have not been updated since 1995 to indicate when a decision should be made to initiate a contact investigation in children under five; however later on in 2007 the the Botswana National Tuberculosis Programme prepared the sixth edition of the national tuberculosis program manual which at least updated the 1995 guidelines In the light of protection of child contacts, the same guidelines have at least considered clinical assessment alone as sufficient for making decision on whether a child contact is well or symptomatic. Therefore routine assessment of exposed contacts does not require CXR or TST (Ministry of Health, 2007) anymore. This approach would be the most appropriate method for endemic areas in resource- challenged setting such as Botswana where the triad (known contact with an adult index case, positive TST as evidence of latent tuberculosis infection, suggestive signs of chest x ray) was used in clinical practice (Khan et al.1995) has reduced accuracy; in the sense that clinical symptoms are nonspecific, skin testing and chest radiographs can not only be difficult to interpret, but are not available at primary health care clinics and health post where the majority of children contact are attended and routine laboratory tests are not helpful (Khan et al.1995).

The 2011 Botswana Ministry of Health TB/HIV collaborative policy guidelines (Ministry of Health of Botswana 2011b) remained silent about isoniazid preventive therapy (IPT) in under five child contacts of infectious TB cases, rather it focuses

more IPT in HIV patients. But at least the updated National Tuberculosis programme manual (Ministry of Health of Botswana 2011a) recommends IPT to all under five child contacts who have no active TB disease.

The prioritisation of contact tracing is determined by the exposure, susceptibility and vulnerability of individual contacts. This section reviews the literature on the type of examination that should be done including the use of the TST. It also discusses the focus on TB prophylaxis in children under five contacts and the treatment of identified TB disease in children which is a challenge to both health workers and contacts.

Contacts should be evaluated by a complete medical diagnostic investigation comprising a full physical examination, tuberculin skin test and chest radiography. Evidences in support of this approach are found in studies conducted in South Africa by Beyers et al. (1997); in Zimbabwe by Mtombeni et al. (2002); in Papua New Guinea by Fuimaono et al. (1997*)*; in the USA by Marks et al. (2000); and in Spain by Alseda & Godoy (2003). All these researchers have shown that in addition to physical examination, both a Mantoux test and chest radiography were required to adequately diagnose infection and disease in children, previously at the time we conducted this research, the above approach was still being implemented and used by most national TB programs including that of Botswana. However now the Botswana National Guidelines, WHO and other many sources such as Marais et al (2006) recommend that child contact of an adult smear positive TB case should be evaluated by a symptom screening alone, hence currently a clinical assessment alone is sufficient to evaluate under five years household TB contact, this evaluation does not require a chest x-ray (CXR) or a

TST, in addition IPT should be given to all children under 5 years if there is no evidence of active TB disease (Ministry of Health 2011a).

Because children with active disease may sometimes be tuberculin negative, chest radiographs have also been recommended in the diagnosis of paediatric tuberculosis in close contacts, regardless of TST results (Marks et al. 2000). Also the National Tuberculosis Controllers Association (NTCA)/CDC workgroup on TB contact investigations recommended the evaluation of under-five child contact with medical history, physical examination, chest radiograph and TST (CDC, 2005). Although these recommendations pertained to the United States of America, they might have been adaptable for use in other countries that adhere to guidelines issued by the World Health Organization, the International Union against Tuberculosis and Lung Disease, and national TB control programs. (CDC, 2005).

Similarly, recommendations from North America have stipulated that every child in contact with a pulmonary tuberculosis suspect person should be clinically examined and get a Mantoux test and chest radiography done (Clark & Cant, 1996). Nevertheless, because TB is easily missed in children, (Clark et al. 1996) recommended that a history of TB contact combined to tuberculin testing and chest radiography can effectively help diagnose TB in children even in western countries where the number of TB cases and deaths from tuberculosis (TB) has been decreasing.

Thus, in the light of a household contact tracing of a child in contact of smear-positive adult TB index case, we supported screening that combines the three methods of evaluation as recommended in the guidelines for investigation of

contacts of persons with infectious tuberculosis by the national tuberculosis controllers association and CDC; but with current developments in TB diagnosis in children and contact tracing we support symptom-based screening as proposed by Marais et al. (2006b) and Ministry of Health of Botswana (2011a). At the time of this study, these recommendations correlated with the previous Botswana guidelines recommending TST, clinical examination and chest radiography which could help to identify children infected and diseased. Therefore in the context of this study, the evaluation of the under-five contacts was conducted according to the old (1995) Botswana national TB programme guidelines which were still in use and not yet revised. Also the previous WHO guidelines regarded TST and CXR as prerequisite tests for adequate screening of household contacts (WHO, 2003); it was in that context that under-five child contacts under this study received TST, chest x-ray and were clinically examined before a conclusion of TB or no TB was made by the researcher during this study. However at the time (year 2015) we are submitting this final research report, Botswana had revised its national TB policy and the current guidelines of 2007 considers now the approach as proposed by Marais et al. suggesting that simple symptom- based screening in child contacts may have considerable value in resource-limited settings (Marais et al. 2006), where these tests are rarely available and where children are often exposed to tuberculosis at a young and vulnerable age. A report from Peru also showed that symptomatic household contacts are those at risk for active tuberculosis (Becerra, & Pachao et al. 2005). Therefore symptom- based screening should drastically reduce the number of children who require further investigation, thereby facilitating the delivery of preventive chemotherapy to asymptomatic high-risk contacts, particularly in resource-limited. This recommendation has been now

included in the most recent WHO guidelines for National tuberculosis Programs on the management of tuberculosis in children (WHO, 2014).

2.3.1. Clinical examination and chest radiography

Early case detection and LTBI remains part of the most important interventions for reducing the risk of TB transmission in the household. Therefore TB contact investigation should be undertaken in line with the standards defined in the national TB control policies. Hence in Botswana any child who has history of close contacts TB must be screened for signs and symptoms of TB using symptom-based approach which is currently recommended by WHO and other sources instead of old guidelines that had focused on TST strategy. All under-five child contacts. Contrary to previous guidelines, the clinical assessment alone is now sufficient to decide whether a paediatric contact is well or symptomatic; and routine assessment of child contacts does not require a chest x-ray (CXR) or a TST (Ministry of Health of Botswana, 2011a). This would mean now that a lack of available TST and CXR experienced by some primary health care facilities especially in rural area of resource- challenged settings, should not be now a barrier to child contact screening and management. In addition, the current Botswana National TB control guidelines recommend that all under-five child contacts children should be given IPT after active TB diseased has been exclude. Similarly WHO recommends that child tuberculosis contacts aged five or under years without any symptoms suggestive of tuberculosis should be started on preventive therapy. But symptomatic children require referral to a level of care where appropriate assessment for suspected tuberculosis can be undertaken. This assessment may include TST, CXR, and sputum examination. (WHO, 2006a). it important to acknowledge that sputum it is difficult to obtain by

expectoration in young children and disease is often paucibacillar (Graham, 2007); the diagnostic yield even when combining smear and culture is usually <50% (Nicol & Zar, 2011). At initial baseline screening (symptom-based screening), Signs and symptoms that are commonly associated include with TB in children include but not limited to: Weight loss or failure to thrive (no weight gain over 3 months); Enlarged lymph nodes (more than 1 x 1 cm); Cough for ≥ 2 weeks; Fever for ≥ 2 weeks; Fatigue/reduced playfulness ≥ 2 weeks; Profuse night sweats ≥ 2 weeks (Ministry of Health of Botwana, 2011a). No one symptom is diagnostic for TB, and symptoms associated with TB disease are often non-specific and may overlap with other chronic diseases, especially in high burden HIV country such as Botswana. The clinical examination require a search of signs of TB in children which are often non-specific and may be related to chronic illness. Key findings may include weight loss and lymphadenopathy on physical examination, while findings on pulmonary examination include coughing, wheezing and respiratory distress. However the chest is usually clear to auscultation. Sometimes children may present with acute severe pneumonia (Ministry of Health of Botswana 2011a) with evident crepitation. An extra pulmonary examination may reveal: Extra pulmonary Tuberculosis (EPTB) which the most common site in children is the lymph nodes, particularly the cervical lymph nodes. TB meningitis is less common but is the most severe form in children. Other sites include the pleura, abdomen, pericardium and bones, including spinal TB (Ministry of Health of Botswana 2011a). However studies have demonstrated that clinical case definitions used to date have been inconsistent (Hatherill & Hanslo et al. 2010). There is therefore, the need for standardized clinical case definitions for the evaluation of diagnostics in prospective research

that include children in whom tuberculosis is suspected but not confirmed by culture of M. tuberculosis (Graham et al. 2012). The consensus standardized clinical research case definitions for intrathoracic tuberculosis in children from an expert panel classified the disease diagnosis into four categories, namely: Confirmed tuberculosis; probable tuberculosis; possible tuberculosis; tuberculosis unlikely and not tuberculosis. As proposed by Graham et al. (2012), these definitions are intended for clinical research and case definition requirements should not render diagnostic studies unfeasible in low-resource settings. The description of each of four categories is a follow: *A confirmed tuberculosis* refers to a suspected patient who presents at least one of the signs and symptoms suggestive of tuberculosis and microbiological confirmation is obtained. *A probable tuberculosis* would be a suspected patient presenting the following: at least one of the signs and symptoms suggestive of tuberculosis, chest radiography consistent with intrathoracic disease TB and at least one of the following: either a positive clinical response to anti-tuberculosis treatment, a documented exposure to M. tuberculosis or immunological evidence of M. tuberculosis infection*. A possible tuberculosis* is when a suspected TB patient presents at least: (1) - one of the signs and symptoms suggestive of tuberculosis and either one of the following: A positive clinical response to anti-tuberculosis treatment, documented exposure to *M. tuberculosis,* immunological evidence of *M. tuberculosis* infection; or (2) - chest radiography consistent with intrathoracic tuberculosis disease. If at least one of (1) and (2) are both present, then this suspected patient should be classified as “probable tuberculosis. *The tuberculosis unlikely* should be a symptomatic patient, but not fitting the above definitions and there is no alternative diagnosis established. Lastly the not tuberculosis would be

a suspected patient fitting the diagnosis for tuberculosis unlikely but with an established alternative diagnosis (Graham et al, 2012).

While a study by Triasih et al. (2015) had provided original evidence that a symptom-based approach the symptom-based approach to screening and managing child contacts recommended by WHO is an effective, simple and safe screening strategy that can be implemented at the primary care level where the index case is being managed; however, the potential problems of recall bias and subjectivity in the reporting of symptoms might be a great challenge. In addition, there are a number of important issues raised by the use of a symptom-based approach for child contacts (Triasih et al. 2012). The first issue is that there will be children presenting abnormal CXR findings such as hilar lymphadenopathy among those evaluated as asymptomatic at baseline. For example, in a South African study of children diagnosed with intrathoracic tuberculosis, 9% reported no symptoms at baseline screening, but all had evidence of primary complex disease on CXR (Marais et al. 2006a). Similarly Triasih et al. (2015) found that 6% of children asymptomatic at baseline had hilar lymphadenopathy on CXR. This should be the raison why Graham et al. (2012) proposed that children enrolled in diagnostic studies should be evaluated at baseline and followed regardless of initial disease classification or treatment decision. Recommended follow-up should be 2 months after treatment initiation or 2 months after baseline if untreated. The second issue is that the symptom-based approach will mean that all under-five children should be given IPT, this includes some under- five young children not infected with M. tuberculosis but will be treated with IPT. A negative TST does not exclude infection, especially recent infection, but nonetheless as many as 50% of the contacts may not be infected at time of screening (Triasih et

al. 2012) This represents a classic public health conundrum where overall population potential benefit needs to be considered against individual potential risk.

With regards to chest x-ray procedures and terminology: CXR is useful in the diagnosis of TB in children. It may show an abnormality even when the clinical exam is normal (Ministry of Health, 2011a). It is an important part of the clinical assessment for intrathoracic tuberculosis in children, and is critical to define “probable” tuberculosis cases. However procedures for review, reporting, and classification of CXRs for diagnostic research proposed by Graham et al. (2012) seems a rigorous approach, and the standardized approach to CXR assessment, including recommendation for evaluation by two independent readers experienced in reviewing paediatric CXRs and blinded to clinical categorization, as well as the use of standardized forms proposed by Graham et al. (2012), might be difficult to achieve at rural field sites, particularly in resource-limited settings with a high tuberculosis burden, and consequently discourage would discourage childhood tuberculosis diagnostic research effort in these settings. Hence there might be a need for its adaptation to local conditions. Fortunately the experts’ panel has acknowledge the stringiness of these requirements.

While CXR is not required in Botswana and many other resource-limited settings, for screening under five child contacts (baselined screening) or before starting a child contact on IPT; The Botswana National Tuberculosis Programme (BNTP) guidelines still consider chest x-ray as a useful procedure in the diagnosis of TB in children, it may reveal an abnormality even when the clinical exam is normal. Hence BNTP recommends both a posterior-anterior and lateral CXR to evaluate

the presence of hilar adenopathy (Ministry of Health of Botswana, 2011a) in the diagnosis of TB in children. Thus during a follow-up, an under five child contact symptomatic suspected for TB after the baselined screening may have a CXR examination. Nonetheless a person of any other age group will be done an anterio-posterior CXR with additional radiography performed at physician's discretion (CDC, 2000). The most common radiological signs proposed by the current BNTP guidelines include: Enlarged hilar and mediastinal lymph nodes, with or without airway compression; miliary pattern; infiltrates when presenting as an acute or sub-acute pneumonia; unilateral pleural effusion (usually in children above five years); unilateral hyperinflation due to lymph node "ball-valve" effect (Ministry of Health of Botswana, 2011a).

Thus, according to anterior guidelines an under-five TB contact should have been investigated through clinical examination and chest radiograph despite the result of their current or previous TB skin tests or history of prior TB disease (CDC, 2005). The study findings by Chauhan & Gahalaut et al. (2012) suggested that active contact screening must be prioritized by revised NTCP so that the diseased children can be diagnosed at the earliest stage.

Difficulties in the collect of sputum specimens from infants and young children, as well as the less likelihood to have a smear positive laboratory test in children constitute a big challenge in the confirmation of clinical diagnosis of TB in children (CDC, 2005). For these reasons, the diagnosis of TB disease in young children is mostly made on the basis of clinical signs and symptoms associated with TB disease; positive tuberculin skin test (TST) or positive TB blood test (IGRA); and chest x-ray suggesting TB disease. For example in a study conducted by

Chauhan, & Gahalaut et al. (2012) in India, chest x-ray was performed in each child, the TST was positive in 39% children, and 68% of child contacts had chest x-ray results suggesting tuberculosis. The same study found a high percentage of clinically asymptomatic children with positive TST, and a CXR presenting evidence of TB disease. Chauhan et al. (2012) also studied the correlation between TST and CXR and their relevance in contact screening in 200 children under five who lived in household contact with an index TB case in India. Their study results showed a correlation between TST and CXR of 83% in the age group 0-1 years compared to 63% in age group 1-5 years.

Thus chest x-ray is important in TB contact screening of younger children; for example evidence in a study by Brailey (1943) showed chest lesions demonstrable at initial x-ray examination in TST positive children; the younger the child, the more frequent the lesions and more serious in extent. When the same study population in Brailey's study was evaluated for the presence of symptoms suggestive of TB, it was found that in the age group 0 – 1 year, out of the TST positive children, 83 % had a positive CXR but only 22 % had clinical signs and symptoms. Whereas in the 1–5 year age group, out of the TST positive children, 63 % had positive Chest X-ray and 40 % had symptoms suggestive of TB. This implies that children may have TB disease but are still clinically asymptomatic. Tuberculosis disease in children cannot be viewed as a single entity, there are clear age-related patterns. Pertaining to this concept, children below 2 years of age (who are considered to be immune immature and illustrate poor disease containment), a positive TST indicates high risk of disease progression (Chauhan et al. 2012). Hence if such children, whether symptomatic or not have positive CXR findings, irrespective of their symptoms, they must be considered to have

active disease and treated accordingly (Marais & Gie et al. 2004). This suggest that even asymptomatic children below 2 years of age, with positive TST and CXR should be considered having active disease the same way like a symptomatic children. This emphasizes the importance of active screening of household contacts, so that diseased children can be diagnosed earlier. These contacts may be symptomatic or asymptomatic (Marias et al. 2004).

However the problem that can be encountered when recommending apparently straightforward chest radiography for a routine contact tracing in children is the limited access to these services in resources limited countries. In Botswana, especially in rural districts, this may be a problematic approach because:

- Firstly, chest x-ray services are not available in clinics and health posts in rural areas, and at hospital there is often shortage of specialised doctors who can correctly interpret a chest x-ray and diagnosis childhood TB.
- Secondly, the increasing number of TB cases due to HIV co-infection results in a very large number of child contacts. The expense of doing chest radiography in all household contacts (including asymptomatic children) will dramatically impact on government budgets, and might unnecessarily increase the workload of radiologist and other staff already overwhelmed by TB and HIV/AIDS work in resource-limited settings such as Botswana.
- Thirdly, the current scenario of long waiting lines and appointment lists at X-ray department in hospitals, mainly due to increase service demand related to HIV/AIDS burden, unavailability of x-ray services at peripheral level of health system such as at main clinics, in addition to limited

resources including radiologists and paediatrics doctors who can read and diagnose CXR in young children.

- Fourthly the majority of patients in rural areas have to travel long distances to have access to a doctor and chest x-ray services. For example in Botswana and in Kweneng district in particular, due to transport difficulties some patients can spend the whole day just to get to hospital for a chest x-ray examination. All these issues might delay the process of contact tracing in under-five children.

As already mentioned above, the importance of chest x-ray can't be overemphasized in the diagnosis of paediatric tuberculosis; but however, recommendations for its use shouldn't be made a "standard golden rule", or its unavailability shouldn't constitute a barrier to the assessment and management of a symptomatic under five child suspected for TB or person of any different age being investigated for tuberculosis especially in resource-limited setting with high incidence of TB, and where health systems often have insufficient or limited x-rays services and radiologist and trained radiographers especially in rural areas. In addition, the most available radiology resources in developing countries are concentrated in public hospitals in the major cities, overwhelmed with high turnover of patients who, either have limited or no affordable access to services from the private health care sector. Other than that, in HIV-infected children the CXR is less useful, due to overlap with other HIV-related lung diseases, such as lymphoid interstitial pneumonitis (LIP) (Ministry of health of Botswana, 2011a). At least currently in Botswana CXR is not a requirement for both the screening of under-five child TB contacts and starting IPT in these children (Ministry of Health of Botswana, 2011a).

In some studies the use of a chest radiograph to rule out TB in contacts was dependent on the availability, accessibility, affordability of this investigation also on the national guidelines and study methodology. For example in the study conducted by Wang et al. (2002) that investigated 11873 contacts of 3903 index patients, all adult contacts received a chest radiography but radiography was only recommended for those child contacts with a positive Mantoux tuberculin skin test result. This methodology may have missed some children with TB but a negative Mantoux test. The same applies to other child contact studies conducted in Gambia, West Africa by Lienhardt et al. (2003); in Kampala, Uganda by Guwatudde & Nakakeeto et al. (2003); and in Botswana by Kenyon et al. (2000) where tuberculin skin test was done without chest radiography.

2.3.2. Tuberculin Skin Testing (TST) and Bacille Calmette Guerin (BCG) vaccination

The tuberculin skin test is an essential and proven standard method for diagnosing TB infection. Although its sensitivity and specificity are not 100%, no better methods have yet been devised (CDC, 2000) especially for developing countries. Its use is widespread. The procedure (administration, reading, and interpretation of TST) is easy and slightly painless, however the perception of the pain stimulus may vary from one person to another, and from mild to severe especially in younger children. A discrete, pale elevation of the skin (a wheal) 6 to 10 mm in diameter should be produced when the injection is done correctly (CDC, 1999). As already emphasized above, the current Botswana National Tuberculosis Program guidelines do not require a TST or CXR for routine assessment of child contacts (Ministry of Health of Botswana, 2011a).

In highly endemic tuberculosis (TB) countries such as Botswana, most children are administered BCG vaccine at birth as part of the national Expanded Programme on Immunization (EPI). This administered BCG vaccine may interfere with tuberculin skin testing (TST) and results into a controversial interpretation of TST reaction. Therefore, the results of TST in BCG-vaccinated children needs to be interpreted with caution in order to prevent over-diagnosis of TB and unnecessary treatment.

With regard to the question on how long BCG can interfere with TST results, a tuberculin skin test survey in a paediatric population with high BCG vaccination coverage from Botswana by BOTUSA (1996) has addressed this subject by outlining that the mean TST size in BCG-vaccinated children varies with interval since vaccination, In addition, previous studies have indicated that TST induration attributed to BCG cross-reactivity decreases with increasing time since BCG administration (BOTUSA, 1996). It is clear that distinguishing between a tuberculin skin-test reaction caused by infection with M. tuberculosis and a reaction caused by BCG vaccination is difficult. However, the probability that a TST reaction results from infection with M. tuberculosis rather than from BCG vaccination increases as the interval between vaccination and tuberculin testing increases (because vaccination-induced reactivity wanes over time and is unlikely to persist for more than 10 years (CDC. 1995).

In BCG-vaccinated persons the CDC recommends that TST reactions should be interpreted using the same criteria for persons not BCG-vaccinated. Individuals in high-risk groups such as TB contacts who present a TST reaction of at least 5 mm of induration should be given LTBI prophylactic treatment (CDC, 2005).

Persons having latent tuberculosis infection (LTBI) are at increased risk of developing TB than the general public (Funk, 2000). Among these persons the most targeted are contacts and family members of TB, young children and adolescents below 18 years old with history of exposure to TB, and people from countries with high endemic TB etc. They should be done a TB skin test.

BCG vaccination is used in many parts of the world to prevent TB. According to ATS and CDC, the commonly used BCG vaccination shouldn't be considered as a contraindication to TST (Funk, 2000). Although unfortunately, there is no reliable method to distinguish PPD reactions caused by BCG vaccination from those caused by TB infection. A significant PPD reaction in a BCG-vaccinated individual should be interpreted as LTBI if the person is from a country with a high incidence of TB, or a contact to person/child with active TB (Funk, 2000). In a highly TB endemic country, a TST reaction of more than 10 mm is usually taken as a positive result (WHO, 2006a). However some studies have suggested that an induration greater than or equal to 15 mm should only be interpreted as a TB infection in BCG-vaccinated children (Wang et al. 2002) and (Grupo de Trabajo de Tuberculosis de la Sociedad Espanola de Infectologia Pediatrica, 2003).

The efficacy of BCG vaccine against all forms of TB is about 50%, but it is higher for serious forms of infection: 64% in cases of tuberculosis meningitis and 78% in disseminated infection (Bannon, 1999). Our study is not specifically concerned with BCG or tuberculin skin testing (TST), however since TST was used in our research methodology, we thought it was necessary to highlight key issues related to both BCG and TST.

The American Academy of Paediatrics (2003) recommends TST for children who are at increased risk of acquiring tuberculosis such as children under five years living with a family member or any other household contacts of an infectious TB case. The technique is very simple but must be applied meticulously (Ministry of Health of Botswana, 1995). The “Mantoux test” is the tuberculin test used in Botswana. The reaction should be read at 48-72 hours, and recorded as the diameter of induration in millimetres measured transversely to the long axis of the forearm. An induration greater than 10 mm diameter is considered as positive (Ministry of Health of Botswana, 1995); bearing in mind that a negative tuberculin test therefore, does not exclude tuberculous infection or disease (Somu et al.1997). Nonetheless in HIV-positive children and severely malnourished children an induration greater than 5mm in diameter should be considered positive. While we admit that a positive reaction indicates TB infection, we have to bear in mind that a negative TST does not completely exclude the probability of TB diagnosis in a child.

The national tuberculosis controllers association and CDC guidelines for the investigation of contacts of persons with infectious tuberculosis recommend that high priority contacts should receive a test within 7 days after they are identified (CDC, 2005). However this should not mean that children who could not be reached and tested within this period of time should be excluded from having a tuberculin skin test after 7 days; especially in the context of underdeveloped countries where socio-economic constraints might be a barrier for many children to be tested within this specified period.

In Botswana the findings of a TST survey conducted among children aged 3-60 months by BOTUSA (1996) indicated that most positive TSTs (induration ≥ 10mm) among children in Botswana were due to TB infection rather than previous BCG vaccination. Therefore the TST remains useful for diagnosing paediatric TB in Botswana (BOTUSA, 1996). Similar findings have been reported from other African countries. For example, a study on a group of Ugandan children in Kampala has demonstrated that BCG vaccination at birth had no important effect on the interpretation of the tuberculin skin test reactivity (Guwatudde et al. 2003), and Lienhardt et al. (2003) showed that a positive TST in a child under five years most probably reflects TB infection rather than previous BCG vaccination.

Nevertheless a study by Tissot & Zanetti et al. (2005) from the low tuberculosis incidence areas in Lausanne, Switzerland concluded that positive TST reactions of 18 mm in 40 year old subjects was likely due to previous BCG vaccination rather than TB infection. They also found that prior BCG vaccination of child contacts from a country with moderate to high endemic tuberculosis were important factors influencing positive TST results in their study. However these conclusions might only be valid in the interpretation of TST results in previously BCG-vaccinated individuals in similar settings (developed countries with low prevalence of tuberculosis). But considering the results from other studies such as the finding of a BCG independently associated with TST reactivity (12.4% prevalence of a positive TST) in the study by García-Sancho & García-García et al. (2006); TST enabled to identify children who were probably TB infected, and could benefit from treatment for latent tuberculosis infection.

Therefore the conclusions of Tissot et al. (2005) study could be misleading in the interpretation of TST results in children in underdeveloped countries experiencing high prevalence of TB such as Kweneng district (Garcia-Sancho et al. (2006).

A positive Mantoux test in a child from a country with a high prevalence of tuberculosis who has received BCG vaccination is far more likely to be due to latent tuberculosis infection than to BCG vaccine. Nevertheless it is important to note that BCG vaccination at birth should have no important effect on the interpretation of the tuberculin skin test reactivity (Mudido & Guwatudde et al. 2001). This claim can be supported by Rathi & et al. (2002) in a household contacts a study in Pakistan. The study found 49.4% of TST positivity independent of BCG scar status of children. For further evidence, Garcia-Sancho et al. (2006) undertook a cross sectional study to find out whether a tuberculin skin test was really useful in the diagnosis of latent tuberculosis infection in children previously vaccinated with BCG. The results of their study clearly showed that BCG scar in a child was not related to TST reactivity.

2.3.3. Treatment (Prophylaxis) of Latent Tuberculosis Infection (LTBI)

In 1962, isoniazid (INH) was demonstrated to be effective in preventing tuberculosis (TB) among household contacts of persons with TB disease (Ferebee & Mount, 1962), since then investigations of TB contacts and treatment of contacts with latent TB infection (LTBI) became a strategy in the control and elimination of TB (Hsu, 1963). An Isoniazid Preventive Therapy Trial (IPTT) conducted by CDC Botswana and BOTUSA from 2004 to 2009, mainly found that that isoniazid preventive therapy (IPT) was highly effective in reducing TB in

people with a positive tuberculin skin test (TST) in people living with HIV (CDC, 2012).

Overall, about 5 to 10% of infected persons who do not receive treatment for latent TB infection will develop TB disease at some time in their lives (CDC, 2010) and children under five years of age who have a positive TB test are among those persons at high risk for developing TB disease. Improving the provision of preventive treatment to high-risk children with exposure and/or LTBI and anti-tuberculosis treatment to those with active disease will dramatically reduce the severe tuberculosis- related morbidity and mortality in children in endemic areas (Marais & Gie, et al. 2006c).

A correctly administered TB prophylaxis can prevent the infection to progress toward the stage of disease in children (Schaaf et al. 2002) as well as in person immuno-compromised. Therefore, NTPs should offer isoniazid preventive therapy (IPT) to children under-five TB contacts and to HIV-positive patients after rolling out active TB disease (Graham, 2007). WHO recommends TB prophylaxis for all under-five contacts who are clinically well (WHO, 2013b). Findings from the study by Jonathan et al. (2014) suggests the use of IPT in older child and young-adult household TB contacts, in addition to children under-five years old. Latent TB infection (LTBI) preventive therapy regimens varies. So each health care system should be realistic and adopt a regimen that can have great impact and takes into account factors such as: drug-susceptibility in presumed source case (if known), cofounding medical conditions and drugs interactions etc.

The Centres for Diseases Control and Prevention recommends two Isoniazid (INH) regimen options: 9-month and 6-month regimen (CDC, 2010) for the treatment of Latent TB Infection.

However the duration of either 9 months or 6 months of INH Preventive Therapy (IPT) absolutely depends on each country programme. But in one case or another the most important issue is to ensure that the contact adheres to IPT and fully complete the treatment. In Botswana, since it's launched in 1975 the Botswana National Tuberculosis Programme (BNTP) had adopted and implementing the 6-month IPT regimen as outlined both in the 1995 and 2007 national tuberculosis programme manuals through the currently used 7th edition of the National Guidelines on the Management of Tuberculosis.

Authors, such as Spyridis & Gelesme et al. (2007) have suggested short-course treatment with isoniazid and rifampin for 3–4 months which they found was safe and seems to be superior to a 9-month course of isoniazid monotherapy. But CDC recommends the 12-week Rifapentine (RPT) regimen as an equal alternative to the 9-month INH regimen for most patients over 12 years who have LTBI and/or factors predictive of developing TB in situations such as exposure to active TB; abnormal chest x-ray with healed adenopathy; HIV co-infected individual (CDC, 2011). However emphasis should be put on the need for careful monitoring of toxic side effects once the regimen becomes widely used.

Preventive treatment decreases the risk of first episode of TB in a susceptible child. Thus WHO previously recommended isoniazid (5mg/kg daily for 6 months) as preventive treatment for all children under five years of age who are household contacts of sputum smear-positive pulmonary TB cases, after active TB disease

has been excluded (WHO, 2003).This INH dosage was still valid and in used at the time we conducted this research (December 2005 through November 2006). Nevertheless the South African policy on management of child contacts, not only emphasizes the need of active contact tracing of children who are household of TB cases, but also recommends isoniazid preventive therapy to children under five years who are household close contacts of smear-positive pulmonary TB cases and the dose of INH preventive therapy previously used was 5mg/ kg/ day, five times a week for six months for children under five years of age with no signs of TB disease (South Africa National Department of Health, 2004). Previously most countries with a high burden of tuberculosis, prescribed IPT to child contacts at dosages of 5 mg/kg/day. But now a paradigm shift and change in guidelines have occurred WHO and most countries recommend isoniazid (INH) dosage of 10 mg/kg/ per day instead of 5 mg/kg/per day previously used.

Botswana 1987, 1995 and 2007 national tuberculosis programme guidelines on contact tracing followed the above recommendation and offers chemoprophylaxis to all TST positive child contacts. An infant has a high risk of getting infected and developing active disease from her breastfeeding mother diagnosed smear-positive PTB. This infant should receive 6 months of IPT, followed by BCG immunisation if there is no scar (WHO, 2006a). In Botswana, a new born baby (less than one month old) of a mother with smear-positive PTB should, be given isoniazid (INH) prophylaxis (5mg/kg daily) for 6 months followed by BCG as stipulated in previous Botswana TB policy of 1995 and the 2007 6th edition of national tuberculosis programme manual, But at the time we are submitting this research report in 2015, the Ministry of health of Botswana has revised its national tuberculosis policy, and the current 2011, 7th edition of national tuberculosis

programme manual revised IPT dose for child contacts, to isoniazid prophylaxis (10mg/kg daily) for 6 months.

Therefore now in Botswana all children must be screened for TB disease before giving IPT. The dose of isoniazid is 10 mg/kg daily for 6 months (Ministry of Health of Botswana, 2011a). Hence the new born baby of a mother with smear positive PTB now should be given isoniazid prophylaxis (10mg/kg daily) for 6 months, followed by BCG. However if the child shows signs of TB, full Anti-Tuberculosis Treatment (ATT) should be started (Ministry of Health of Botswana, 2011a).

All children under five years contacts of adults with smear positive pulmonary TB (PTB), regardless of HIV status should receive IPT (Ministry of health of Botswana, 2007). It is not only the Botswana national TB programme that supports and provides TB prophylaxis to child contacts of infectious cases. Botswana guidelines are consistent with other recommendations such as: the CDC recommendations setting the age cut-off point at under five years for assigning priority and recommending primary prophylaxis (American Thoracic Society et al. 2005); American academy of pediatrics also recommends primary prophylaxis for children aged less than 4 years (American academy of paediatrics, 2003). Under the India's Revised National Tuberculosis Control Programme (RNTCP), household contacts children below six years old are eligible for Isoniazid Preventive Therapy (INH 5 mg/kg body weight/per day) for 6 months (Pothukuchi & Nagaraja al. 2011). Isoniazid plasma concentrations in a cohort of children conducted by McIlleron & Willemse et al. (2009) in South Africa found a median peak concentrations of INH in children receiving a dose of 4–6 mg/kg of 58% lower than those in children receiving a dose of 8–10 mg/kg. In contrast,

children who received a dose of 8–12 mg/kg achieved peak concentrations approximating those in adults treated with 300 mg of INH daily. Hence they recommended a daily isoniazid dose of 8–12 mg/kg in children. Current international guidelines as outlined by the World Health Organization (WHO), Centers for Disease Control and Prevention, USA and National Institute for Clinical Excellence, UK and most national tuberculosis control programmes including the Botswana National TB Programme (BNTP) recommend and implement isoniazid (INH) dose of 10mg/kg/per day. However during the treatment for LTBI children should be regularly (monthly) monitored by health care provider to reinforce adherence, evaluate possible toxicity and progression to TB disease.

Finally, it is important to acknowledge that although TB preventive therapy is effective, its difficulty to be implemented on a large scale limits or restrains its use to particular high-risk groups such as children under five in household contact with smear-positive index cases in developing countries (Datta & Swaminathan, 2001). The World Health Organization recommends IPT for people living with HIV and under five years child contacts. This IPT strategy if effectively executed can have a great impact on morbidity and mortality reduction in children. But despite the benefit of such recommendations, the implementation of IPT programme for household contacts is not given much attention in most high TB burden settings (Jonathan et al. 2014).

CHAPTER 3: RESEARCH METHODOLOGY

This chapter describes the methodology used to achieve the study objectives.

3.1. Study design

The overall research design was similar to a nested case-control study. Essentially we undertook a case-control analysis within a retrospective cohort study of children under five in household contact with smear-positive pulmonary tuberculosis index cases diagnosed between March 2003 and February 2005. Information on all child contacts was collected at the start of the study period. Data was collected by face-to-face interviews with the child care givers using a pre-designed data collection tool during visits to each household. The interview included information about initial contact tracing by the local health services and any subsequent TB disease. Child contacts were investigated between December 2005 and November 2006 by means of clinical examination, Tuberculin Skin Test (TST) and chest radiography. The chest radiography was done regardless of the tuberculin test result. The case-control analysis compared risk factors between those children in the cohort that had TB at the time of the later follow-up (the “cases”) and those that did not have TB (the “controls”).

3.2. Study population

The study population was constituted by all children under five years of age (0-59 months) who have been exposed to tuberculosis by living in close household contact (regardless of duration) with adult smear-positive pulmonary tuberculosis index cases registered by health facilities in Kweneng, Botswana between March 2003 and February 2005. All child contacts and their respective index cases were Botswana nationals

3.2.1. Research setting

The study was a household based contact study in the rural district of Kweneng in Botswana. Under-five child contacts were also subsequently examined at their most convenient/nearest public clinic or health post in Kweneng during the study period (December 2005 through November 2006).

3.3. Sampling

3.3.1. Sampling strategy

A total of 200 households of smear positive pulmonary tuberculosis index cases were selected at random (using Stat Trek's Random Number Generator) from the sampling frame of all smear-positive pulmonary tuberculosis cases. In detail each registered smear-positive pulmonary tuberculosis case was listed and assigned a number on same list ranging from 1 to 329 PTB cases. Then using Stat Trek's Random Number Generator, a table of 200 random number of smear positive pulmonary tuberculosis cases was generated according to the following specifications: Numbers were randomly selected from within the range of 1 to 329 and duplicate numbers were not allowed.

We then went to the households of the selected index cases and recruited all the children under five years of age in each household to participate in the study. This yielded a total cohort of 497 children to be evaluated.

This sampling frame for cases was drawn from the list of all adult TB cases entered in the Kweneng district electronic TB register. Because some TB cases might have not been entered in this electronic TB register by the district TB coordinator, we first checked the electronic data for completeness and missing data, and then updated the electronic TB register using clinic and health post

records (health facility manual TB registers). From the updated electronic register we then produced a complete list of all smear-positive TB cases registered by public clinics and health posts in Kweneng from March 2003 to February 2005. Study households were selected at random from this list. For households with more than one index tuberculosis cases, only one case was considered per household and a replacement household was then selected randomly from the remaining cases in the sampling frame until the required number of 200 households to visit was reached.

3.3.2. Sample size

The key study outcome measure used for the sample size calculations was the proportion of children initially screened by the health service. Therefore, the required sample size was estimated using the calculation for a single proportion in Statcalc of Epi Info version 6,04d. The estimated proportion of children screened was unknown so the maximal figure of 50% was used. For an infinite population, a confidence level (1-α) of 95% and a worst acceptable result within 5%, the required sample size was 384 children under five years.

Assuming an expected follow-up rate of 80% the sample size required was at least 480 children:

$$384 \div \frac{80}{100} = 480$$

Considering that the mean number of children per household in Botswana is 2.54 (Central Statistics Office, 1994), we calculated that we would need to visit 189 households to recruit 480 children for this study.

$$480 \div 2.54 = 189$$

We decided on a final sample of 200 households in case there were slightly fewer children per household in our district.

3.4. Data collection

3.4.1. Procedures

The study process for data collection was as follows:

The data collection tool was designed by the researcher and household interviews were done by the Family Welfare Educators (FWEs). To minimise study bias, FWEs were trained on how to record information during interviews. Also it was explained to FWEs and nurses that the study was not meant to evaluate or assess the performance of individuals involved in the follow up of TB cases. The researcher also worked closely with and supported FWEs to ensure quality of data collection through supervision, regular verification of data collected and immediate follow up on incomplete or inaccurate data if any.

After the interview, children who were identified as TB contacts in the households of index cases were transported to the local public health facility (clinic or health post) where they received a Mantoux test. This was part of routine health care services provision in the district since public health services are free and clinics and health posts avail free transport to patients. The district health team management (DHTMT) had also sensitise all clinics and health posts to support the study and ensure that children in under study were given adequately evaluated and handled with due care. Children who did not report to the nearest clinic or health post were followed up by the researcher or field workers within 48 hours.

The TST was administered by a nurses at health facility or the researcher. The subject was instructed to keep the test site clean, uncovered, and to not scratch or rub the area. Child contacts returned to the clinics or health posts for the reading of TST reaction within 48-72 hours after the injection. The nurse read and recorded the TST result. The researcher worked closely with nurses at research site/ health facility and participated in the reading of TST, by performing a quality control through re-reading of a sample of five to seven TST's in each health facility. These sample were selected at random by the researcher. Any inadequate quality of TST found was discussed with the nurse at end of the session. The researcher's participation in TST reading provided the opportunity to support the research team, monitor research progress and address technical and operational issues. The researcher clinically examined child contacts at the same health facility (clinic or health post) immediately after the reading and recording of TST result. At the end of this examination, the researcher ordered a chest radiography which was done at Scottish Livingstone district referral hospital (SLH) and further sent to Princess Marina Hospital (PMH) for reading and reporting by a radiologist. Child contact were progressively transported at no cost by a clinic or health post's vehicle to the hospital for chest radiography together with other referral patients with the approval of the DHTMT. Normally the health care system in Kweneng provides free transport to most patients referred to SLH or PMH hospitals in Molepolole/Kweneng or Gaborone respectively. However any parent or child caregiver who chose to transport his or her own child to hospital was not denied to do so, provided that the child was not delayed. CXRs were read and reported on non-standardised reporting form by a radiologist at PMH in Gaborone. Finally the CXRs films and its reports were brought to the clinic/health post. The

researcher recorded the TST, examination and chest radiography results on the research tool and on the child's welfare clinic (CWC) card.

3.4.2. Investigations

3.4.2.1. Interviews:

The households of randomly-selected smear-positive TB index cases in Kweneng were visited by FWEs, and a face to face interview was conducted using a pre-designed standardised data collection tool. All under-five child contacts of the index TB cases were identified and detailed information on each child contact were collected. After interview under-five child contacts were referred to their local clinic or health post for evaluation including further investigation.

Ideally, the person interviewing the index case should be familiar with the social and cultural context of the index case (Stapledon & Viney, 2010) for this reason, in our study the FWEs were the most appropriate persons to conduct interviews. Generally FWEs are community health workers who are stationed at public clinics or health posts and work in their respective communities and catchment area. They are the link between the clinic and the community, there are allocated specific wards in each village and are responsible for the follow-up of TB cases and other community health issues in their respective wards. Thus they know each and every TB case registered at the clinic or health post.

Face-to-face interview technique was used for data collection during household visits. According to Marais (1990), the interview method allows the interviewer to interact directly and develop rapport with the interviewee. The study information sheet (Appendix B) and consent form (Appendix D) were translated into Setswana (Appendix C and E respectively). We developed a structured data collection tool /

questionnaire (Appendix F). This tool was completed by field workers who visited each selected household and interviewed the respondents after obtaining informed consent. The work for this study was designed and analysed principally by the researcher. However, the field work was done by FWEs who assisted in administrating the interview questionnaire in their respective catchments areas under the coordination of the researcher. All 29 field FWEs who usually follow up TB patients were recruited locally to assist in data collection for the study. They received one day of training by the researcher on the study objectives, their roles and responsibilities, data collection and interview methodology. The training was to ensure standardised data collection and improved communication. For the first few interviews each of the FWEs was monitored and supervised by the researcher. Thereafter, feedback sessions were regularly held in their respective areas in order to guide the field work and ensure the quality of information gathered.

From the electronic register we had the physical address of the households of each individual TB case household to visit, which was easily traced because in each village the FWEs know all TB cases and their residential addresses. The trained field FWEs carried out the interviews for each household in 26 villages under the supervision of the researcher. However we need to understand that culturally in Botswana, especially in rural area such as Kweneng West where the literacy rate is low, a Motswana (people of Botswana) is prude of her/his language/Setswana. He feels confident and comfortable by expressing her/himself in Setswana (official language used in most official business meetings, sometimes in combination with English), language that identified her/him as a Motswana. Hence it was important to administer the questionnaire in Setswana

which built trust and empowered interviewers to be more open during interview. All these FWEs who administered the questionnaire are Botswana native who fluently speak Setswana (FWEs are from the same area/village where they work, they are well familiarised with their respective community). However due to the large size of the three major villages/sites where at least many people are fluent and easily communicate in English, the researcher join the FWEs, and directly conducted a series of interviews as part of the team in these three sites. Each of us visited the households and administered the pre-designed questionnaire to either the TB index case themselves, parent, guardian or primary care giver of the child after obtaining their informed verbal consent. The researcher could not speak fluent Setswana, therefore the most questionnaire were administered by trained FWEs, the researcher language (Setswana) barrier constituted a study limitation, which at least was overcame in the above three sites /large villages through an effective couple of interviews conducted by the researcher with interviewees fluently speaking English who preferred to be interview in English and did not use Setswana throughout the administration of questionnaire.

Index TB patients were being asked to recall detailed information after a certain period of time; some may have not clearly remembered a number of details. However, due to high level of stigma related to TB and HIV in Kweneng other TB cases, may have intentionally provided vague or inconsistent information. In this case, the interviewer re-emphasized the importance of accurate contact identification and stressed confidentiality. However in some households that were visited by the FWEs, the TB index patient was unavailable for interview (after several scheduled visits) or able to communicate due to ill health condition. In these cases, either the parent of child, guardian or caregiver was interviewed. But

in most cases, the primary care givers or parents were the heads of the households, and they felt they were the responsible persons for the welfare of their children. Therefore they were excited and open to participate in the interview and more likely to get more engaged in the follow-up process of their children. Additionally in some other cases it happened that the caregiver or parent of the child was also at the same time the care giver of the TB case, and therefore had much more information to share with the interviewer.

The interview was conducted in English or Setswana, according to the respondent's choice. The nurses in clinics and health posts who participated in the study had the role to inject TST to children as part of routine procedures in each health facility. All TST injections were done under supervision of the researcher. The nurses were also briefed on the research. The briefings discussed routine procedures for children evaluation and treatment (TST injection, reading and recording, chest- radiography and clinical examination by the physician researcher, INH and TB treatment) the compliance to confidentiality during this research and care of the non-infected children were among key issues emphasised on during this briefing.

Two weeks before conducting the fieldwork, we took advantage of various scheduled community meetings and village gatherings (Kgotla meetings, village extension team meeting, and district development committees meetings) to sensitize and inform community leaders as well as community members in the concerned villages about the research. In each village the nurse in charge of the local public clinic or health post and the researcher briefed the Kgosi (village

chief). We also briefed the district health management team (DHTMT) staff on the research prior to starting field work.

At the end of each interview the interviewer checked the questionnaire for completeness of data. This tool comprised 3 sections:

1. The identification of respondent.
2. Description of index case.
3. Description of children.

For the purpose of this research most questions were closed-ended (Appendix F). Data about the children under study was mainly collected in section 3 of the tool which included three categories of variables:

- The demographic profile of the children included the sex and the age of each child which was categorised into two age groups: 0 - 24 months and 25 - 59 months
- Follow-up variables describing initial contact screening and investigation that was used to determine the number of child contacts previously screened for tuberculosis and the number of children initially missed for tuberculosis screening by the health care system. This section explored the tuberculosis contact history of each child and the initial investigations carried out (clinical examination, tuberculin skin test and chest x-ray).
- The last category described the current TB status of the child, according to the modified WHO classification of tuberculosis (WHO, 1998) as either active tuberculosis or latent tuberculosis infection (LTBI). Children were systematically evaluated by the mean of clinical examination, tuberculin

skin test (TST) and chest x-rays. Thereafter a final decision “TB”, “LTBI” or “No TB” was be made.

As earlier indicted in this section, under-five children contacts were referred to the local clinic or health post where TB disease and LTBI in children were ascertained through clinical examination, tuberculin skin tests (TST), chest radiographs.

3.4.2.2. Mantoux Tuberculin Skin Test (TST)

TST was administered and read at the clinic or health post by skilled nurses. The clinical method/ procedure consisted in the injection of 0.1 ml of PPD into the top layers of skin (intradermal injection: just beneath the surface of the skin) of the palm-side-up surface of the forearm, about 2 to 4 inches below the elbow. The injection was made using a disposable 27-gauge tuberculin syringe with the needle bevel facing upward. Universal precautions for infection control were followed during the procedure (e.g. wearing of gloves, cleaning the injection site with an alcohol swab and wiping the top of the vial of tuberculin). In other words with a needle, the skin is punctured shallowly, resulting into a discrete, pale elevation of the skin (a wheal) of 6 mm-10 mm in diameter was produced upon injection of 0.1 ml of PPD.

Measurement and reading of the tuberculin skin test were made between 48 and 72 hours after administration. The induration (palpable, raised, thickened/ hardened area around the site of injection) was the key element assessed. Thus the Erythema (redness or bruising) was not measured. The induration was measured in millimetres across the forearm (transverse dimension to the long axis of the forearm) using a tuberculin skin testing ruler (small, plastic, flexible ruler marked in millimetres). The result was recorded in millimetres.

A standard range for a positive tuberculin skin test used in this study was ≥ 10 mm (irrespective of BCG status). It is safest to ignore BCG immunisation when interpreting the TST. Children with BCG scars or BCG vaccination record in the immunization card, were considered as vaccinated; the remainder were considered as unvaccinated.

After completing the procedure the person accompanying the child was issued a verbal and written appointment to return for TST reading and was informed about the:

- Normal mild itching, swelling or irritation that usually disappears within one week.
- Care of the injection site by avoiding scratching and keeping the site, clean and dry. As well as avoiding application of any creams, lotions, or adhesive bandages.
- Importance of returning to the health facility within 48 to 72 hours for test read and recording.

3.4.2.3. Clinical Examination

Tuberculosis contact screening form (Appendix I) was filled for each child. The physician researcher performed a full physical examination of children, and documented the presence and location of a BCG scar. During this examination the examiner asked about symptom such as cough, other respiratory symptoms, fevers, night sweats, malaise, loss of weight/poor weight gain, other localising symptoms.

3.4.2.4. Chest X-Ray (CXR)

Plain chest radiography (posterior-anterior and lateral) of child contact was taken at Scottish Livingstone district hospital (SLH); thereafter it was read and reported

by a radiologist (who was not part of the immediate study team) at Princess Marina Hospital (PMH) as part of normal routine case investigation.

Our conclusion was made based on the following typical radiographic findings reported by the radiologist: CXR normal (No evidence of PTB), hilar Lymphadenopathies consistence with PTB, miliary pattern consistent with PTB or simply radiological evidences consistent with PTB.

However this approach (CXR evaluation by one reader, CXR processed as part of the routine case management, and the none use of standardised form with predetermined terminology to describe CXR abnormalities) could be one of our study limitations; since the panel on the evaluation of tuberculosis diagnostics in children that applied a rigor to the development of standardized approach to CXR assessment, has recommended an evaluation of CXR by two independent readers experienced in reviewing CXRs in children and blinded to clinical categorization in addition to the use of standardized forms with predetermined terminology to describe radiologic findings (Graham et al. 20*12*).

However, as these authors themselves highlighted it, it is evident that such recommendation might be difficult to achieve and not feasible both at rural and urban sites in the context of a resource-challenged setting with high TB burden like Botswana where scarcity of qualified and specialized Medical professional (Physicians, Radiologist, paediatricians etc.) is common. Nevertheless these approaches are not part of the BNTP. The same approaches might be stringent and need to be adapted to local situation especially in developing countries in order to encourage childhood TB diagnostic research in these countries.

The most common leading radiographic sign in pulmonary tuberculosis in children is hilar lymphadenopathy, but parenchymal changes were clearly identified in the diagnostic work-up for pulmonary tuberculosis in these children.

3.4.3. TB status and management

Based on clinical examination findings, results of tuberculin testing, CXR report; children were categorized in 3 groups: uninfected/No TB, infected/LTBI, and with disease/TB. Basic clinical case definition criteria [which closer to recent criteria published by Graham et al. (2012)] were used to categorize children in one clinical diagnostic group or another as follow: - Disease/TB: at least 1 of the signs and symptoms suggestive of tuberculosis [persistent cough (more than 2 weeks), non-remitting cough, weight loss/failure to thrive, persistent (more than 1 week) and unexplained fever (more than 38°C), persistent, unexplained lethargy or reduced playfulness, additionally pneumonia, unexplained hepatosplenomegaly or sepsis like illness]; TST positive or negative; CXR consistent with PTB disease or normal. **-** LTBI: TST positive with no signs and symptoms suggestive of tuberculosis with a normal CXR. – No TB: no signs and symptoms suggestive of tuberculosis, negative TST and normal CXR.

The case management was approached in accordance with Botswana guidelines. Hence infected (LTBI) children were evaluated for prior to consideration for six-month Isoniazid Preventive Therapy (INH) with pyridoxine supplement to prevent risk of neuropathy due to INH. Children diagnosed with TB disease were received anti-tuberculosis treatment according to the Botswana National Tuberculosis programme guidelines, and uninfected children were referred to expectant

conduct at their respective clinics/health posts for Integrated Management of Childhood Illness (IMCI).

3.5. Pilot study

An initial pilot of the data collection tool was conducted to ascertain that interviewers and informants understood the tool, and to determine the time needed to administer the interview questionnaire. To allow time for revisions, pre-testing of the data-collection tool was conducted 1-2 weeks before starting the fieldwork. One FWE from the DHTMT, two FWEs from two different villages and the researcher pre-tested the questionnaire with a sample of 6 households in Letlhakeng village. The result of this field pre-test allowed a discussion with the interviewers on the understanding and simplicity of the tool in both English and Setswana. The information obtained from this pilot resulted in changes and corrections to the questionnaire tool. The 6 households participating in the pilot were excluded from the final study.

3.6. Data processing and data analysis

The data were entered and analysed using the Epi Info 2002 statistical software package.

Data was analysed using the hypothesis test for comparison of two proportions. P-values below 0.05 were considered as significant. The prevalence of LTBI and TB disease were calculated as the number of prevalent cases expressed as a proportion of the size of the at-risk population/children.

3.6.1. Data management system

The researcher was responsible for data management. After the data was collected, the data collection tools and informed consent forms were immediately forwarded to the researcher's office where they were kept under lock to limit access and assure confidentiality.

A database with 22 variables was designed in Make view in Epi Info 2002 statistical software package. A relational database was created to link each child contact results to those of the household TB case. Data was entered into the database using a password- protected file. Patient names were not entered into the database but a unique anonymous string variable was created to identify each case.

3.6.2. Data verification and collation

The entered data was first checked for completeness of data, and for obvious errors and inconsistencies. This was done by:

1. The use of the CHECK programme in Epi Info 2002.to define legal values, ranges, required fields and skip patterns for data entry in order to minimise errors.
2. The use of frequency checks for each variable in order to identify unusual entries. A data table containing undesired and inconsistent information was identified and corrected during the cleaning of the database. All discrepancies identified during analysis were corrected on the allow dates listing in Epi Info 2002. The updating procedure was repeated until no error was found in the data.

3.6.3. Data analysis

Epi Info 2002 and Stata statistical packages were used for descriptive data analysis including the computation of frequencies, means and tabulations. Graphs and tables were finalised in Microsoft Excel for Windows 2003. The analysis was done in three steps. Firstly, we described the data for household respondents and TB index/source cases. Secondly, the child contact data was analysed. Most analyses were disaggregated by sex and age group (0 – 24 months and 25 – 59 months). Although this age group classification is unequal, it was used to be able to compare the study results with the Botswana National TB guidelines on tuberculosis in children (Ministry of Health of Botswana, 1995). According to these guidelines any BCG non-vaccinated child under 2 years of age who is tuberculin positive, should be regarded as suffering from active disease requiring treatment, as should any BCG-vaccinated child of the same age group whose tuberculin test result is strongly positive (10 mm and above). The same criteria applies to any child between 2 and 5 years with history of tuberculosis in immediate family. Therefore in this study the interpretation of a positive TST was not dependent on the BCG-vaccination status.

Thirdly, the relational data of child was then linked to the TB case data in order to compute the various proportions and cross-tabulations as outlined below.

Appropriate proportions, frequencies and cross tabulations of different variables were used in order to answer the study objectives. 95% confidence intervals (95% CI) were calculated for single estimates. Statistically significant associations in cross tabulations were tested by means of a chi-squared test at the 5% level of significance. The strength and significance of associations were evaluated by computing the odds ratio (OR), p- value and chi-square statistic.

3.7. Ethical considerations

Basic ethical codes of behaviour were applied throughout this research. The main ethical issues in this study were those concerning informed consent of interviewees and the confidentiality of all information obtained in the course of the interviews. This study considered and respected the autonomy and dignity of study participants as a basic principal of ethics, the social and cultural environment were also taken into accounts in all circumstances. For example interviews were conducted in Setswana which is the local language which is also commonly used in official business meetings. However for those who chose to be interviewed in English, we respected their choices. The village's traditional leader in Kweneng and in Botswana in general, is the custodian of the tradition and s/he is highly respected by the community members. Thus before getting to the community in each village, we first paid a curtesy visit to the traditional leader and his team of elders in a Kotla meeting. The purpose of such visit was to brief and inform the village leadership on the study and its benefit, also explain the processes such as the interviews and evaluation of children that were going to take place in the village.

Interviews were conducted on appointment and at most convenient time of the household since people go to work at farms and cattle posts or other businesses. Also due to high level of stigma and discrimination attached to HIV/AIDS and cultural believes associating with HIV/AIDS. In this respect the traditional leaders convened our message to their respective communities that our study had nothing to do with HIV, and children household TB contacts will be tested for TB and not for HIV. Confidentiality was maintained, for example interviews were specifically conducted in a household setting, excluding any curious neighbours or other

persons. There was neither recording nor photography of indigenous people in the village, TB index cases, and interviewees or under five children during the investigations.

The research proposal was submitted to the postgraduate committee of the University of the Witwatersrand and an approval to conduct research was granted. The Ethics Committee for research on human subjects also reviewed the research proposal and issued an ethical clearance (Appendix G). A copy of the protocol including the interview-questionnaire was also submitted to the health research and development committee at the research unit of the Ministry of health of Botswana and an authorisation to conduct the study was granted (Appendix H). Approval was also obtained from the diagnostic radiology department at the Scottish Livingstone hospital where the chest x-rays were done.

Informed consent was an important step toward the inclusion of participants into the study. Informants were fully explained about the study its benefits, risks, confidentiality and procedure as part of routine healthcare services, thereafter each informant had the opportunity to freely make an informed decision on whether to participate or not, or to withdraw from the study at any time with no penalty. Illiterate informants who could not read and sign; the interviewer read on their behalf and explained the content of consent form. The consenting process for illiterate persons used finger printing; Instead of signing at least illiterate informant applied a thumb finger print.

The parent or child caregiver/guardian gave written consent on behalf of study subjects /children by signing the same informed consent form (Appendix D and E). The subject's information sheet and the consent form were available in both in

English and Setswana which is the local language (see Appendix B and C respectively). Participation in the study was completely voluntary and child care givers were free to accept or refuse to take part into this study at any stage without discrimination. Participants' identity, all documentation and all clinical results were kept strictly confidential. Personal information was not mentioned in the research report and results were never linked to the informants as an individual.

This study produced direct benefits to children under study. Children tuberculosis suspects discovered were registered for follow up at local public clinic or health post. However tuberculosis prophylaxis was recommended to those children with a positive TST result or who met other BNTP criteria for LTBI. Children with active tuberculosis were put on a full course of TB treatment (DOTS). Generally the BNTP recommends TST and CXR as part of the routine investigation in children under five contacts of tuberculosis cases. Tuberculin skin testing poses very limited risks and there are no data to suggest that TST poses an increased risk to children infected with HIV. Blisters at the test site are sometimes observed. Usually this blistering heals without medication within 3 to 4 days. However in our study none of the children experienced this complication. Also no children developed severe delayed-type hypersensitivity reactions which would have necessitated treatment with topical steroidal cream. chest x-rays are part of routine examination and the diagnostic radiology department at Scottish Livingstone Hospital (SLH) which conducted the chest x-rays approved that there was no risk of radiation from a single medical radiation exposure.

CHAPTER 4: RESULTS

The purpose of this chapter is to present the research findings. It includes written descriptions of the findings, as well as tables and graphs to clarify the text. The results of the statistical tests are also presented. This chapter is divided into seven sections. The first 3 sections describe the index cases, the caregiver interviewees and the child contacts respectively. Sections 4.4 and 4.5 summarise the results of the initial screening by the health care system while the last 2 sections present the results of the investigations into the current TB status of the children.

4.1. Description of TB index cases

The households of 200 TB index cases were visited in 27 villages. 200 child caregivers or TB cases were interviewed. 497 children under five years of age exposed to those index cases were identified and investigated for tuberculosis in this study.

Of the 200 smear-positive TB index cases, 96 (48.0% [95% CI: 40.0% - 55.2%]) were female and 104 (52.0% [95%CI: 44.8% - 59.1%]) were male as indicated in Table 4. The mean age of the female index cases was 34.4 years with a standard deviation of 13.5 while the mean age of the male index cases was 45.9 years with a standard deviation of 77.2. Thus among the registered index cases, the men where older than the women. Table 5 shows that the highest proportion of TB index cases were from public clinics (49.0% [95% CI: 41.9% - 56.1%]) and health posts (47.0% [95% CI: 39.9% - 54.2%]). Only 8 cases (4.0% [95% CI: 1.7% - 7.7%]) had received TB care at hospitals.

Table 4: Sex of TB index cases

Sex	Frequency
Female	96 (48.0%)
Male	104 (52.0%)
Total	200 (100.0%)

Table 5: Health unit of index TB cases

Type of TB Health Unit	Frequency
Clinic	98 (49.0%)
Health Post	94(47.0%)
Hospital	8 (4.0%)
Total	200 (100.0%)

4.2. Description of interview respondents

Interviews were conducted with the available caregiver of the child contacts. The 200 respondents interviewed were analysed by sex, their satisfaction about screening (follow-up) of child contacts, and their relationships with the primary case and the child. Data did not capture the sex/gender breakdown since it was not

4.2.1. Sex of respondents

Of the 200 respondents interviewed 162 (81.0% [95% CI: 74.9% - 86.2%]) were female, whereas 38 (19.0 % [95% CI: 13.8% - 25.1%]) were male (Table 6).

Table 6: Sex of respondent

Sex	Frequency
Male	38 (19.0%)
Female	162 (81.0%)
Total	200 (100.0%)

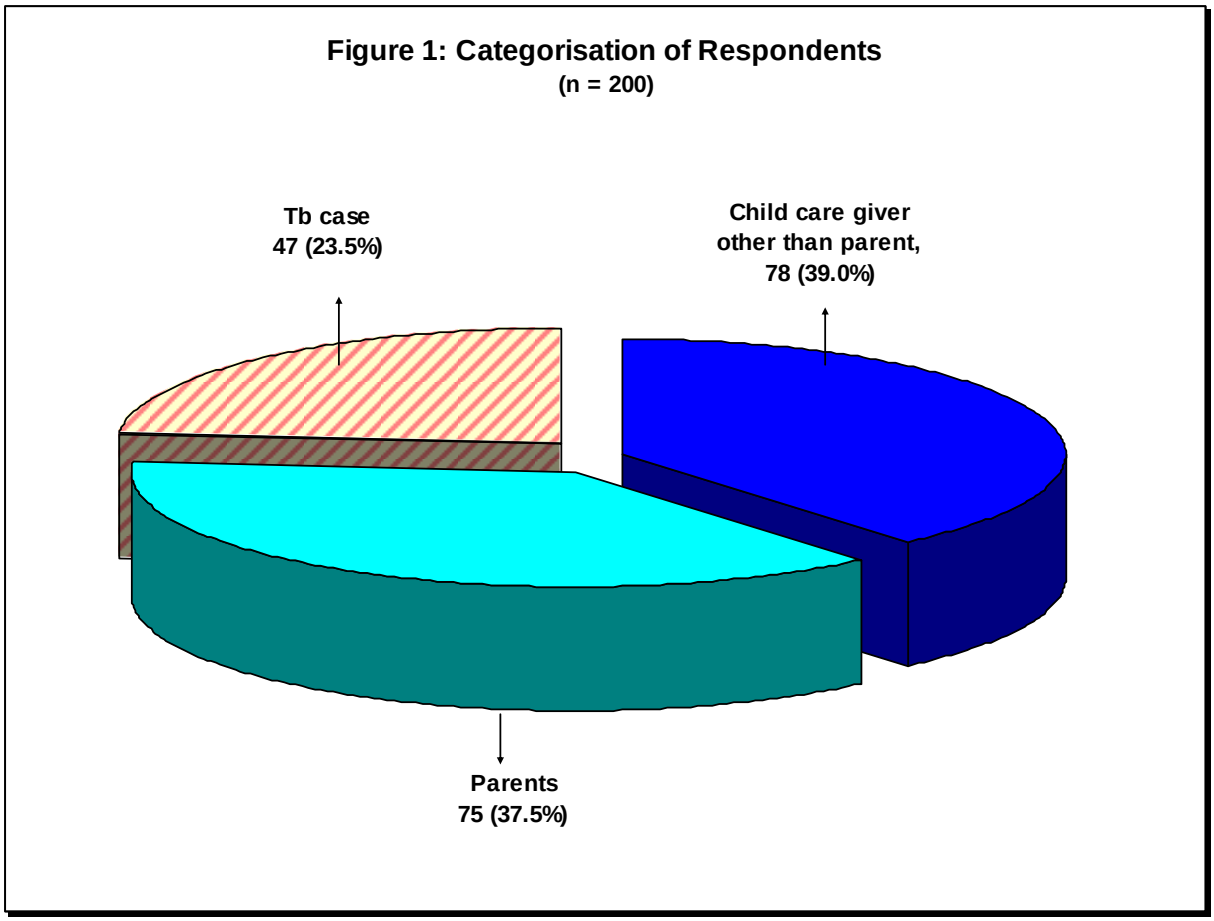


Figure 1: Categorisation of respondents

4.2.2. Categorisation of respondents

Of the 200 respondents interviewed, 47 (23.5%) were the index TB cases themselves, whereas 75 (37.5%) were parents of the child contacts and 78 (39.0%) were child caregivers other than parents (Figure 1). For each of the three categories, data was not segregated into sex/gender breakdown since it has no relevancy to the study objectives.

4.2.3. Respondents satisfaction about screening (follow-up) of child contacts

163 (81.5% [95%CI: 75.4% - 86.6%]) of the respondents were not satisfied with the health care system's follow-up of children who have been exposed to TB (Figure 2). The reasons for this dissatisfaction were not explored in any more detail. The analysis of dissatisfaction by category of respondent is shown in Table 7. Although there were only 6 fathers among the respondents all of them were dissatisfied, followed by caregivers other than parents 66 (84.6%). The difference between groups of respondents was not statistically significant ($X^2 = 4.536$, $p = 0.209$).

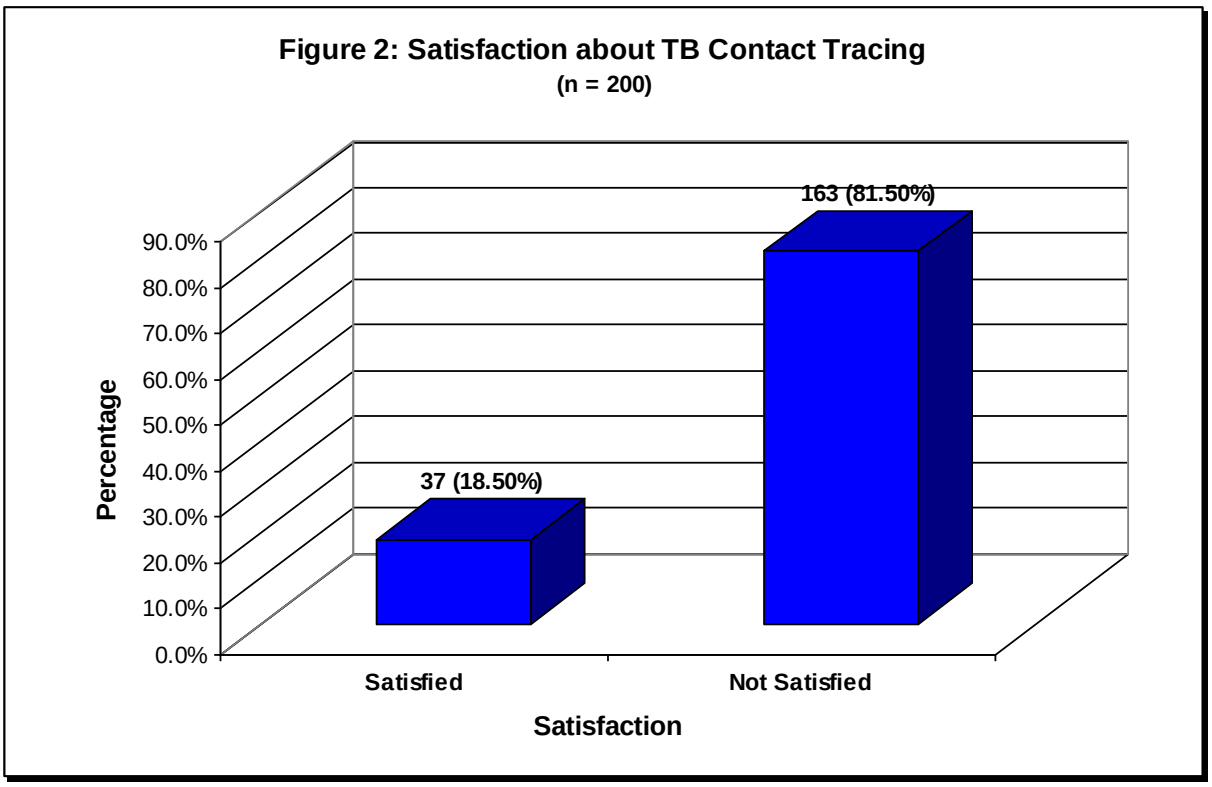


Figure 2: Satisfaction about TB contact tracing

Table 7: Satisfaction about follow-up by category of respondent

		Satisfied with follow-up?	
Respondent	**N**	**Yes**	**No**
TB case	47	13 (27.7%)	34 (72.3%)
Mother	69	12 (17.4%)	57 (82.6%)
Father	6	0 (0.0%)	6 (100%)
Caregiver other than parent	78	12 (15.4%)	66 (84.6%)
Total	200	37 (18.5%)	163 (81.5%)

4.3. Description of child contacts

In the 200 households visited a total of 497 children under five years of age were identified as having been exposed to infectious TB.

4.3.1. Characteristics of child contacts under study

The mean age of children in the sample was 3 years and 9 months at the time of the study evaluation. As indicated in Figure 3 below, 278 (55.9% [95%CI: 51.4% - 60.3%]) were girls and 219 (44.1% [95%CI: 39.7% - 48.6%]) were boys. The predominance of girls seems disproportionally with the sex ratio at birth in Botswana which is estimated at 103 males per 100 females (United Nations Department of Economic and Social Affairs, 2013). Child contacts were categorised into two age groups according to the Botswana National TB guidelines on tuberculosis in children. Thus 51 (10.3% [95% CI: 7.8% - 13.4%]) of the contacts were aged 0-24 months and 446 (89.7% [95% CI: 86.6% - 92.2%]) were between 25-59 months as shown in Figure 4 and Table 8.

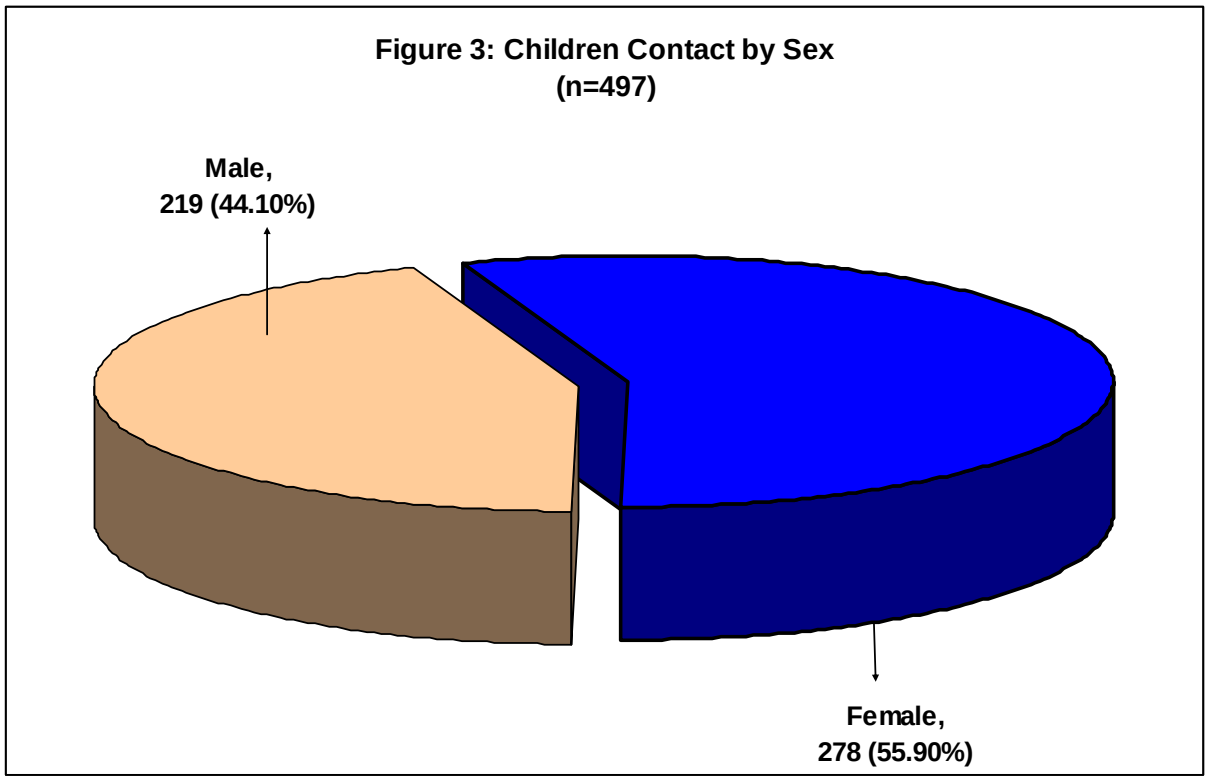


Figure 3: Children contact by sex

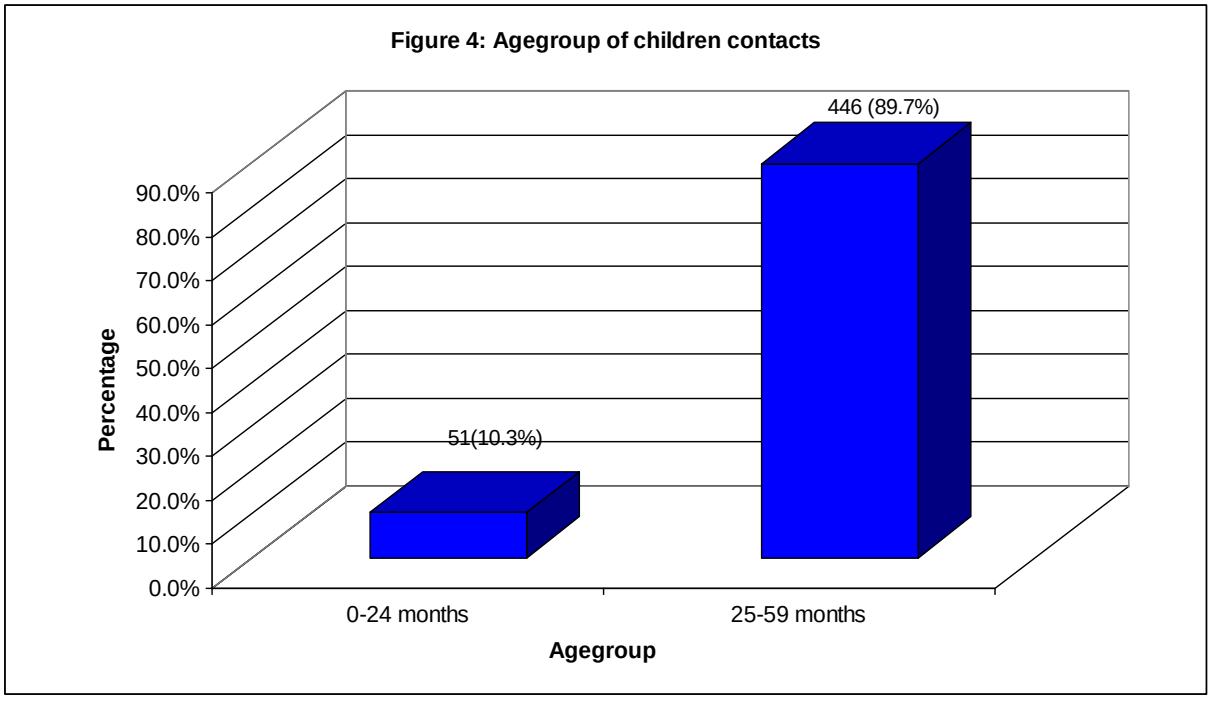


Figure 4: Age group of children contacts

Table 8 below shows that the proportion of girls children was higher to that of boys in both the younger (0 – 24 month) age group and the older (25 – 59 month) age group of children.

Table 8: Sex and age breakdown of child contacts

	Age group		
Sex of child	**0 to 24 Months**	**25 to 59 Months**	**Total**
Female	30 (58.8%)	248 (55.6%)	278 (55.9%)
Male	21 (41.2%)	198 (44.4%)	219 (44.1%)
Total	51 (100%)	446 (100%)	497 (100%)

Table 9: Social proximity to TB case

Relationship to TB case	Frequency
First degree relatives	185 (37.2%)
More distant relative	304 (61.2%)
Not related	8 (1.6%)
Total	497 (100.0%)

4.3.2. Relationship of child contacts to the index TB cases

Children were assessed and categorized by their relationship to the index case as follows: first degree relatives (TB case being the father, mother, brother or sister); more distant relatives (TB case is the uncle, aunt, cousin, grandfather, grandmother); and non-relatives (where TB case is a visitor, friend to the

household, housekeeper or others). Of the 497 child contacts, 304 (61.2% [95%CI: 56.7% - 65.4%]) were more distant relatives compared to 185 (37.2% [95%CI: 33.0% - 41.7%]) first degree relatives (Table 9). Only 8 (1.6% [95%CI: 0.8% - 3.3%]) of contacts were not related to the cases.

4.3.3. Duration of contact with TB case

The duration was measured as the time the child has been in contact with TB case during the likely period of infectiousness which was approximately estimated from 3 months before symptoms onset or first positive finding consistent with TB disease in index case whichever is longer till at least the 2 conventional months or more after starting anti TB treatment. The period after 2 months is included simply because some patients on TB treatment may be potentially infectious for longer than 2 months after starting treatment (Carter, 2010).

Hence the children's duration of exposure to an infectious tuberculosis case ranged from 1 to 4 months. The majority of children (96.2% [95%CI: 94.0% - 97.6%]) were in contact with the index case for more than three months, as shown in Figure 5.

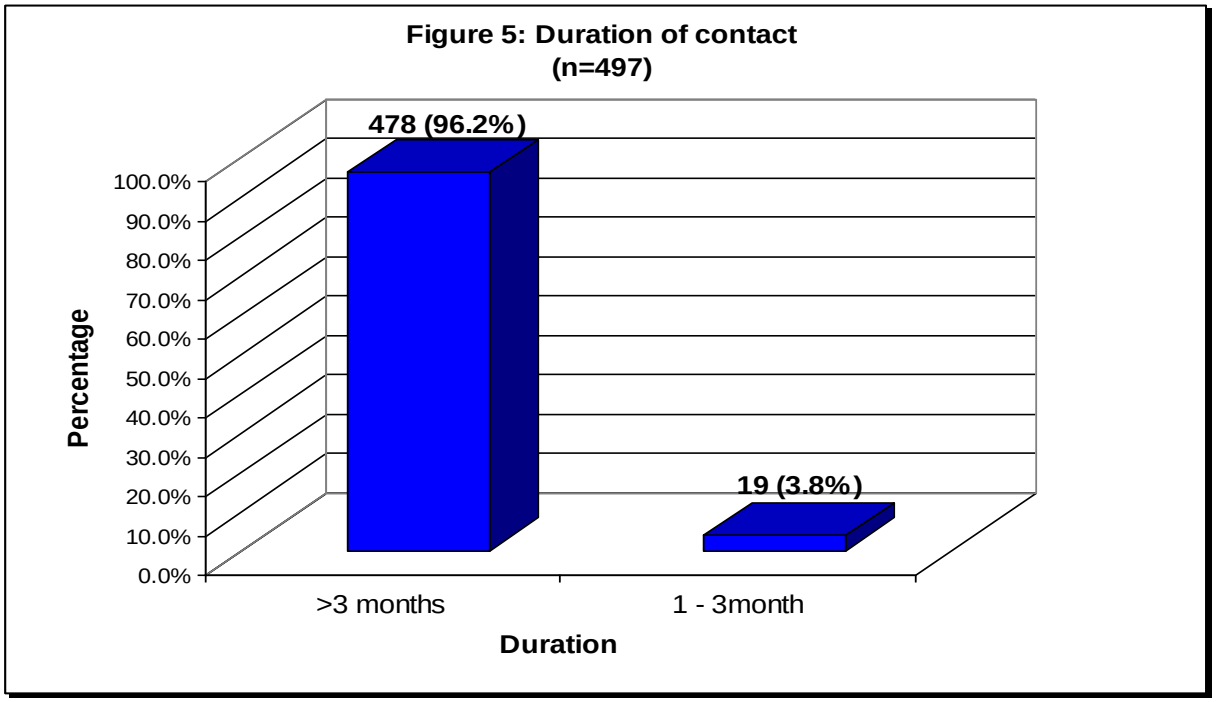


Figure 5: Duration of contact

4.3.4. BCG vaccination status of child contacts

Table 10 below reveals that 19 (3.8% [95% CI: 2.4% - 6.0%]) of the 497 children had never received a BCG vaccination.

Table 10: BCG vaccination status of contacts

BCG vaccination	Frequency
Yes	478 (96.2%)
No	19 (3.8%)
Total	497 (100.0%)

4.4. Initial follow up and screening of child contacts

This section summarises the results from the respondent interviews about the initial contact tracing done by the local health services at the time the index TB was diagnosed.

4.4.1. Patterns of follow up

The local health services attempted to follow up some of the children although there was clearly no standardised contact tracing system in operation. The various experiences are mapped in the flowchart in Figure 6. In 127 (25.6%) children, the index TB patient had been told that all child contacts should be brought to the nearest clinic for investigation, while 87 (17.5%) children had actually been visited by a nurse or community health workers and the child contacts referred for TB screening. Certain children complied with this advice and went for TST screening but even 13 (2.6%) children who were neither told to go to the clinic nor had been visited at home, received a TST on a subsequent visit to the local health facility (Figure 6). A total of 104 (20.9%) children eventually received a TST but 349 (70.2%) children had absolutely no TB contact tracing interactions with the health service.

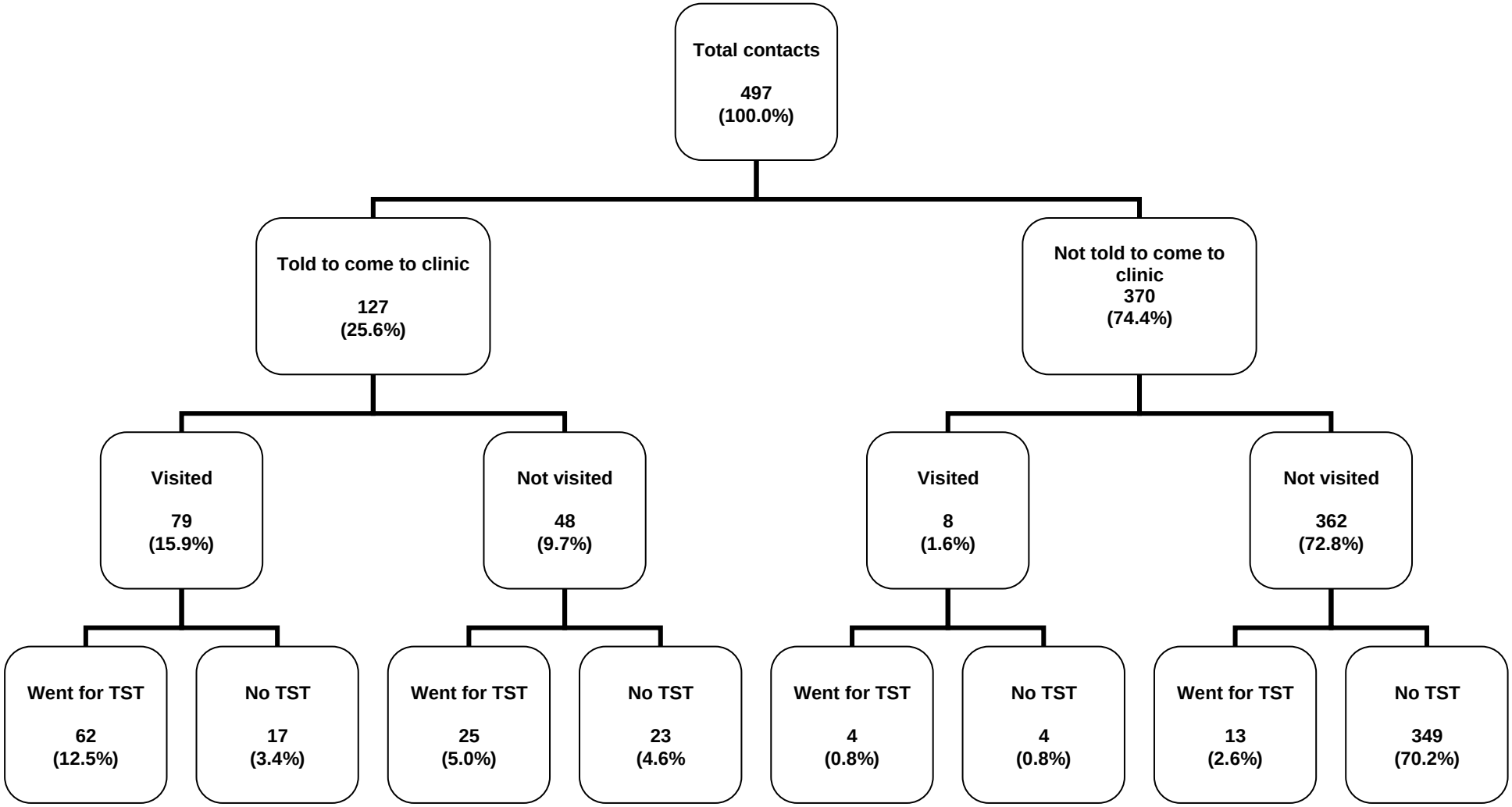


Figure 6: Flowchart summarising experiences of contact tracing

4.4.2. Proportion of children screened at the time of TB case diagnosis

The minimum definition of effective screening of TB contacts is the undertaking and reading of a TST test. In this study, of the 497 children in household contact with 200 index cases, only 104 (20.9% [95% CI: 17.5% - 24.8%]) had TST screening for TB at the time the TB case was diagnosed (Figure 7). This means that despite the emphasis in the BNTP guidelines on TB contact tracing, only one in five children were effectively followed up by the health care system in Kweneng and received TST screening. The remaining 79.1% were missed for TB contact tracing and were at significantly higher risk of tuberculosis infection and disease than the general population.

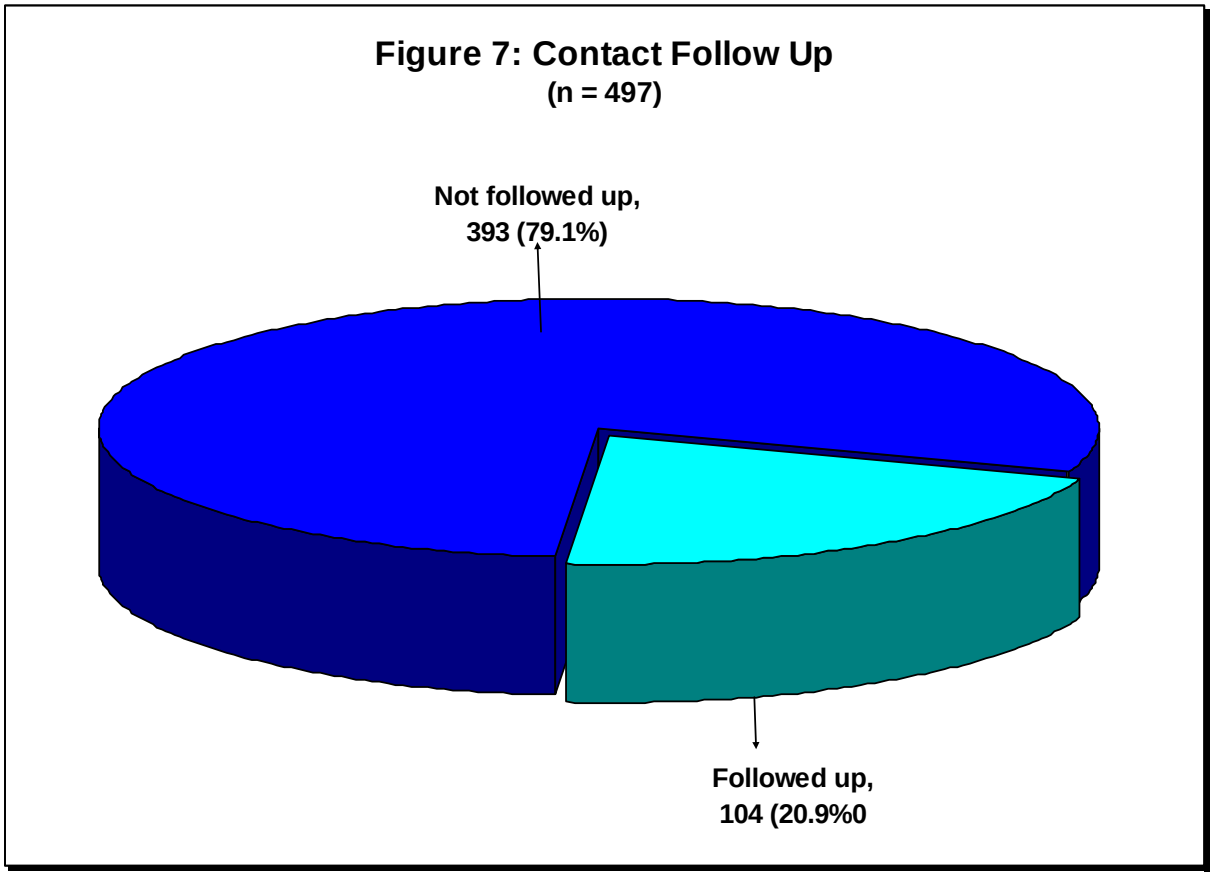


Figure 7: Contact follow up

Tables 11 and 12 show the breakdown of follow-up status (TST screening) of the children by sex and age group respectively. Sex was not statistically associated with screening status but children older than 2 years of age (25 – 59 months) were twice as likely to have received TST screening than those under 2 years of age (Table 12). However, this difference was not statistically significant at the 5% level of significance ($X^2 = 2.882$, $p = 0.09$).

Table 11: Contact TST screening (follow up) by sex

Sex of children	Children screened	Children not screened	Total
Female	63 (22.7%)	215 (77.3 %)	278 (100.0%)
Male	41 (18.7%)	178 (81.3%)	219 (100.0%)
Total	104 (20.9%)	393 (79.1%)	497 (100.0%)

Table 12: Contact TST screening (follow up) by age group

Age group of children	Children screened	Children not screened	Total
0 -24 months	6 (11.8%)	45 (88.2%)	51 (100.0%)
25 – 59 months	98 (22.0%)	348 (78.0%)	446 (100.0%)
Total	104 (20.9%)	393 (79.1%)	497 (100.0%)

4.4.3. Initiation of TB screening in children

For the 104 children who initially received TST screening, the caregivers were asked about who initiated the contact screening. In 62 (59.6%) of the 104

children, contact screening was initiated by health workers, whereas the mother or child caregiver initiated the screening in 36 (34.6%) children (Figure 8).

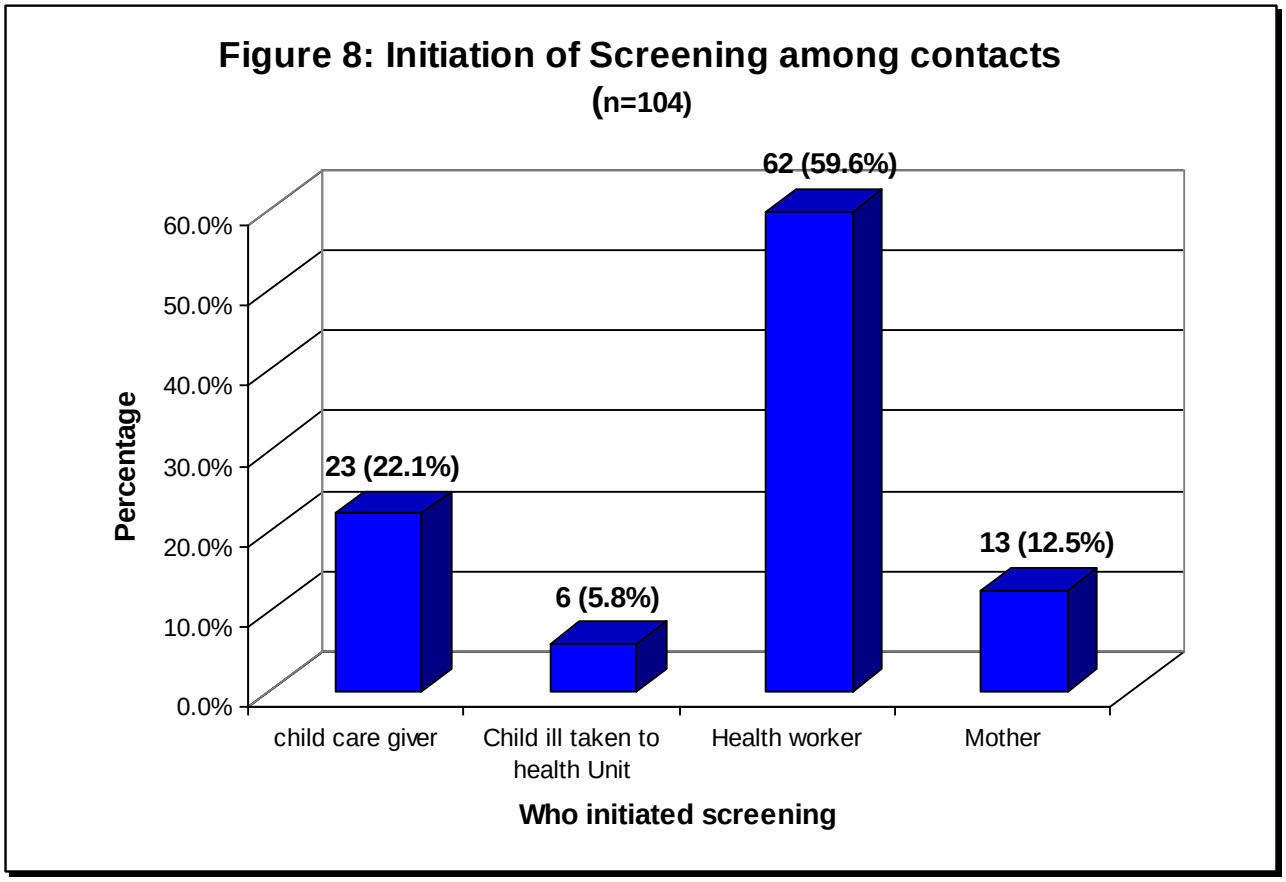


Figure 8: Initiation of screening among contacts

4.4.4. Clinical investigations during initial screening of child contacts by health workers

We analysed which investigations were carried out during initial contact screening by Kweneng district health services. All 104 contacts followed-up had a TST. The other investigations conducted on these 104 children are shown in Table 13. Of the 104 child contacts screened by TST, 45 (43.2%) were evaluated by clinical examination, 3 received a chest x-ray, and only 2 (1.9%) children had both a clinical and radiological examination.

Table 13: Additional investigations performed on contacts screened by TST

	Clinical examination		
Chest X-ray	**Done**	**Not done**	**Total**
Done	2 (1.9%)	1 (1.0%)	3 (2.9%)
Not done	43 (41.3%)	58 (55.8%)	101 (97.1%)
Total	45 (43.2%)	59 (56.8%)	104 (100.0%)

A breakdown of investigation by age group is described in Table 14 below. The rate of clinical examinations was similar in the two age groups. Children under two years of age were more likely to receive a CXR though this difference was not statistically significant (p = 0.165, Fisher's exact test).

Table 14: Contact investigations by age group during initial screening

		TST		CXR		Clinical Exam	
Age group (months)	**n**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
0 - 24	6	6 (100.0%)	0 (0.0%)	1 (16.7%)	5 (83.3%)	2 (33.3%)	4 (66.7%)
25 - 59	98	98 (100.0%)	0 (0.0%)	2 (2.0%)	96 (98.0%)	43 (43.9%)	55 (56.1%)
Total	104	104 (100.0%)	0 (0.0%)	3 (2.9%)	101 (97.1%)	45 (43.3%)	59 (56.7%)

4.4.5. Outcomes of initial TB screening

The outcomes were determined by the computation and analysis of collected data.

Table 15 below summarises the outcomes of the 104 child contacts screened at the time the index TB case was diagnosed. 6 (5.8% [95%CI: 2.1% - 12.1%]) children were initially diagnosed with active TB, while 9 (8.7% [95%CI: 4.0% - 15.8%]) were found to have latent TB infection (LTBI). Obviously with known frequent diagnosis of TB disease in a child having TST negative, these outcomes suggest that 15 (10.7%) or less children out of 104 had a positive TST at the time the index TB case was diagnosed.

Table 15: TB outcomes among children initially screened

Outcome	Frequency
TB Disease	6 (5.8%)
LTBI	9 (8.7%)
No TB	89 (85.6%)
Total	104 (100.0%)

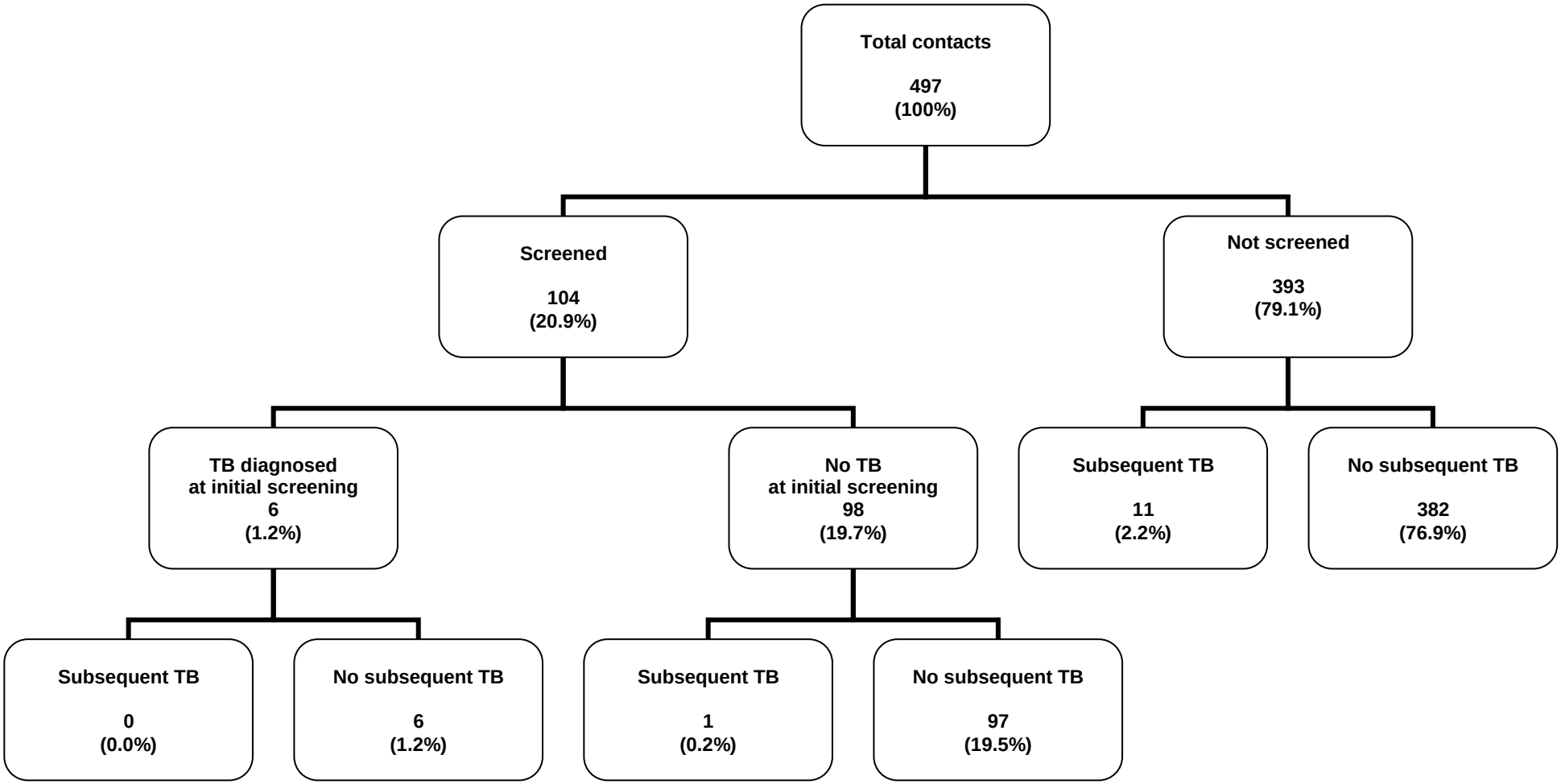


Figure 9: Flowchart showing development of active TB

4.4.6. Subsequent development of TB disease

Figure 9 summarises the history of TB disease in all 497 child contacts after the initial exposure to the adult TB case. 6 (1.2%) children were diagnosed with active TB at the time of original TST screening. One child who was negative during the original screening, developed TB disease later, and 11 (2.2%) children of those who did not received TST screening subsequently developed active TB. Therefore, of the 497 child contacts, 18 (3.6%) had developed TB disease prior to the screening at the time of this study. Not surprisingly, TB diagnosis was higher in those that were screened, so there was a significant association between TB screening and initial TB diagnosis ($p<0.001$, Fisher's exact test) (Table 16). Although, TST screening was protective against the subsequent development of TB disease, the prevalence in the screened was less than half of those not screened, this difference was not statistically significant (OR = 0.358, $p=0.475$, Fisher's exact test).

Table 16: Prevalence of TB among children initially screened

	TB disease diagnosed at screening			TB disease developed subsequently		
Initial TST Screening	**Yes**	**No**	**Total**	**Yes**	**No**	**Total**
Yes	6 (5.8%)	98 (94.2%)	104 (100.0%)	1 (1.1%)	103 (99%)	104 (100.0%)
No	0 (0.0%)	393 (100.0%)	393 (100.0%)	11 (2.8%)	382 (97.2%)	393 (100.0%)
Total	6 (1.2%)	491 (98.8%)	497 (100.0%)	12 (2.4%)	485 (97.6%)	497 (100.0%)

4.5. Follow up and screening of child contacts during present study

4.5.1. Tuberculin Skin Testing (TST)

100% of the 497 children in the study sample were tested with a TST at the time of the evaluation during this study. Thus there was no miss to follow-up, this achievement was a result of both the cooperation of parents/care givers (who understood the benefit of this evaluation), and dedication of an enthusiastic team (FWEs, nurses and the researcher) that closely followed-up all identified child contacts to ensure none of them misses access to services (TST and other investigation and treatment) at their respective health facility. A duration of 2 - 4 days elapsed between the interview and the TST injections at the nearest health facility. Parents and child caregivers who did not bring their children for the reading of TST reaction and recording within 72 hours were immediately followed up the next day.

TST testing of the child contacts at period of this study revealed: 174 (35.0% [30.8% - 39.4%]) were TST positive, 295 (59.4% [95% CI: 54.9% – 63.7%]) were TST negative, and 28 (5.6%) false were recorded (Figure 10). These false positives were identified during clinical examination of child contacts by the researcher.

3 different issues were identified: - Incorrect interpretation of reaction by measuring the diameter of induration longitudinally to the axe of the forearm instead of a reading across the forearm. -TST reading included the area of redness /erythema. - Subjects with TST injected in area of previous scars.

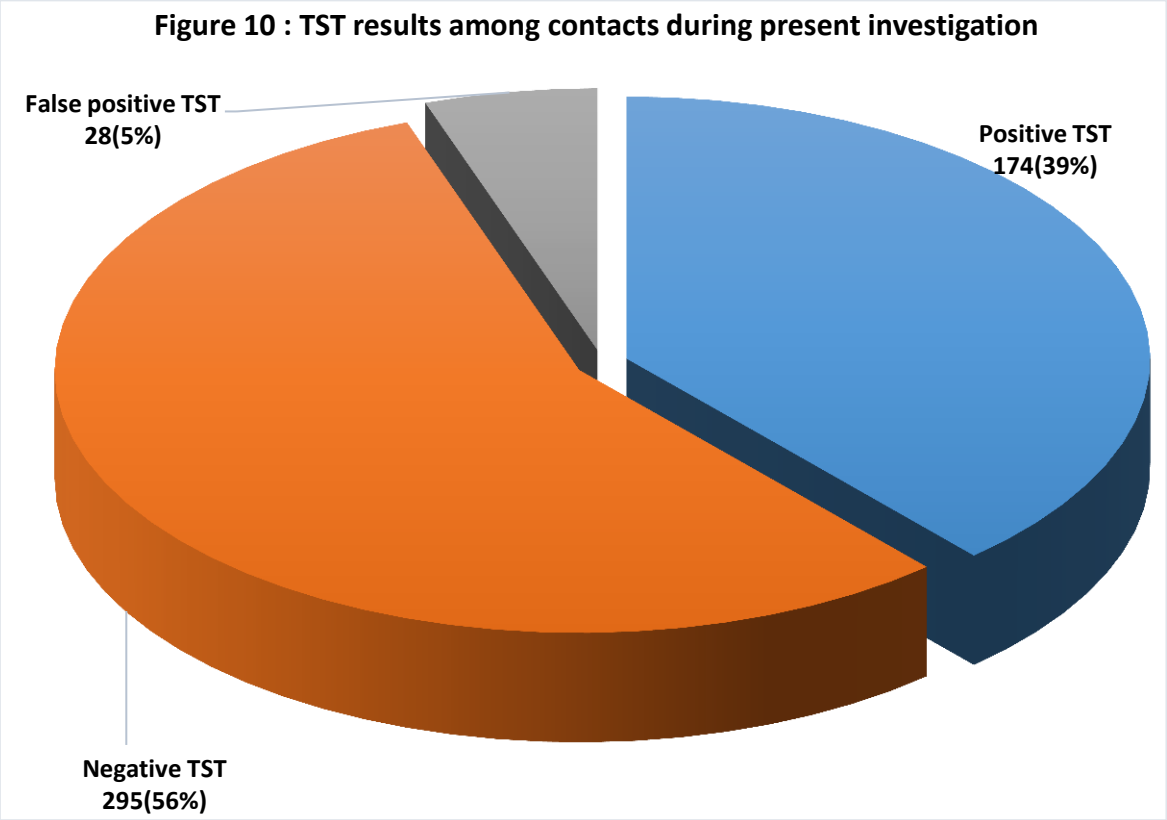


Figure 10: TST Results among contacts during present investigation

As indicated in Table 17 below, TST positivity was 57.9% in those children who had not received BCG vaccination compared to 40.0% in those children who had been vaccinated but this difference was not statistically significant (OR: 2.066, X^2 =2.437, p = 0.119).

Table 17: TST Reactivity and BCG vaccination in children under five

	TST Reactivity		
BCG vaccination status	**TST Negative**	**TST Positive**	**Total**
Vaccinated	287 (60.0%)	191 (40.0%)	478 (100.0%)
Not vaccinated	8 (42.1%)	11 (57.9%)	19 (100.0%)
Total	295 (59.4%)	202 (40.6%)	497 (100.0%)

4.5.2. TB outcomes at the time of present study

4.5.2.1. *TB status at time of present study*

The researcher clinically examined each of the 497 child contacts in the study and based on clinical findings, TST and CXR results coupled with the history of exposure to TB, a diagnosis of Active TB, Latent TB Infection (LTBI) or No TB was made. Of 497 contacts evaluated at the time of this study, 17 (3.4% [95% CI: 2.1% - 5.5%]) children had active pulmonary tuberculosis, 174 (35.0% [30.8% - 39.4%]) had LTBI and 306 (61.6% [95% CI: 57.1% - 65.8%]) had no evidence of tuberculosis infection, as shown in Figure 11. During the clinical evaluation of children, 28 (5.6%) false positive TST related to incorrect reading by nurses were identified.

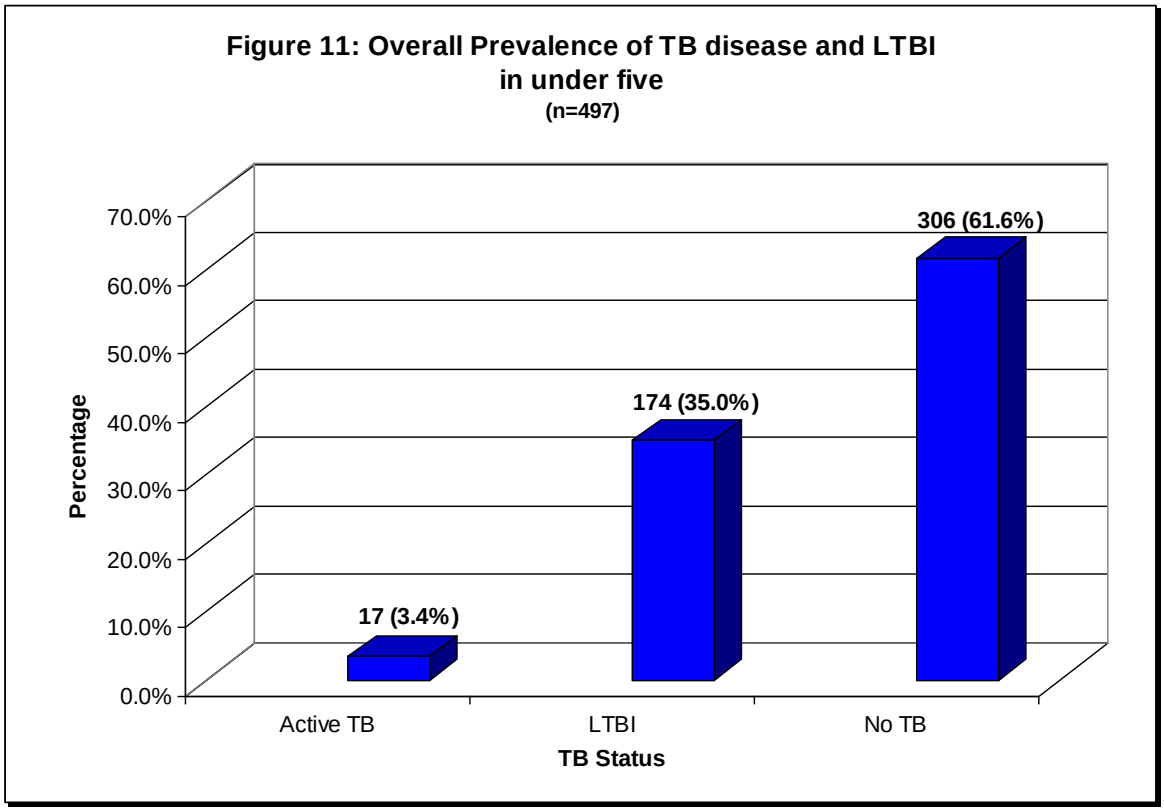


Figure 11: Overall Prevalence of TB disease and LTBI in under fives

4.5.2.2. TB status by age group at time of study

As indicated in Table 18 and Figure 12, 2.0% of children under 2 years of age were identified with active TB while 39.2% had LTBI. In the older children (2-5 years) 3.6% had TB disease and 34.5% had LTB. Statistically there was no association ($X^2 = 0.711$, $p = 0.701$) between the age group and TB status.

Table 18: TB status by age group at time of present study

	TB infection			
Age group in months	**TB disease**	**LTBI**	**No TB**	**Total**
0 – 24	1 (2.0%)	20 (39.2%)	30 (58.8%)	51 (100.0%)
25 – 59	16 (3.6%)	154 (34.5%)	276 (61.9%)	446 (100.0%)
Total	17(3.4%)	174 (35.0%)	306 (61.6%)	497 (100.0%)

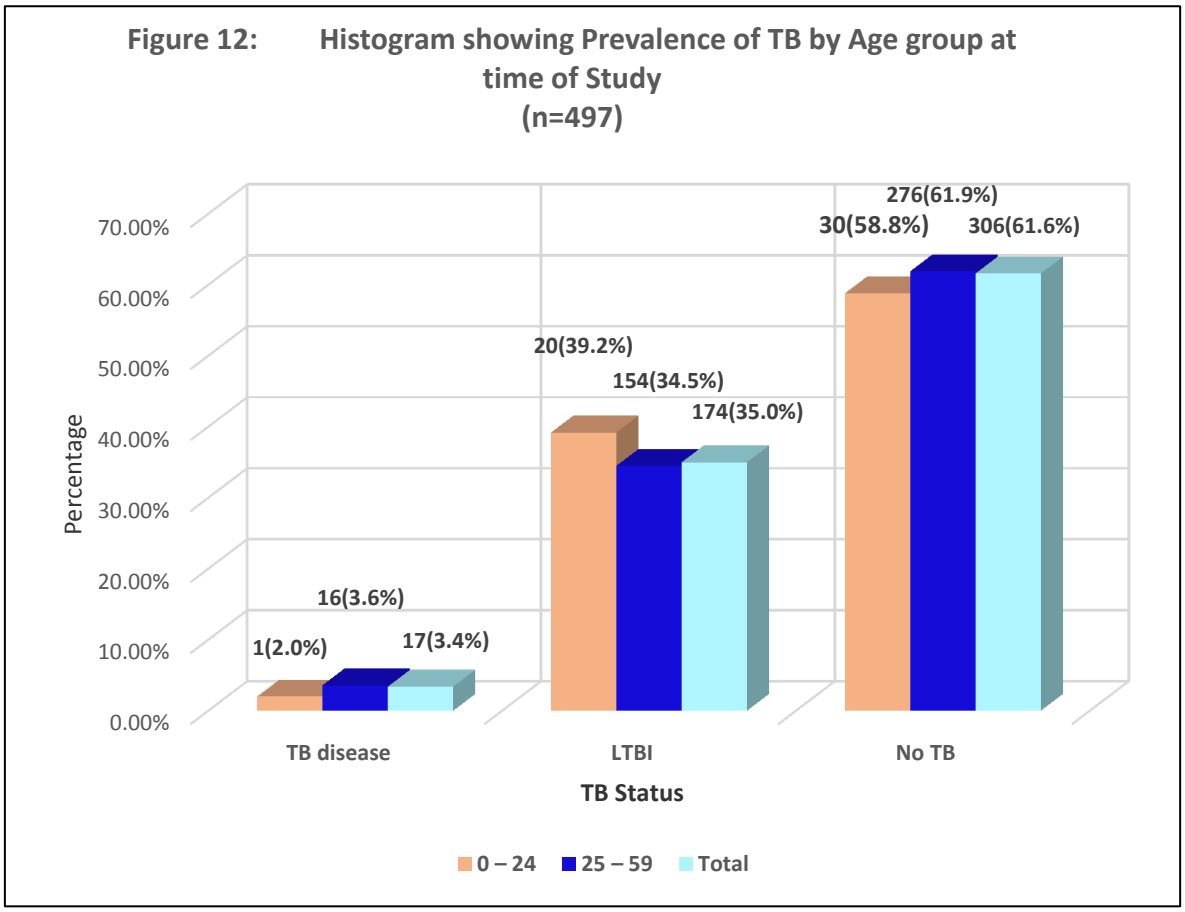


Figure 12: Histogram showing prevalence of TB by age group at time of study

4.5.2.3. TB status at time of present study evaluated by initial screening

Table 19 analyses the TB status of the children by whether or not they were originally screened by the health system at the time the index case was diagnosed. Of the 104 children who were screened, 5 (4.8% [95%CI: 1.6% - 10.9%] had active TB and 17 (16.3% [95%CI: 9.8% - 24.9%] had LTBI. For those children who had not been screened initially 12 (3.1% [95%CI: 1.6% - 5.3%] had TB disease and 157 (39.9% [95%CI: 35.1% - 45.0%] had LTBI. Overall, the children who had been screened had significantly lower rates of TB infection than those that had not been screened (OR: 0.296, X^2 = 20.202, p < 0.001) suggesting that early contact tracing is protective against later TB infection. However as

shown in Table 20 below, the probability of not developing TB given that the child was screened is 0.93.

Table 19: TB status by initial TST screening among contacts at time of present study

	TB status at time of present study			
Initial TST screening	**Active TB**	**LTBI**	**No TB**	**Total**
Screened	5 (4.8%)	17(16.3%)	82 (78.9%)	104 (100.0%)
Not screened	12 (3.1%)	157(39.9%)	224 (57.0%)	393 (100.0%)
Total	17 (3.4%)	174 (35.0%)	306 (61.6%)	497 (100.0%)

Table 20: Conditional probability of TB given screening status during evaluation of child at time of present study

	No TB	**TB**	**Total**
Screened	0.93	0.07	1
Not screened	0.95	0.05	1
Total	0.95	0.05	1

4.6. TB treatment of child contacts

The 17 children identified with active TB at the time of this study (see section 4.5.1.1) were all new TB cases and were started on DOTS. The 174 contacts diagnosed with LTBI were given isoniazid preventive therapy (IPT).

4.7. Overall occurrence of TB in child contacts

Table 21 compares the total number of TB infections identified in this study between those children who received initial contact tracing and those that did not.

Table 21: Overall occurrence of tuberculosis

		Initial TB		Later TB	TB during at time of study		Total	
Initial screening	**n**	**Active TB**	**LTBI**	**Active TB**	**Active TB**	**LTBI**	**Active TB**	**LTBI**
Yes	104	6 (5.8%)	12 (11.5%)	1 (1.0%)	5 (4.8%)	17 (16.3%)	12 (11.5%)	29 (27.9%)
No	393	0 (0.0%)	0 (0.0%)	11 (2.8%)	12 (3.1%)	157 (39.9%)	23 (5.8%)	157 (39.9%)
Total	497	6 (1.2%)	12 (2.4%)	12 2.4%)	17 (3.4%)	174 (35.0%)	35 (7.0%)	186 (37.4%)

For the 497 child contacts exposed to the 200 index TB cases, a total of 35 children were identified with TB disease and 186 were diagnosed as having LTBI during the period covered by this study giving a combined cumulative incidence of TB infection of 44.5% (221 out of 497). 41 (39.4%) of the 104 children who received screening originally had evidence of TB infection and disease compared to 180 (45.8%) of those who have not been screened (Table 20). TB disease and infection were 2.8 [95%CI: 1.77- 4.09] times more likely in children not initially screened than those screened (OR: 2.824) but this difference was not statistically significant at the 5% level of significance ($X^2 = 1.355$, $p = 0.244$).

CHAPTER 5: DISCUSSION

“Tuberculosis remains a major public health challenge in Botswana with an estimated 10.000 people falling sick annually” said the Botswana Vice President Mokgweetsi Masisi, while speaking at the 2015 World Tuberculosis Day on 24 March in Francistown-Botswana (The Namibian, 2015). In such country with high TB incidence: 505 per 100,000 in 2009 (Ministry of Health of Botswana, 2011a), children who are in close contact with an infectious TB case especially an adult diagnosed smear-positive case in a household setting are at risk and children aged under five years are particularly at higher risk of TB infection and disease. While the investigation of contacts of patients with TB is increasingly being considered in resource-limited settings (Fox et al. 2013); but despite the emphasis by the WHO and the Botswana national TB guidelines on prioritising children under five years of age, household contact screening was not effectively implemented in Kweneng district at the time we conducted this investigation. Our study provides original evidence that a household TB contact tracing approach in under five in a rural setting is a doable and can be effectively implemented at the primary care level help identify.

In this study only 20.9% [95% CI: 17.5 – 24.8%] of under-five household child contacts were initially screened and followed up for TB by the health care system in Kweneng (Figure 7), with 79.1% of under-five children who were missed for contact tracing by the same health care system at the time index were diagnosed and treated. In addition, most respondents 163 (81.5% [95%CI: 75.4% - 86.6%]) in this study were not satisfied with the health care system’s follow-up of children who have been exposed to TB (figure 2). Unfortunately, we did not explore in any

more detail, the reasons for dissatisfaction, as it was not part of the study objectives. Meantime this result (81.55%) is similar to the 66% of interviewed patients during the Botswana program review in May 1999 who felt that families were not sufficiently informed by health care workers about tuberculosis in family members of contacts of tuberculosis patients currently under treatment in districts (BOTUSA, et al. 1999).

At the time this study was conducted, there were very few published studies on household TB contact tracing in under five children close contacts of smear positive adult TB case in Botswana. However recently Puryear et al. (2013) published at least a Botswana study on household TB contact conducted in 2009 through December 2011. Compared to our study, in deed their study is a reverse contact tracing using paediatric index cases, and not focusing on exclusive evaluation of younger children as subjects. This means, Puryear et al. (2013) study index cases were paediatric subjects (age ≤ 13 years), and the household contact subjects screened were individual of any age (not necessary younger children) more likely adults, for example the median age of the 2.2% (12/548)–diagnosed new TB cases, was 31 years (IQR 23-38). Although Puryear et al. study represents an urban sample (Gaborone-Botswana), at least the finding of 2.2% new cases of TB disease among household contacts justifies the need for strengthening contact tracing.

Nevertheless, the results of this study might be similar to the 7.8% (21 children) of tuberculosis diagnosed clinically and 37.9% (102 children) of infection at baseline screening in the recent prospective cohort study conducted in Indonesia by Triasih et al. (2015). Although both studies performed clinical assessment,

tuberculin skin test and chest radiography, outcomes might not be compared directly due to the heterogeneity, particularly in outcome definitions (TB disease or TB infection), the criteria used for determining TB infection and disease, and the different age-groups of subjects (children): ≤15 and 5 ≤ years respectively in the study by Triasih et al. and our study. Most TB contact tracing studies we reviewed have mainly focused on the evaluation for active tuberculosis, LTBI and risk factors associated with active disease after exposure to infection. Few of previous studies have attempted to evaluate how contact tracing was undertaken especially in the context of a rural setting in resource-limited countries. This study is the first in Botswana that has addressed this concern. In addition to TB disease and LTBI outcomes, the study has revealed that most under-five child contacts were not screened. The greatest strength of our study is that we followed child contacts who were initially screened at the time TB case was diagnosed, given the fact that the natural history data suggest that the majority of children exposed to and infected with M. tuberculosis who develop tuberculosis disease will do so within 1 year of infection (Marais et al. 2004).This study determined important outcomes such as the proportion of asymptomatic children who later developed disease. A previous study in South Africa also aimed to evaluate the symptom-based screening approach (Kruk & Gie et al. 2008). However, this cross-sectional analysis focused on evaluation of symptoms to predict the presence of tuberculosis, and no follow-up on children who had previous baseline screening was undertaken; therefore, outcomes such as the proportion of asymptomatic children who were screened before and developed disease could not be determined.

In our study, the yield of TB infection and TB disease among child contacts shows that the proportion of LTBI infection was higher (35.0%) than that of active TB disease (3.4%).This difference derives directly from the pathogenesis mechanism of tuberculosis itself - not all infected persons will become diseased. This pattern is congruent with the results in most studies with the exception of a paradoxical result of 14% of infection and 34% diseased in a study of a population of 155 children younger under five contacts of 80 index cases (Beyers et al. 1997). Furthermore the present study identified an overall TB disease rate of 3.4% which is among the highest reported. It is similar to that encountered by Hussain & Watura et al. (1992) in Wales where tuberculosis was diagnosed in 3.5% of 170 close contacts; while infection developed in 25% of the children, 9.6% of children progressed toward active disease. Furthermore our finding of 3.4% is similar to the 3.8% TB incidence reported in the study conducted in Brazil by Santana *et al*. (1997). However results in our study for this outcome should be compared with caution to other studies due to the heterogeneity across these studies in outcome definitions.

One particular contribution of this present study is the uncovering of 3.4% cases of active TB among under five children in the community which represents 17 vulnerable TB diseased children who were previously undiagnosed until this research picked them up for investigation. Nevertheless it should be emphasized that virtually all of these 17 children were apparently healthy and unaware of being TB infected and diseased until this study found they had TB disease. This finding could be an evidence showing that TB is still under-diagnosed and under reported in younger children in rural settings in Botswana. In the absence of this study these children would have further developed advanced disease or

complicated TB that would have contributed to the district child morbidity and mortality, as Infants and young children are at particularly high risk for severe, disseminated TB disease and for TB-related mortality (WHO, 2013b). Finally the 17 new TB cases would have contributed to the formation of a large pool of potential TB cases that could further propagate the epidemic as outlined by WHO (2013b). Our study findings have demonstrated that household contact investigations can help to diagnose TB in earlier stages. Such sound approach should be prioritize to strengthen the diagnosis of TB in children at an asymptomatic phase and have an impact on the interruption chain of transmission of disease.

Although child tuberculosis contact screening and management can enhance case finding and prevent tuberculosis disease (Triasih et al. 2015); a finding of a high proportion of 79.1% (393) of children who were not screened by the Kweneng health care at the time the TB case was diagnosed or treated demonstrates that the health care system in Kweneng district is not adequately prioritizing TB contact tracing for under five children who are at high risk. This can be supported by the results showing that most respondents included in this study 163 (81.5%) were dissatisfied with the provision of follow up services by the health care system to children exposed to TB. Again our finding (79.1%) is closely similar to and supports the results of the interviews with patients during the May 1999 Botswana programme review, that revealed that only 20% of household members were checked for tuberculosis within the past 6 months (BOTUSA et al. 1999), meaning that 80% of household members in Botswana were not checked for tuberculosis within 6 months.

However, there are reasons for caution when interpreting our results. For one thing, the recruitment of contacts in contact investigations is almost always subject to selection bias (Fox et al. 2013). For example, only TB cases identified by the health care services were eligible for inclusion, we selected index cases with the most infectious form of TB, and multiple contacts were investigated for each index case. The selection of smear positive TB cases ensured that all study recruited participants were exposed to proven pulmonary tuberculosis cases. Although sputum smear–negative TB cases less likely transmit infectious than sputum smear-positive cases; but they significantly contribute to TB transmission (Tostmann & Kik et al. 2008). Hence this study did not include smear negative TB index cases, their inclusion would have under-estimated the transmission rates to household contacts (Noertjojo &Tam et al. 2002).

Another potential problem could be the recall bias and subjectivity of respondents in reporting an exaggerated high dissatisfaction rate of 81.5% in order to complain against by in other to complain about health workers for not taking appropriate action to prevent their children from TB.

Nevertheless, we acknowledge that no microbiological (AFB Testing: Acid-Fast Bacilli) was used to confirm new cases, hence that could be one of the limitation too, in addition to the nutritional and HIV status which were not evaluated in our study. .

Another limitation in our study is that we did not investigate a control group of under-fives in the household without a TB case to measure and compare the background community risk of TB infection and disease. We also did not investigate the nutritional status of children in our study. Considering the fact that

poor nutritional status decreases TST reactivity in children (Lienhardt et al. 2003), our reported prevalence of 35% for LTBI may be an under-estimate. It is also probable that in a country with high prevalence of HIV/AIDS such as Botswana, LTBI prevalence among children may be underestimated, since TSTs for LTBI are much more likely to be falsely negative in HIV co-infection (Espinal & Perez et al. 2000). We did not evaluate the HIV status of children under this study. All enrolees in this study were local people, but although in general employment, low literacy rate, poverty, alcoholism might be major challenging factors in this rural setting / Kweneng where the only principal activity is artisanal cattle rearing; a specific socio-economic status of subjects was not assessed under this study. Hence the socio-economic could be an additional study limitation as it would be for the HIV/AIDS status.

A range of 2 - 4 days elapsed between the household interview and the TST during our current screening evaluation. This delay was due to the observed short term unavailability of Mantoux skin tests in some health facilities because of limited and irregular supply of essential drugs to rural Kweneng by the national Central Medical Store. Nevertheless for the purpose of this study, the researcher facilitated the supply of TSTs from the Central Medical Store and some TSTs were obtained from Scottish Livingstone referral hospital in Molepolole. Although our research was not intended to conduct a comprehensive evaluation of the TB programme; from our observation, the unavailability of TSTs in some health facilities might be one of the barriers limiting the health care system to effectively and consistently provide routine tuberculin skin testing to under five child contacts. Thus, if the availability of TSTs at primary health care was evaluated, it would have provided an indication on whether the unavailability of TSTs was one of the

contributing factors toward the lack of provision of TST screening in 349 (70.2%) children in the initial follow up by the health care system. Hence additional reasons for non-provision of TSTs still need to be explore further by the healthcare system or an external assessment. However with the current Botswana updated National TB guidelines (Ministry of Health of Botswana, 2011a) there is a paradigm shift from the use of TST and CXR at based-line contact tracing to symptom-based screening approach, the unavailability of either TST or CXR shouldn't be any more a barrier to contact tracing and provision of IPT. As findings supporting current WOH recommendations for example have, demonstrated that symptom-based screening of child tuberculosis contacts should improve feasibility in resource-limited settings and seems to be safe (Kruk et al. 2008).

While all children living in proximity with a household TB individual are at high risk of becoming infected and diseased; additional underlying factors might have contributed to risk increase. In our study, given the fact that Kweneng is a rural and poor district, most of the households of the index case in this study were living in poverty, and in overcrowded, poorly ventilated huts. Additionally malnutrition is a burden affecting many children in Kweneng. It is also noted that most under-five children are not yet attending school. Thus, under-five children unfortunately spent most of their time and activities at home together with the TB case, who also often stays at home (especially during the infectious period) due to their TB (sickness and stigmatization associated with TB and HIV/AIDS). Therefore these circumstances might prolong close exposure of the child to an infectious TB person and increases the risk of transmission.

Factors such as sex, age group of children and BCG vaccination status were not, significantly associated with the outcomes (LTBI and TB disease) in our study. Beyers et al. (1997) study in South Africa found that children below two years of age were the most infected and diseased, but we found no evidence of association between age group and LTBI or TB disease. We were also not able to explore other factors which might have influenced TB transmission such as the: nutritional status of the child contact, duration of exposure, degree of activities shared in the household with the TB case, household condition, ventilation of the hut, etc. Since our study was carried out at a single evaluation, possible TST conversion and evolution of LTBI into active disease over time, could not be observed and included in the *present* results, and is a further limitation of our study design.

Our study identified 393 (79.1%) eligible children who were never followed up for TB screening by the health care system. Similar poor responses were observed elsewhere. In Malawi, screening compliance rates below 10% were reported (Claessens et al. 2002b; Nyirenda & Sinfield et al. 2006); and they were under 3% in South Africa (Wyk & Reid et al. 2011). However, a study in Thailand reported a compliance rate of 52% which indicates that better results are possible (Tornee & Kaewkungwal et al. 2005).

Although we did not directly evaluate the reasons behind the non-screening or poor adherence to screening guidelines in our study, some of our findings suggest possible explanations. The 370 (74%) of TB cases not requested to bring their child contacts for follow-up, could be an expression either of attitudes toward contact tracing or limited knowledge of health care workers about TB contact

tracing practices. These two factors could be some of the barriers to the initiation of TB screening. Limited knowledge of health care givers and their compliance to TB screening can also be seen through our finding that 59 (56.8%) of the 104 children contacts who initially received TST screening were not clinically evaluated, presumably because health care workers thought that clinical examination was not worthwhile. Additionally, more children may have been diagnosed at the initial screening if the health workers conducted a complete investigation by combining all three examinations (TST, chest x-ray). Unfortunately, a complete evaluation was done in only 2 (1.9%) children.

The 40 (8.0%) TB contacts that were told to come to the health facility for contact tracing but that did not do, suggests some factors attributable to parents/caregivers or barriers to care. These barriers including the cost and time of travel to the clinic/health post, and the lack of adequate community information and education (IEC) on TB contact tracing. On the other hand, 8 (1.6%) children were brought to the health facility for TST screening by their parents or caregiver without being told to do so by the health care worker. Although this proportion is very low it does indicates that there is a certain degree of awareness and acceptance of child TB contact tracing among households in the community.

The BNTP policy (Ministry of Health of Botswana, 1995) recommends the administration of BCG to all neonates immediately after birth irrespective of their HIV status. So if a child missed BCG vaccination at birth, s/he should be soon vaccinated on first contact with the health service. Curiously our study discovered 19 (3.8%) under five contacts in the study population who were never vaccinated with BCG. All child contacts subjects under study were nationals born in

Botswana, they were expected to have been BCG vaccinated as the country seems to have a strong immunization programme. However a more detailed population studies might be require to investigate if this is representative of BCG vaccination coverage in Kweneng. Meanwhile we did use the opportunity to refer these 19 children to their local clinic for completion of their immunization schedule.

In this study previous BCG vaccination of an under five child was not statistically associated with protection against LTBI (Table 17). However, our study had limited statistical power for this comparison. Nonetheless, the non-association of TST positivity with BCG vaccination results in our study supports the BNTP guidelines that do not consider BCG status when evaluating TST of under five children TB contacts. Despite a confirmed BCG vaccination status, a positive TST in a child TB contact is assumed to represent tuberculosis infection. Our finding is also congruent with a previous TST survey conducted in Botswana by BOTUSA (1996) among children aged 3 - 60 months which revealed that most positive TSTs in children are due to TB infection rather than to previous BCG vaccination. A study by Lienhardt et al. (2003) has also demonstrated that a positive TST in an under-five year child is much more likely to reflect TB infection rather than previous BCG vaccination.

Our research study goes beyond what has been done in the similar studies discussed above. In the present study, we examined and compared the prevalence of active tuberculosis and LTBI between initially screened and children not initially screened for TB by the health care system. TB disease and infection were 2.8 times more likely in children not initially screened. The identification of 5

(4.8%) active TB and 17 (16, 3%) among children initially screened by the health care system are an indicator that TB contact practices in Kweneng do not follow protocols for complete contact investigations and are putting children at risk. We tried to understand and determine what investigations were carried out by the district at initial screening and we found that full screening or complete contact investigation (TST, chest radiograph couple with clinical examination) was achieved only in 2 (4.4%) children. Unfortunately the majority 58 (55.8%) of children screened were neither clinically examined, nor had a chest x- ray (Table 13). Being in a rural area the above can be partly explained by limited human resource capacity (doctors and nurses) to conduct a comprehensive investigation during follow up of TB exposed children.

The higher LTBI prevalence in children not initially screened than in those who were screened suggests that TST screening by the health service is protective in preventing early cases. If TB screening was correctly conducted, it would have probably averted the occurrence of the 11 (2.2%) active TB cases that subsequently developed among under five children who were not initially screened (Figure 9). However, there was still a 7% chance of developing TB even if the child was screened (Table 20).

In summary, our study revealed that most under-five child contacts were neither followed up, nor fully screened for TB, by the Kweneng health care system. We showed a high risk of TB infection and active disease among under-five contacts of household TB cases. Our results suggest that household contact investigation is an efficient method for discovering a number of new TB cases and infections;

and may have a significant impact on early diagnosis of TB disease among under-five children.

CHAPTER 6: CONCLUSIONS

In regard to screening of child contacts of tuberculosis cases, the 2011 Botswana National Tuberculosis Programme guidelines (Ministry of health of Botswana, 2011a) and the WHO updated guidance for national TB programmes (NTPs) on the management of tuberculosis in children currently recommend symptom-based screening approach in low resource setting. This WHO recommendation is supported by a research findings from Cape Town in South Africa demonstrating that symptom-based screening of child tuberculosis contacts should improve feasibility in resource-limited settings and seems to be safe (Marais et al. 2008). The approach does not require CXR or TST as these methods have limitations and are often not readily available in most resources-limited settings (WHO, 2006a) like Kweneng district.

This study was conducted before the release of these new guidelines, when the use of TST and CXR was still recommended and being implemented by the Botswana national TB programme.

The purpose of this study was to describe the TB contact follow-up, evaluate child contacts and determine TB outcomes in children under-five household contacts of smear positive adults TB cases in the rural Kweneng district between December 2005 and November 2006.

This is a comprehensive study of a representative rural sample of household under five child contacts of adults with AFB smear-positive pulmonary TB disease.

Findings of high rates of TB infection (35.0%) and active TB disease (3.4%) in our study suggest that under- five children living in the same household with a TB

case in rural Botswana are at high risk of LTBI and active TB disease. This stresses the importance of contact tracing of child under-five household contacts of smear positive TB cases, which is a universally recommended approach that enhance case finding and prevent tuberculosis disease (Triasih et al. 2015).

This present study has further shown that contact tracing of under-five children is not given priority and rarely implemented in Kweneng. Most people were not satisfied with the way the Kweneng health care system provides TB contacts services to and management of younger children, specifically those living in the same household with a confirmed TB case. This study is the first study in Botswana evaluating under five children in a household contact with an adults smear-positive pulmonary tuberculosis cases.

Our study is among the few studies of children under five that measure the extent to which contact tracing is undertaken in a rural setting. What is also particular to our study, is the comparison of outcomes between children initially screened and those initially not screened by the district TB program. This study serves as a baseline for further qualitative studies focusing on factors correlated with outcomes, as well as the successes and way forward to improve TB contact investigation in younger child contacts of TB cases.

The major findings on the transmission of tuberculosis and the risk of infection and disease in the 497 children under study were as follows:

Firstly, to some extent the district tuberculosis programme does conduct household contact tracing, however the study shows that only one child in every five children was screened for tuberculosis. In 1999 the interviews with patients during the May 1999 Botswana programme review (BOTUSA et al. 1999), had

found similar result (only 20% of household members were checked for tuberculosis within the past 6 months in Botswana). These evidences are an indication that indeed there is a real household TB contact tracing problem in Botswana that need to be addressed at Because such inadequate implementation of contact tracing approach contributes towards missed opportunities for diagnosing childhood TB and offering TB treatment and IPT in Kweneng. The factors contributing to weak contact tracing efforts in Kweneng were not evaluated by this study because it was not part of the study objective. However there might be a great need for exploring these factors in near future.

The weakness of the TB programme in Kweneng can evidently be seen through the large proportion 393(79.1%) children not screened. Even among those children who were screened by TST, 56.8% of them still were never examined clinically. These deficiencies could explain why most households interviewed were not satisfied about the TB screening services in children provided by the health care system.

Despite the high risk of infection and disease among household children exposed to infectious tuberculosis from an adult smear positive, and the emphasis of Botswana National Tuberculosis programme guidelines on screening and treatment of child contacts, in addition to modelling studies suggesting that improving the detection and management of childhood TB could have a far greater impact on the health of children than improving detection and treatment of adults with TB (WHO, 2013b); still TB contact policies seem not being translated into consistent operational plans for an effective implementation by the Kweneng primary health care facilities. Whenever a TB case is diagnosed, health workers in

Kweneng do not give much attention and priority to screening all under five household contacts of TB cases.

Our study did not investigate the reason why the Kweneng health care system did not give priority to TB screening of younger children in its TB programme. However the characteristics of a rural health care setting in Botswana may suggests a couple of contributing factors that may need to be explored by future studies: such as the unavailability of TST; limited human resources including FWEs, nurses and doctors who are already overwhelmed with increased HIV/AIDS patients load; inadequate training, contact, limited supervision by the TB programme at higher levels, neglect by parents/ or child care givers as this study shows that only 34.6% of parents/mothers and caregivers took the initiative to bring the child at health facility for TB screening at time TB case was diagnosed.

Secondly, the investigation of under-five tuberculosis contacts offered a high yield of detection of 35.0% infected contacts and 3.4% of new tuberculosis cases. Without intervention these infected children constitute a reservoir of source cases from which new TB infection can arise and negatively impact on infant morbidity and mortality in the district. This shows the need for correct screening not only for detection of active TB but also for childhood primary TB infection.

Thirdly, In Kweneng district, the cumulative incidence of infection and disease were relatively higher in children not initially screened than in those initially screened by the TB program. This justifies the need for strengthening contact tracing and effective provision of therapeutic management of identified under-five children.

Fourthly; Although the probability of not developing the disease given that the child was TST screened remained high 98%, but still 7% of children stand the chance of getting TB disease even if they were TST screened. Therefore, there is a need for consistent follow up.

Fifthly; TB disease and LTBI outcomes (3.4% and 35.0% respectively) are similar to previous contact studies such as in Taiwan, South Africa, Gambia, Zimbabwe and elsewhere. However, due to some limitations in our study, these outcome might have been under-estimated. Regardless of some of these study limitations, the findings of this study provides useful baseline data that can be utilised by policy makers and TB programme implementers to target TB programmes policies and procedures that can enhance evidence-based TB contact investigation in younger children.

Sixthly, this study was not intended to explore the BCG vaccination status, but data analysis identified a proportion of 3.8% of under five children who were never BCG vaccinated.

Lastly; our findings have demonstrated that in an area with high tuberculosis incidence such as Kweneng, household contact investigations can help to diagnose tuberculosis in earlier stage. Such approach can significantly contribute to the overall reduction of new TB infection and acceleration of disease elimination. Only, a minimal one fifth of children were screened for tuberculosis. Also guidelines on contact tracing have not been properly followed during screening procedures for example chest radiography to identify primary tuberculosis was done only in 1.9% children and provision of chemoprophylaxis was effected only in a third (33.3%) of infected children. This is an indication that

health care providers, with the participation of both TB cases and their families, can strengthen efforts in the follow up of under-fives exposed to the risk of acquiring TB from a household TB diseased family member of relative. This effort will contribute to the reduction of TB infant morbidity and mortality on the one hand, and to the prevention of increased TB transmission on the other.

CHAPTER 7: RECOMMENDATIONS

The purpose of these recommendations is to assist the Kweneng health district and the Botswanan National TB control programme to strengthen TB contact tracing among younger children exposed to infectious cases of TB.

Political commitment: This is critical for ensuring: effective policy and guidelines, availability of resources needed for an effective provision of health care service, prioritisation of monitoring & evaluation and research. New public health policies based on scientific evidence are progressively to keep up with rapid turnover and new development in TB and contact contacting approaches. Perseverance and renewed political commitment are urgently needed to achieve goals in TB contact tracing in younger children and ultimately improve the district tuberculosis control outcomes. However, emphasis should be put on the translation of national TB policy and contact tracing guidelines into scalable operational plans at local level; in addition to the provision of adequate resources.

Policy: Although guidelines often exist and were updated in 2011, still there is big gap between policy and practice of contact tracing in young children at primary health care facility (clinic and health post) level. Tools and guidelines on TB contact tracing at the time of this research were old (1995) and needed to be reviewed and updated to accommodate new developments. User-friendly tools for district health workers such as TB contact tracing and prophylaxis charts also need to be developed and adapted to local situation. A targeted tuberculosis contact tracing approach with an emphasis on the most at risk under five children should be made a priority by the BNTP. The policy need to clarify who is

responsible and accountable for TB contact tracing services at each level: district, health facility and community level.

Performance Auditing of the Botswana Tuberculosis Program by the Office of the Auditor General (OAG) needs also to address and include the review of TB contacts tracing issues and prevention in its processes, instead of mainly focusing on the diagnosis and treatment of TB case, drug supply and distribution, program supervision, recording and reporting as shown in the performance Audit report no 4 of 2007 for the period under review 2001-2005 (Office of the Auditor General, 2007). The inclusion of TB contact tracing aspects may in one way or another influence policy making, resources allocation and implementation performance at both health facility and community levels.

Coordination and supervision: The District Health Team Management (DHTMT), district TB coordinator, and the national TB program team need to strengthen supervision and communication to ensure that contact tracing is effectively implemented and monitored.

The DHTMT and the BNTP need to assess and explore why the implementation of TB contact tracing in under five is sub-optimal and ineffective.

Health care service provision: Efforts towards contact tracing and screening for TB among children contacts of TB cases should be enhanced. The DHTMT has the mandate to implement targeted TB contact tracing, and use the current symptom based screening approach recommended by the 2011 BNTP guidelines. Althpugh it is known that isoniazid preventive therapy (IPT) has proven efficacy in preventing TB disease in under five child contacts who have no evidence of TB disease (WHO, 2006a), (Smieja & Marchetti et al. 2000), (Hsu,1984); but yet in

practice IPT is rarely provided (Triasih et al. 2012) to under five TB contacts. For example a study in India suggested that, of 84 child contacts aged younger than 6 years, only 16 (19%) were initiated on IPT (Rekha & Jagarajamma. et al. 2009). In Malawi, 23 (6%) and 6 (2%) received IPT and anti-TB treatment but in 4 (1%), no action was taken (Claessens & Gausi et al. 2002a). Hence, the DHTMT should make continued efforts to motivate and ensure that health care providers at all levels (hospital, clinic and health post) in Kweneng are trained, committed to and accountable for the provision of adequate contact tracing services, and management of LTBI through provision of IPT to all under five children who have no evidence of TB disease.

Through capacity building and coaching, the District Heath Team Management (DHTMT) needs to improve human resource capacity and ensure that guidelines and procedures on TB contact tracing in under five stipulated in the National TB manual are effectively understood by health workers, and translated into district adequate action plans and activities.

Management of child contacts of infectious adults (sputum smear positive): The implementation of a contact tracing programme should be integrated into the local healthcare services to ensure their long-term sustainability. We further recommend the adoption and consistent use of the WHO flowchart shown in Figure 13 below, for the identification and management of contacts across all health facilities in Kweneng (WHO, 2004).

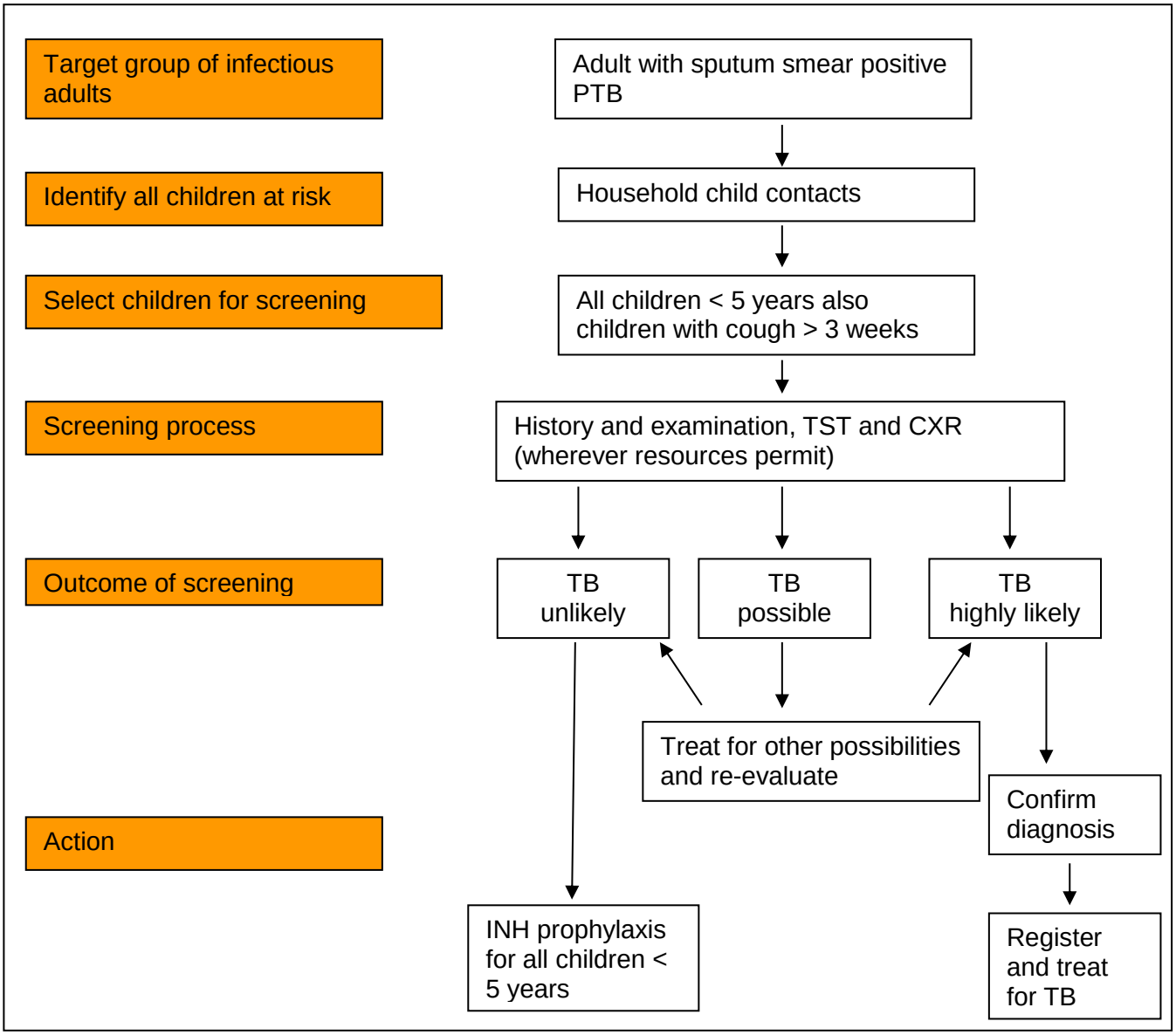


Figure 13: Flow chart summarizing the identification and management of child contacts

A full TB contact investigation needs to be conducted for each under five child contact of index cases with smear-positive pulmonary TB. Health workers need to ensure that each child undergoing a symptom based screening is adequately assessed in order to exclude active TB/disease prior to the provision of IPT.

Training: The DHTMT in collaboration with the National TB program team need to consider an improved and continued training of TB programme personnel in all

health facilities in rural Kweneng using, for example, the new CDC contact investigation training curriculum and tools.

Targeted community interventions: There is also a need to strengthen community strategies such as integrated community services delivery (immunization, HIV/AIDS and TB contact tracing) through mobile clinics which can overcome some of the barriers (distance and cost of transportation) contributing to limited to access health care services and TB contact tracing in this rural district. Strengthening advocacy and Behaviour Change Communication (BCC) strategies will promote, build community capacity development and foster ownership and sustainability.

Monitoring & evaluation: TB contact routine surveillance should be made part of the TB programme at both National and district levels. There is a need to keep a reliable database on TB contact tracing which will enable implementers to monitor trends.

Research: Continued research in household contact tracing and evaluation of limitations is required, it will enable an evidence-based programming and decision making of TB contact tracing by the BNTP. Such research might include a qualitative review of issues surround the implementation of contact investigation.

Finally the research's need in Botswana should be targeted and focus on to both rural and urban health system constraints to improving TB contact tracing at all level. This should include both, an toughly audit from top to bottom of the health care system particularly, TB patients and community behaviours impacting the access to TB contact tracing in Botswana.

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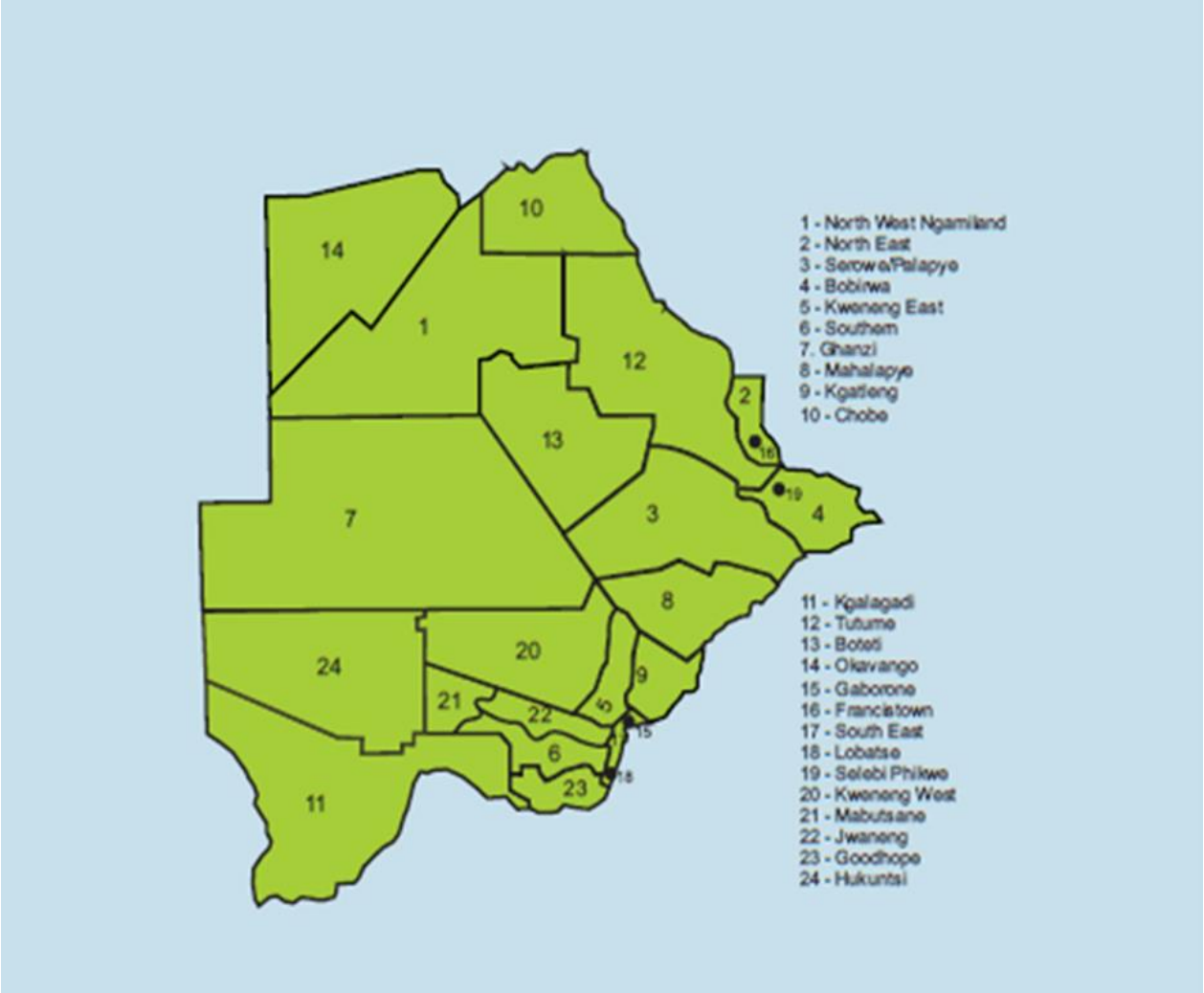
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APPENDIX A: MAP OF HEALTH DISTRICTS IN BOTSWANA SHOWING THE STUDY SITE/ KWENENG DISTRICT.



**Source: Ministry of Health of Botswana. 2007 Botswana ANC Second Generation HIV/AIDS Sentinel Surveillance Technical Report.*

APPENDIX B: SUBJECT'S INFORMATION SHEET

Hello Sir /Madam, My name is ……, I am from Kweneng District Health Team / clinic /Health Post.

We are conducting a study on household tuberculosis contact tracing among children under five years here in Kweneng. As you might be aware, tuberculosis is common in Kweneng and younger children living in same household with a tuberculosis patient are at risk of getting this disease. Thus your taking part in this research will help us to understand better, important issues related to this subject.

The final research report will be submitted to the Ministry of Health of Botswana and to the School of Public Health at the University of the Witwatersrand, Johannesburg in South Africa for Dr Frank. Mpoyo's partial fulfilment for the award of the degree of Master of Public Health. The information obtained will be kept anonymous, confidential and in any circumstance the study result will never be linked to you as an individual.

The study involves a chest radiology at Scottish Livingstone hospital in Molepolole and a mantoux skin test (the injection is only slightly painful. Sometimes it can give a sensation of an insect bite at the site of injection for 1 or 2 minutes. Rarely a child can develop a blister or ulceration at the test site that usually heals without medication within a few days) at the clinic/health post. These procedures are a normal/routine part of contact tracing of any under-five child who has been exposed to tuberculosis.

Although there are no direct benefits, certainly children diagnosed tuberculosis infected or diseased will be respectively recommended for tuberculosis

prophylaxis or treatment at the clinic/health post. Participation in this study is voluntary, and you can withdraw your consent and discontinue participation at any time. If you choose to not participate or withdraw there will be no consequences, except your child will miss the opportunity to be screened for tuberculosis. A signed copy of this form will be made available to you should you require one. I have fully explained.

Thank you

Researcher / Dr F. Mpoyo

Signature: _____ Date: _____ / ___ / ____

APPENDIX C: PAMPIRI YA MOTSAYA KATROLO

Dumela Rra/Mma, ke nna_____ ke tswa mo lephateng la botsogo la kgaolo ya kweneng/kokelwaneng.

Re tsamaisa dipatlisiso mo kamanong ya bolwetsi jwa kgotlholo e tona mo lwapeng ga bana ba dingwaga tse di kwa tlase ga botlhano gone mo kgaolong ya kweneng. Jaaka o ka tswa o itse, kgotlholo e tona e atile thata mo Kweneng le gore bana ba nnang le molwetsi wa Kgotlholo etuna ba ka tsenwa ke bolwetsi jo. Ka jalo go tsaya karolo gago go ka re thusa go tlhaloganya botoka dintlha tsa botlhokwa mabapi le dipatlisiso tse.

Maduo a dipatlisiso tse a tla isiwa kwa le phateng la botsogo la Botswana, le kwa sekolong sa Public Health mo University ya Witwatersrand mo South Africa, e le mangwe a maiteko a ga Ngaka Frank Mpoyo a go abelwa tlotla ya settankang sa Bogaka mo “Master of Public Health”.

Dikitsiso tsotlhe di tla a tseiwa e le sephiri, le gore maina a batsaya karolo a tla a lobiwa ka dinako tsotlhe. Maduo ga a kitla a amanngwa le wena ka gope ka nako epe.

Dipatlisiso di tla akaretsa go boneswa mahatlha(seipone) kwa sepateleng sa Scottish Livingstone mo Molepolole, le mokento wa tlhatlhobelo mogare wa kgotlholo e tona kwa kokelwaneng (mokento o ga o botlhoko bope fela, ka dinako dingwe o ka utlwala jaaka malomo a ditshidinyana sebaka sa motsotso kgotsa e le mebedi. Ga se gantsi ngwana aka nna le borurugo kgotsa ntho fa mokentong mo e bile go folang mo malatsing a makhutshwane kwa ntle ga kalafi). Go

bonesiwa, le mokento o o dirwang o, ke tse di tlholang dirisiwa dinako tsotlhe fa ngwana a tlhatlhobelwa mogare kgotlholo e tona

Le fa ntswa go sena dipoelo dipe, gone mme bana ba ba fitlhelwang bana le mogare kgotsa bolwetsi jwa kgotlholo e tona ba tla tsenngwa mo lenaneo la thibelo mogare kgotsa mo kalafing kwa kokelwaneng. Go tsaya karolo mo dipatlisisong tse go a ithaopelwa, o kgona go emisa tetlelelo ya gago o bo sa tsweledise go tsaya karolo nako nngwe le nngwe. Ga o tlhopa go sa tseye karolo kgotsa o emisa, ga gona ditlamorago dipe, kwa ntle fela ga gore ngwana o tla tlhoka tshono ya go tlhatlhobelwa mogare wa kgotlholo e tona. Pampiri e e tladiwang e tla nna teng gore o e bone fa o e tlhoka. E tlhalositswe ka botlalo. Ke a leboga

Researcher/Ngaka F. Mpoyo

Monwana: _____ Letsatsi: ____ /_____/___

APPENDIX D: INFORMED CONSENT FORM

I have been fully informed about the research on household tuberculosis contact tracing among children under five years here in rural Kweneng. I am aware of the procedures (that are a normal/routine part of tuberculosis investigation in any under-five child contact), benefits and risks involved. I understand the activities that will occur and I am free to decide to participate or withdraw my consent and discontinue my participation in this study at any time with no penalty.

I also understand that confidentiality and anonymity will be maintained all the times.

I certify that the nature and purpose, the potential benefits and risks associated with participating in this research have been fully explained to me. I have not been coerced and I give my consent to participate in this study. However this agreement shall stand only for the purpose of this research.

Signature: _____ Date: _____/ _____/ ____

APPENDIX E: PAMPIRI YA TETLELELO

Ke utlwile ka botlalo ka dipatlisiso tsa kgotlholo e tona mo lwapeng ga bana ba ba dingwaga di kwa tlase ga botlhano. Ke tlhaloganya tsotlhe tse di tla a diragalang le gore ke gololesegile go ka tsaya karolo kgotsa go emisa tetlelelo ya me le go sa tsweledise mo dipatlisisong tse ka nako nngwe le nngwe go sena ditlamorago dipe.

Ke tlhaloganya gape gore sephiri sa maduo le go sa buiwe ga maina go tla a nna teng ka dinako tsotlhe. Ke netefatsa gore tsamaiso le mosola, dipoelo le diphatsa tse di amanang le dipatlisiso tse, ke di tlhaloseditswe ka botlalo (Tsamaiso e e dirisiwang ke e e tlwaelesegileng go dirwa mongwaneng mongwe le mongwe wa dingwanga tse dika fa tlase ga botlhano fi a tlhatlhobelwa mogare wa kgotlholo e tona a kile amana le molwetsi wa kgotlholo e tona).

Ga ke a pateletswa jaanong ke ithaopela go fa tetlelelo yame go tsaya karolo mo dipatlisisong tse. Le fa go ntse jalo, tumalano e, e tla a nna teng fela go direlela gore dipatlisiso di tswelele.

Monwana: _____ Letsatsi: ____ /_____ /

_____

APPENDIX F: DATA COLLECTION TOOL FOR HOUSEHOLD TB CONTACT TRACING AMONG CHILDREN YOUNGER THAN FIVE YEARS- 2004

Site / village: …… Study ID Number: | | | |

■ ***Section I: Identification of respondent***

1. Date of Interview: _____ /_____ / ____

Day / Month / Year

2. Interviewee (Tick appropriate):

□ Mother □ Father □ TB case □ Child caregiver

3. Sex: of respondent (tick where appropriate): □ Male □ Female

4. Interviewer: First Name: …… Last Name ……..……..…

■ ***Section II: Description of index case***

5. Type of health facility where TB case treatment was initiated: (Thick where appropriate): □ Hospital □ Clinic □ Health post.

6. Date of TB diagnosis: _____ /_____/_____

Day / Month / Year

7. Name of the TB case: ……..…

8. Surname of the TB case: ……

9. Sex of the TB case: (Tick where appropriate): □ Male □ Female

10. Date of Birth of the TB case: _____ /_____/_____

Day / Month / Year

11. Home address:

APPENDIX G: RESEARCH CLEARANCE CERTIFICATE ISSUED BY HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) – UNIVERSITY OF WITWATERSRAND.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Mpoyo

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M051021**
PROJECT	Household Tuberculosis Contact Tracing among Children Under Five in the Rural Kweneng District - Botswana
INVESTIGATORS	Dr FN Mpoyo
DEPARTMENT	School of Public Health
DATE CONSIDERED	05.10.28
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 05.11.22 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr D Blaaw

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX H: RESEARCH PERMIT (AUTHORISATION TO CONDUCT RESEARCH) ISSUED BY THE HEALTH RESEARCH ETHICS UNIT OF MINISTRY OF HEALTH – BOTSWANA.

TELEPHONE: 3914467
FAX:3914697
KOPANYOHOUSE
PLOT: 5131
STATION ROAD
GABORONE

HEALTH RESEARCH UNIT
PRIVATE BAG 0038
GABORONE
BOTSWANA

REPUBLIC OF BOTSWANA
MINISTRY OF HEALTH

REFERENCE No: HRU-13/18 C Vol V (127) October 22, 2004,

Dr Frank Ngoy Mpoyo
Kweneng District
Molepolole

Research Permit: Household Contact Tracing an Opportunity For Preventing Tuberculosis among Children younger than 5years of age in the rural Kweneng District - Botswana.

Your application for a research permit for the above stated research protocol refers.

We note that you have satisfactorily revised the protocol as per our suggestions. **Permission is hereby granted to conduct the above-mentioned study.** This approval is valid for a period of 1 year, effective October 22, 2004.

This permit does not however give you authority to enter any household without prior approval from the household. Furthermore, permission should be obtained from the parent or legal guardian before contact with the study subject.

There should be clear communication and understanding with the District on the TST's and X-rays that will be undertaken during this study.

The research should be conducted as outlined in the approved proposal. Any changes to the approved proposal will need to be resubmitted to the Health Research Unit in the Ministry of Health.

Furthermore, you are requested to submit at least one hardcopy and an electronic copy of the report to the Health Research Unit, Ministry of Health upon completion of the study.

Approval is for academic fulfillment only.

Thank you,

S. El-Halabi (Head- Health Research Unit)
For Permanent Secretary Ministry of Health

PERMANENT SECRETARY
MINISTRY OF HEALTH
RESEARCH UNIT
22 OCT 2004
P/BAG 0038
GABORONE
REPUBLIC OF BOTSWANA

APPENDIX I: TUBERCULOSIS CONTACT SCREENING FORM.

Name of TB Patient: .....TB Case ID:☐☐☐☐☐

Physical Address: ……....

Date Started TB Treatment: …. /…. /….

Day /Month/ Year

TB Case CONTACTS

First Name & Surname							
Gender [M/F]							
Age							
Relation to case							
Cough>2 weeks [Y/N]							
Presence of sputum [Y/N]							
Unintentional Weight Loss [Y/N]							
Loss of appetite [Y/N]							
Fever > 1 week [Y/N]							
Chest pains [Y/N]							
Mantoux test date							
Result							
Sputum: Result 1							
Sputum: Result 2							
Chest X-Ray Result							
Date referred to Doctor							
Clinical findings /Result							
Remark							

Date: …. /…. /….

Name & signature of health care provider:

……