PREVALENCE OF TUBERCULOSIS INFECTION IN CHILDREN EXPOSED TO ADULTS WITH SPUTUM SMEAR POSITIVE PULMONARY TUBERCULOSIS IN NAIROBI.

A dissertation presented in part fulfillment for the degree of Master of Medicine (Paediatrics) in the University of Nairobi.

DR. JULIANA MWIKALI MUIVA

DECLARATION

This thesis is a result of my original work and has not been presented for a degree in any other university.

Signed _____

DR. JULIANA MWIKALI MUIVA

M.B.Ch.B. (Moi)

This thesis has been submitted in part fulfillment of the degree of Masters of Medicine in Paediatrics and Child Health with our approval as University supervisors.

Signed
Dr. E. Maleche-Obimbo _____ Date Nov 25th 2009
Senior Lecturer, Department of Paediatrics and Child Health,
University of Nairobi.

Signed
Dr. D. Wamalwa _____ Date 25/11/09
Lecturer, Department of Paediatrics and Child Health,
University of Nairobi.

Signed
Dr. E. Amukoye, _____ Date 25/11/9
Acting Director,
Centre for Respiratory Diseases and Research,
Kenya Medical Research Institute.

DEDICATION

To my husband Ron and daughter Kirigo who have unreservedly supported me through out this research; and to my late father Dr. Peter Muiva who inspired me to take up Peadiatrics for service to children and to my mother who believes in service to others as the highest calling.

TABLE OF CONTENTS:

LIST OF ABBREVIATIONS

ATS- American Thoracic Society

BCG – Bacillus Calmette-Guerin

CDC- Centres for Disease Control

DTH- delayed type hypersensitivity

HIV – Human Immunodeficiency Virus

INH - Isoniazid

LBW- low birth weight

NLTP – National Leprosy Tuberculosis Programme

PCR- Polymerase Chain Reaction

PPD – Purified Protein Derivative

TB – Tuberculosis

TST – tuberculin skin test

TU – Tuberculin units

VCT- Voluntary Counseling and Testing

WHO – World Health Organization

SUMMARY

Background

Tuberculosis is a global health problem with 9 million people having active disease, of whom 1 million are children, and causing up to 2 million deaths annually. Children often contract tuberculosis from an adult with active tuberculous disease. The infected child is at high risk of progressing to active tuberculosis disease. Children exposed to infected adults may be screened using simple tests such as clinical signs, Mantoux(TST) test and chest X-ray for early detection and treatment of disease.

Study Objective

The study objective was to determine the frequency of tuberculous infection and/or active disease in children under 12 years age living with adults confirmed to have open pulmonary tuberculosis.

Methods

This was a cross-sectional survey. Adults on treatment for pulmonary tuberculosis were recruited from the tuberculosis clinic and general medical wards in Kenyatta National Hospital, Mbagathi District hospital and the Nairobi City Council clinics. Their child household contacts were screened for tuberculosis by clinical features, chest X-ray, and TST test.

Results

A total of 160 children from 82 different families were screened between November 2007 and June 2008. The children were aged from six months to 13 years. A positive TST was

seen in 61 (38%) children i.e. TB infection. These children came from 47 different families. Of the 61 children infected 33 children (21%) had active TB disease. 98 children (61%) were found to be healthy by the screening procedures used.

Conclusion and Recommendations

Tuberculosis infection was common among child contacts of open TB. Progression to active disease had occurred in more than half of those infected. Tuberculosis screening for child contacts should be increased to allow for early case detection and treatment. Early screening of children as soon as the adult is diagnosed will allow for effective prophylactic care and treatment of new cases before the onset of severe disease.

INTRODUCTION AND LITERATURE REVIEW

Epidemiology.

Tuberculosis(TB) is an air-borne disease caused mainly by *Mycobacterium tuberculosis* that affects up to 9 million people annually(1) of whom 1 million are children aged less than 15 years. An estimated 2 million people die of tuberculosis annually. A high percentage of tuberculosis disease burden (80%) is from countries in the developing world with Kenya being one of the 22 high TB burdened countries. The World Health Organization estimates that 250,000 children are infected with tuberculosis annually and 100,000 will die each year from tuberculosis.

In 2007 Kenya reported a total of 116,723 cases of tuberculosis (2), giving a case notification rate of 338/100,000 population. The National Leprosy and Tuberculosis Programme (Kenya) reports that 11% of these were in persons aged less than 15 years. Childhood tuberculosis usually indicates recent transmission in the child's surrounding (3), most likely from an undiagnosed adult case. The highest number of tuberculosis cases in adults in 2007 occurred in the age group 25-34 years (2) which is also the reproductive group. Thus many adults with tuberculosis are likely to be parents or caretakers of young children. Studies have shown that there is significant transmission of infection to household contacts of tuberculosis patients. Some of the studies on transmission to children from an adult case are listed as follows.

Table 1. Summary of studies showing prevalence of TB infection.

Author, year	Country	Age (range)	Sample size(n)	Design and follow-up duration	%TB infection	% TB disease
Tornee S.et al. 2003 (4)	Thailand	<15 years	500	Cross-sectional	47	-
Salazer-Vergara et al. 2003 (5)	Phillipines	<15 yr	153	Prospective, 3 month follow-up	69	3.3(x-ray) 0.65(culture)
Madhi et al. 2000 (6)	Paris, France	3 mon-17 yr	91	Prospective study, 3 mon follow-up	22	9
Gessner et al. 1998,(7)	Alaska	<15 yr	282	Prospective study, 3 month follow-up	25	9.6
Beyers et al, 1987-1994 (8)	South Africa,	<5 yr	155	Prospective study, 3 month follow-up	14	34
Christian Lienhardt et al, (9)	Gambia	<5 yr	384	Cross-sectional study	35	-
Sinfield R, et al.(10)	Malawi	<5 yr	195	Prospective	45	23

As shown in Table 1 a quarter to half of children living with adults with pulmonary tuberculosis will be infected by Mycobacterium tuberculosis. A smaller proportion will actually manifest symptoms of disease. Two of these studies were carried out in populations with improved standards of living where TB is not considered a disease of huge magnitude to the health sector. In developing countries higher rates of TB infection are observed in household contacts. However in sub-Saharan Africa, where disease burden is even greater, there are only a few studies which have documented rates of transmission in African household contacts. These studies demonstrate the utility of active case finding in children who are contacts of tuberculosis patients.

Pathogenesis and Pathophysiology of Tuberculosis Disease.

Transmission of tuberculosis is usually from person to person via infectious droplets that are coughed up. (11) The smaller droplets of 1-5 micrometers are suspended in air and are capable of reaching the alveolus in the lungs when inhaled. Once in the lungs the bacilli multiply in the alveolae and some are carried to regional lymph nodes via the lymphatics. Immunity to the disease is from delayed type hypersensitivity, a cell mediated immune response. Macrophages engulf the bacteria and are stimulated by cytokines produced by T-lymphocytes to kill them by phagocytosis. The effectiveness of the immune response largely determines whether the disease will be contained locally or widespread dissemination occurs. Development of delayed type hypersensitivity (DTH) response to infection takes from two to twelve weeks and leads to resistance against the disease. With the DTH response regional lymph nodes enlarge and both regions undergo caseous necrosis and encapsulation. Nodes can then be visualized on chest X-ray.(11)

Children are at a higher risk of developing tuberculosis (active disease) after infection. The risk of developing tuberculosis after exposure has been estimated at 43% in infants, 24% at age 1-5 years, and 15% in adolescents. Adults have a lifetime risk of 5-10% if they are immunocompetent. Children also more commonly suffer from extra pulmonary forms of tuberculosis with 25-35% manifesting extra-pulmonary tuberculosis as compared to 10% of adults.

It is important to note that while children less than 4 years are most likely to manifest tuberculosis within 2 years of infection(3) and in some cases within three months of infection(12), older children may become chronic carriers of the bacilli within their lungs. This generation in future will be among the one third of the world's population who will contribute to the burden of disease from tuberculosis.

In Kenya babies are immunized with bacillus Calmette-Guérin (BCG) vaccine at birth. This vaccination is known to protect against severe forms of tuberculosis especially Tuberculous meningitis (13) but may not offer good protection against pulmonary tuberculosis. BCG has been shown not to protect against TB of any kind in children with HIV (15).

Early Identification of Tuberculous Infection.

Contact tracing forms an important part of control strategies for tuberculosis. This is especially important for children who are easily infected by adults (14) but in themselves are considered low risk for spread of tuberculosis.

A. Tuberculin Skin Test (TST)

The most commonly used method of screening for tuberculous infection in children is the tuberculin skin test (TST) also known as the Mantoux test. Tuberculin Skin Tests (TST) are based on the fact that people exposed to *Mycobacterium tuberculosis* have delayed type hypersensitivity mediated by T lymphocytes. Thus they can have a reaction on challenge with similar antigens again. A positive TST reaction is taken at a cut-off point of 10mm in persons without malnutrition or immunosuppresion, and at 5mm in persons who have either or both of the previously mentioned conditions.

The accuracy of TST may be influenced by various factors. False positives may occur in individuals infected with non-tuberculous mycobacteria, or vaccination with BCG, a live

attenuated mycobacterial strain derived from *Mycobacterium bovis*. BCG vaccination in infants has been thought to have an effect on subsequent tuberculin skin testing for up to six months. A study from Guinea Bissau(19) in infants found that only 25% of BCG vaccinated children had a positive TST reaction (i.e. >5mm) at age 6 months. Of Iranian children(29) vaccinated with BCG at birth 68% had lost TST reactivity by the age of four years. However most reactions greater than 10mm are usually caused by infection with *Mycobacterium tuberculosis*. A tuberculin survey was recently carried out in Botswana(32) where most children are vaccinated with BCG at birth. Children aged 3-60 months had a TST equal or greater than 10mm in 14%. Of these a significant proportion had recent contact with a known PTB case. Similar results are reported from a study in Brazil(33), which also has BCG vaccination at birth with high national coverage. In this study children under 15 years age who were exposed to a known tuberculosis case and control cases not exposed were given a TST. Readings of greater than 10mm occurred in 47.5% of the exposed children and 3.6% of controls. These studies suggest that the TST is a useful screening test for tuberculosis in populations with high BCG coverage.

False negative results are possible in persons with immunosuppression from various causes e.g. HIV infection, malnutrition, severe viral infections, cancer, immunosuppressive drugs, and severe disseminated TB. Malnutrition is known to suppress immunity, however mild to moderate malnutrition does not significantly interfere with tuberculin reactivity. Verma et al investigated immune response to tuberculin(30) in a group of children of low birth weight(LBW), malnourished and normal children without a significant statistical difference was seen between the various groups.

The American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC) use a cut-off point for TST in their population as 5mm.(3) In countries with routine BCG immunization at birth a higher cut-off point of 10mm is used. Children with severe immunosuppression secondary to HIV and severe malnutrition have their cut-off as 5mm. Even then a negative TST test may still not rule out tuberculosis in these children and diagnosis is based more on other clinical features present.

B. Radiology

The Chest X-ray may be used to screen for TB disease in children. The following radiological features suggest tuberculosis:

- unilateral hilar or paratracheal adenopathy with collapse/consolidation, with localised hyperinflation from partial bronchial obstruction or, particularly in infants, with bronchopneumonia has been used to document tuberculosis.
- A definitive radiological feature is the finding of miliary shadows in non HIV-infected children. (20)
- Older children and adolescents may suffer from reactivation tuberculosis and can present with features similar to those in adults such as apical infiltrates, cavitation and pleural effusions.

Children with reactive TST test but without signs and symptoms of disease are said to be tuberculosis infected but not diseased.

Other Methods of Diagnosis.

C. Bacteriological Identification

Culture positive tuberculosis is often difficult to prove with children. Tuberculosis at this age is often paucibacillary. Young children less than 10 years age do not cough up sputum but swallow it instead. Gastric lavage after an overnight fast is used for collection of culture specimens. However the yield with this method has been low (0-20% sensitivity) and it requires hospital admission so that three consecutive specimens may be obtained. The use of nebulised saline for sputum induction(21) has been tried in South Africa with remarkable success. Researchers there found that with good techniques one sample of induced sputum could yield the same as three samples of gastric lavage specimens(87% vs. 65% for induced sputum vs. gastric lavage on total yield from microscopy and culture). Advantages of this method include application on outpatient basis; it's much less invasive and therefore can be used in children of all ages. Its main disadvantages include a risk of inducing bronchospasms, and that it requires the use of a physiotherapist trained with chest maneuvers. It also requires good isolation techniques to prevent TB transmission.

D. Scoring Systems for Diagnosis of Tuberculosis in children.

The use of scoring systems for the diagnosis of tuberculosis in children has ceased after findings that in populations with high prevalence of HIV the scoring systems lose sensitivity and specificity. Van Rheenen(17) noted that the scoring system in Zambian children had sensitivity of 88%; but low specificity was of 25%. He concluded that the

scoring system should not be used as a diagnostic tool in countries with a high HIV prevalence, like Kenya.

The World Health Organization currently recommends that a child should be suspected to have tuberculosis if sick, with a history of contact with a suspected or confirmed adult tuberculosis case and with suggestive symptoms and poor response to standard antibiotic treatment.(25, Appendix 4)

E. Immune Based Assays

The fact that the TST may be influenced by other factors leading to false positives and false negatives has lead to further research on immunological methods to identify the infected persons more accurately. Currently focus is on the use of T-cell based assays such as the Quantiferon-GOLD(18) or the ELISPot assays. Research from Italy shows that the ELISPot assay(23) had a sensitivity of 70% and a specificity of 91%, thus making it more accurate than the other assays and even the Tuberculin skin test. The tuberculin skin test lacks sensitivity, particularly in HIV-infected individuals, and has poor specificity because of antigenic cross-reactivity with BCG vaccination. Zambian studies(24) show that ELISPot is a more specific diagnostic tool to use in populations with high HIV prevalence.

Tuberculosis and HIV

The association between TB and HIV infection has been well documented. The NLTP(2) estimates that the biggest factor behind the increase in tuberculosis prevalence in Kenya

is HIV infection. Lawn et al in South Africa(36) found that 50% of children aged 0-9 years with tuberculosis in the year 2004 were also HIV infected. Chintu C. (35) found that Zambian children with TB had HIV prevalence of 37% and the risk of TB attributable to HIV infection in this group was 29%. HIV is not only a potent risk factor for the reactivation of tuberculosis but also increases risk of progression of tuberculosis disease in HIV positive individuals.(22) Bhat et al(15) in 1993 found that children with HIV had an eight-fold increase in susceptibility to TB infection.

HIV infection makes the diagnosis of tuberculosis more difficult. These children commonly suffer from other respiratory infections such as *Pneumocystis jiroveci* pneumonia, lymphoid interstitial pneumonitis, and viral, bacterial or fungal pneumonia. They are often anergic to the TST. Classical features of TB may not be found on X-ray. However any child with close contact to a TB patient should be screened for disease with a high index of suspicion. Those not infected have been found to benefit from Isoniazid prophylaxis. Children with HIV are even more at risk for disseminated and extrapulmonary TB. TB treatment forms an important part of therapy for these children. Children with severe immunosuppresion have a higher mortality rate on treatment as compared to their HIV negative counterparts. Hessling et al in South Africa(37) looked retrospectively at a group of HIV-positive children aged from one month to 13 years with culture confirmed tuberculosis. Of 87 children analyzed 18 died during TB therapy but the overall mortality was 34 i.e. 39.1%. A large number of deaths were caused by opportunistic infections. The study also noted TB treatment failure (i.e. culture positive after completing six month treatment) in 13% of children despite good compliance to treatment, another problem common in HIV infected children. Similar findings are reported from Cote d'Ivoire.(38)

Economic Cost of Tuberculosis.

Okello D. et al(26) have estimated that the cost of treating one tuberculosis patient in Uganda would be $391 with community based care and $911 with hospital based care. Brazilian researchers(28) found that the average cost of treating one new case of tuberculosis was around US$103. The cost to the public services consisted of 65% on hospitalization, 32% on treatment, and only 3% was spent on prevention. In this study families committed around 33% of their income on expenses related to tuberculosis. In Australia patients(27) admitted to hospital during treatment for tuberculosis run up total treatment bills of up to AUS$5447. Patients treated as outpatient for the duration of treatment cost the health services AUS$2260, which is 41% of the inpatient cost. The studies show that generally it is more cost effective to treat tuberculosis early and while it is at less severe presentation at which stage treatment then can be successfully accomplished on out patient basis. This cost will however be balanced against the increased costs incurred by screening more contacts.

STUDY JUSTIFICATION AND RATIONALE

Kenya is one of 22 countries that hold 80% of the worlds' tuberculosis patients. The National Leprosy and Tuberculosis Programme reports that from the early 1990s TB cases have been on the rise. This has been attributed to an increase in the HIV prevalence rates till a peak in 2002, from where the HIV infection rates have now declined to a level of 7.4% in 2007.(32). Transmission rates for tuberculosis especially with appropriate circumstances of household crowding, smoking and immunosuppression from various causes can be as high as 50%. Progression to active disease occurs in as many as 45% of children exposed, the risk being higher among younger and immunosuppressed children. Children may have more severe forms of disease and delay in diagnosis increases the severity of illness at presentation. Ideally every child thus exposed to TB should be screened for early management of disease.

The National Leprosy and Tuberculosis Programme(NLTP) estimates that the case detection rate of tuberculosis in Kenya is now at approximately 70%. Efforts that have led to this improvement included routine screening of contacts of known tuberculosis cases. A national policy of chemoprophylaxis to all TB exposed children and full treatment for those with tuberculosis disease is now in place. Children less than 5 years old exposed to a tuberculosis patient and with no evidence of active disease should receive Isoniazid prophylaxis. Treatment to those presenting with more severe forms of illness costs more than for those children identified early in the course of their illness. Ultimately the morbidity and mortality as a result of delayed treatment for tuberculosis is greater.

It is with this background that this study was formulated. Local studies on prevalence of disease in children are not available easily and the prevalence of infected

children after close contact with infected adults is not known. The study was to determine the prevalence of TB infection and/or active TB disease in children exposed to adults with sputum smear positive TB attending Kenyatta National Hospital and other health centres for treatment. The results obtained in the study will be forwarded to the administration and other relevant bodies. They will be used as a guide on how to improve early case detection and management of child contacts of TB patients.

STUDY QUESTION

What are the rates of tuberculosis infection and/or disease in children living with adults that have smear positive tuberculosis.

OVERALL OBJECTIVE

To determine the frequency of tuberculosis infection and/or disease among child contacts of adults with smear positive pulmonary tuberculosis.

SPECIFIC OBJECTIVES

1. To determine the frequency of tuberculosis infection among children from age six months to 12 years living with adults with sputum smear positive pulmonary tuberculosis.
2. To determine the frequency of tuberculosis disease among children from age six months to 12 years living with adults with sputum smear positive pulmonary tuberculosis.

CASE DEFINITIONS:

There were specific case definitions for TB infection and TB active disease in the children, depending on their nutritional status and whether they were immunosuppressed or not. Definitions for the immunosuppressed children

- A HIV infected child was any child with two positive results from the rapid tests for HIV or one positive rapid test and a confirmatory HIV ELISA test. In children aged less than 18 months a positive PCR test was also required for diagnosis.
- Malnutrition (moderate to severe) was defined as a child with a weight-for-height that was minus two standard deviations from the mean expected for age and gender. Any child who showed obvious wasting and oedema with the criteria mentioned also was treated as severe malnutrition. (41)

1. **Tuberculosis Infection**:

A. HIV non-infected/ $\geq$ 1.99 SD weight-for-height or length/no obvious wasting or oedema:

- TST induration $\geq$ 10mm

B. HIV-infected/ weight-for-height or length $\leq$ 2SD with or without obvious wasting/oedema:

- TST induration $\geq$ 5mm

However in any group a negative TST test did not exclude TB infection.

2. **Tuberculosis Disease**:

A diagnosis of active TB disease was made if the child met two or more of the criteria below:

A. Criteria for TB infection as defined above

B. HIV non-infected/ ≥ 1.99 SD weight-for-height/no obvious wasting or oedema:

- Clinical symptoms suggestive of TB including at least three of the following:
  - Chronic unremitting cough > 2 weeks
  - Persistent fever > 38°C, and no response to effective antimalarial drugs
  - Weight loss or failure to thrive
  - Change in mental status, convulsions or coma

- Clinical signs of TB including one or more of the following
  - Enlarged painless cervical lymph nodes i.e. nodes >1 cm, mobile or matted, +/- scrofula, in one or more regions of the neck
  - Spinal deformity(Gibbus)
  - Firm, non fluid, non traumatic swelling of joint
  - Unexplained abdominal swelling or ascites
  - Pleural or pericardial effusion

- Radiological features including one or more of the following:
  - Unilateral hilar or paratracheal adenopathy +/- collapse or consolidation or localized hyperinflation
  - Miliary shadows
  - Ghon complex
  - Atypical pneumonia
  - Pleural effusions
  - Cavitation and/or apical infiltrates in older children

C. HIV-infected/ weight-for-height or length ≤ 2SD with or without obvious wasting/oedema:

- Clinical symptoms of TB as above
- Clinical signs of TB as above
- Radiological features as above.

Key Features Suggestive of TB

The presence of three or more of the following should strongly suggest a diagnosis of TB:

- Chronic symptoms suggestive of TB
- Physical signs highly suggestive of TB
- A positive tuberculin skin test
- Chest x-ray suggestive of TB.

[Guidance for national tuberculosis programmes on the management of tuberculosis in children.(42)].

METHODS

Study Design:

A cross-sectional survey.

Study Area:

The study was carried out at Kenyatta National Hospital which is a tertiary National Referral and Teaching hospital in Kenya. The University of Nairobi Medical School which is situated within the hospital uses it as a teaching ground for the university students. It also receives many patients who present for primary care without referral. The hospital has a 2,000 bed capacity and sees over 500 outpatients daily. The hospital has several clinical disciplines, one of which is the diagnosis and management of tuberculosis patients. The medical wards in Kenyatta National Hospital have adult patients newly diagnosed with pulmonary tuberculosis while the clinic is a diagnosis, treatment and follow-up center for tuberculosis patients. It acts as a referral centre for the greater Nairobi area, seeing up to 30 patients each day, of whom, on average, 2 - 3 will have open tuberculosis.

The primary investigator also visited Mbagathi District Hospital and several Nairobi City council clinics to recruit patients. Mbagathi hospital, also formerly called the Infectious Diseases Hospital, serves as a treatment and referral centre for many illnesses including tuberculosis diagnosis and treatment for both children and adults. The Nairobi City Council Clinics receive patients from other referral areas who would like to access treatment from a centre near their area of residence.

Source Population:

The study subjects were recruited from children who are household contacts of adults attending the tuberculosis clinic in Kenyatta National Hospital or admitted to the medical wards. Children were also recruited from adults attending the tuberculosis clinics at Mbagathi District Hospital and the Nairobi City Council health centres at Rhodes, Kayole, Kangemi and Riruta.

Study Population

The study population was comprised all adults with sputum positive PTB and their child household contacts. Adults with the required characteristics (i.e. sputum smear positive tuberculosis) were identified from their medical records at the adult TB clinic and from adult medical ward notes. Children recruited into the study were household members of the adults' family who meet the required criteria. Child subjects were interviewed and assessed at the TB clinic in Kenyatta National Hospital.

Inclusion Criteria

A. Adult Patient

1. An adult whose records show clearly the sputum smear positive PTB and is on anti-tuberculous therapy.
2. An adult whose demographic data is available and has at least one child living with him/her.
3. An adult able to understand the study and able to give consent.

B. Child Subjects

1. Children aged from six months to twelve years of age.
2. Child should have been living for more than six weeks with the index adult found to have sputum smear positive PTB.
3. Children living with the index adult whose PTB symptoms began at least six weeks prior to recruitment into the study.

Exclusion Criteria

1. Children already on treatment for tuberculosis.

Sample Size

The sample size was calculated using the prevalence of 14% tuberculosis infection drawn from a South African study by Beyers et al in child household contacts.(8) The formula below was applied

$$n = \frac{Z^2\ p(1-p)}{d^2}$$

Where n = minimum sample size,

p = prevalence of TB infection (Beyers, 14%)

d = absolute precision (estimated at 95%)

$$n = \frac{(1.96)^2\ (0.14)(0.86)}{(0.06)^2} = 128$$

Thus the minimum required number of patients was 130 children.

STUDY PROCEDURES

Patient Recruitment

Adults meeting the study requirements were identified. Consecutive sampling method was applied. Adults were asked to list their children who meet the study criteria and each adult was asked to bring in children from their household. Once the adult client understood the study requirements informed consent was taken from them. The adult thus recruited was asked to meet the cost of transport for his/her self and the children. Special consideration and financial assistance with transport costs was given to extremely needy patients to assist in the screening of their children. The adult's details were recorded in a questionnaire and they were allowed to complete their visit at the clinic. They were then given an appointment to come back with the children who met the study requirements on another day.

Initial Visit.

Children brought in for assessment by their parent/guardian first sat down with the interviewer to fill out a coded questionnaire (Appendix 1). Their sociodemographic characteristics were assessed and details as to TB exposure were taken. They then had a physical examination which was done looking at general condition of the patient, their height (or length) and weight and then completed by a systemic survey. (Appendix 4). The child's assent was obtained for study procedures for any child over the age of seven years.

Clinical Procedures

1. The Tuberculin Skin Test

A Tuberculin skin test was administered to all children on the volar surface of the right forearm.

The TST was performed by injecting 5 tuberculin units (TU) of purified protein derivative (PPD) intradermally in the anterior aspect of the forearm. After 48 to 72 hours the client returned back for reading of the TST. The size of induration was recorded in millimetres. If the participant had no induration, the result was recorded as 0 mm.

Positive Result:

- HIV non-infected/ $\geq$ 1.99 SD weight-for-height/no obvious wasting or oedema: TST induration $\geq$ 10mm
- HIV-infected/ weight-for-height or length $\leq$ 2SD +/- obvious wasting/oedema: TST induration $\geq$ 5mm

2. Radiological Examination:

Chest x-rays in both antero-posterior and lateral views were done on all children. The films were taken to the Department of Radiology, University of Nairobi, for reporting. Two radiologists reported on the films independently, none of whom had knowledge of the patient's details or of the reports of the other. In the event of 2 different opinions a third report was done by a third radiologist and the two agreeing opinions were accepted as final. The X-ray was availed to the patient once the results were recorded.

3. Blood Investigations.

Tests for HIV and PCR analysis for HIV were done on children whose parents gave consent. Equipment for the tests such as gloves, sterile needles and syringes, EDTA bottles or plain bottles as required, container for sharps disposal and a cool box for transportation to the laboratories were prepared before hand. Sterile filter papers and sealable plastic envelopes were used for PCR sample collection.

(i). *HIV Testing.*

The child and the guardian were taken through pre-test counseling before a HIV test was administered. Counseling was done in a private area with little risk of disturbance. The principal investigator or assistant or a trained VCT counselor stationed in the TB clinic performed the counseling and testing. A child of 7 years and above was asked for assent prior to testing. Bioline and Unigold test strips were used as parallel tests to determine HIV status. Children below 18 months had a sample of blood taken for PCR analysis in an EDTA bottle if their antibody test was positive. The sample was taken to the Immunology laboratory. The results were given back to the parent or guardian and post test counseling given.

All children found to be HIV positive were referred to the Comprehensive Care Centre of Kenyatta National Hospital for long term follow up.

4. Bacteriological Confirmation:

Sputum for culture was not obtained in any child. No child reported a cough with sputum production. Sputum production by way of nebulisation was not possible because of lack of proper containment procedures during the nebulisation.

Review Visit.

A return visit was scheduled for review with results after 72 hours in Kenyatta National Hospital. Some results were also returned to the centre of recruitment on appointment with the parent/guardian. On return the TST test reading was done across the widest area of induration using a non-stretch tape measure. The measurements were done by the principal investigator or the TST administrator in the TB clinic to reduce inter-observer error. The result was recorded in millimeters. The x-ray report was also available at this time. Children found to have tuberculous disease were commenced on treatment. Children who were infected without active disease were referred to the TB clinic for Isoniazid prophylaxis and follow-up according to the guidelines from the NLTP. All results of investigations done were availed to the follow-up centre.

ETHICAL CONSIDERATIONS

Approval to carry out the study was given by the Ethics Committee of Kenyatta National Hospital.

Approval to recruit patients from Mbagathi District Hospital was given by the Medical Superintendent in charge. Permission to recruit patients from the Nairobi City Council Clinics was given by the Medical Officer in charge at Nairobi City Council.

Patients were assured that their details were kept confidential. Those who declined to take part in the study were assured that they were able to continue to receive clinic care as usual.

Patients who were found to have tuberculosis infection or tuberculosis disease were referred to the Tuberculosis treatment clinic of their areas of recruitment for treatment and follow-up. All results of investigations carried out were given to the patients.

Patients found to have HIV infection were referred to the Comprehensive Care Centre in Kenyatta National Hospital for treatment and follow-up.

DATA ANALYSIS

Information obtained in the study was entered into a data page in SPSS, following the format in the questionnaire. Results were analyzed using SPSS software, and EPIinfo Nutritional Statistics for z scores. Tables and pie charts were used to display data as necessary.

RESULTS

A total of 160 children exposed to 82 adults with open pulmonary TB were recruited into the study, from November 2007 and June 2008. This was an average of almost two children (1.95) per family. The adults and children were from 82 households and were recruited from various centres as shown in Table 2:

Table 2. Distribution of Study Subjects and Adult Cases across Recruitment Sites.

Recruitment site (Adult)	Number of adults	Percentage	Number of children recruited from site	Percentage
Mbagathi D H[#]	17	20.7	30	18.7
Kayole H C[§]	11	12.2	20	12.5
Rhodes H C[§]	11	12.2	23	14.4
Kangemi H C[§]	7	8.5	16	10
Riruta H C[§]	9	11.0	20	12.5
Kenyatta Hospital	10	12.2	23	14.4
Others[*]	17	20.7	28	17.5
TOTAL	82	100	160	100

District Hospital, § Health Centre.

* Includes patients from other NCC clinics such as Ngara, Eastleigh and Mathare North, and private patients and patients from missionary centres.

The majority of those recruited (55 adults or 67%) were from the city council clinics and from Mbagathi hospital. Kenyatta hospital had patients with TB but these were often referred to their nearest city council clinic to continue with treatment.

A. SOCIODEMOGRAPHIC CHARACTERISTICS OF ADULT TB CASES.

Adult characteristics were further defined as follows:

Table 3. Sociodemographic Data of Adult TB cases.

(n = 82)

Characteristic		Frequency or Median	Range or Percentage
Age (years)		29	17 - 59
Gender	Males	40	49%
	Females	42	51%
Marital status	Single	16	19.5%
	Married	61	74.5%
	Separated/divorced	5	6%
	Widowed	0	0
Education status	None	1	1.2%
	Primary	27	32.9%
	Secondary	45	54%
	College/University	9	11%
Occupation	Unemployed	29	35%
	Self-employed	35	43%
	Formal employment	18	22%

There was an almost equal proportion of gender balance in the adults recruited into the study as shown in Table 3. The majority of these were in stable long- term relationships; 61(74.5%) married and had a steady source of income. The highest number of unemployed persons was house wives, 18 of 29 (62%). More than half the group i.e. 54 people (65%) had completed secondary school education or progressed higher. The most common symptom reported by the adults was cough in 75 (91.5%) of adults reported a cough while 46 (56%) had fever and 39 (48%) had night sweats as their main complaints.

Most adults (81 of 82) were newly diagnosed tuberculosis cases but one adult was a retreatment case from the year before.

Table 4. Household Characteristics

Characteristic		**Frequency or Median**	**Range or Percentage**
Family size (no. of children)		3	1 – 6
Household size (no. of rooms)		2	1 - 6
Cooking fuel	Charcoal/paraffin	65	79%
	Electricity/gas	17	21%
HIV status	Negative	55	67%
	Positive	11	13%
	Don't know	16	20%

The median number of children screened in a family was three and ranged from one to six children per household. These families lived in houses with a median of two rooms per house with a range of one to six rooms. Several families (33 or 40.2%) lived in a one roomed house. The median number of windows per house was two with a range from one to eight. A large number of families used charcoal or paraffin as cooking fuel.

The HIV status of 66 adults (80%) was established. The HIV status was extracted from the recruitment site clinic records for 60 adults, with their permission. A further six were tested when bringing their child contacts into Kenyatta Hospital for screening. Of the

adults with HIV results 55 (83%) were HIV negative and 11 (17%) were HIV positive. No HIV results were available for 16 adults (20%) as they were unwilling to undergo HIV testing, even as they attended their regular TB clinic. This was due to various reasons that included: fear that the information could leak out to their marital partner or caretaker they were living with and the desire to complete TB treatment before facing up to a new problem. For five individuals no explanation was offered as to why the test was declined.

B. CHILDREN'S DATA

A total of 160 children from 82 different households were enrolled into the study. Their characteristics are summarized as follows in table 5:

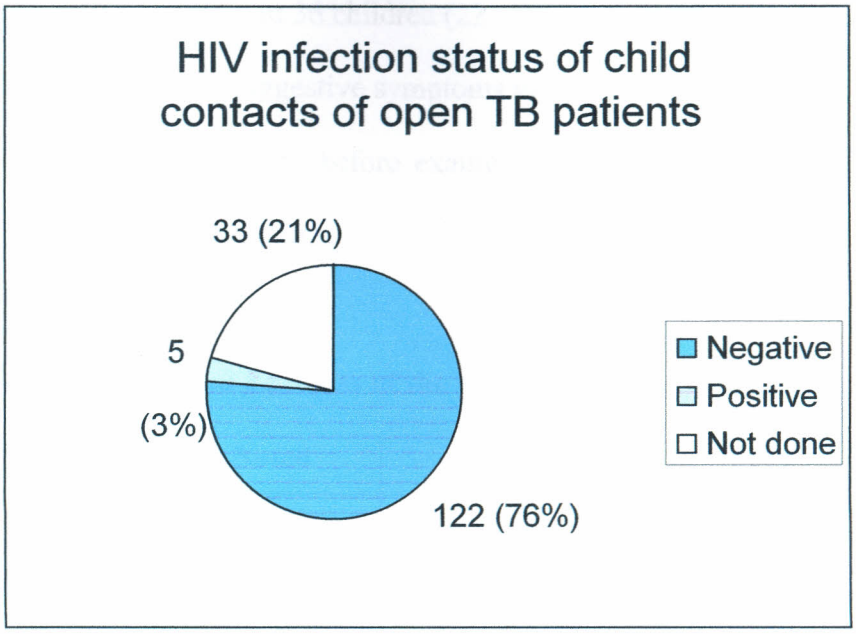
Table 5. Descriptive Characteristics of the Children.

(n = 160)

Characteristic		**Frequency**	**percentage**
Age (months)	Median	48	6 - 156
	<12 mo	12	7.5
	12-59 mo	86	53.8
	60+ mo	62	38.7
Gender	Males	92	57.5
	females	68	42.5
WH z scores	≥ - 1.99	147	92
	≤ -2	13	8
BCG scar	Present	127	80
	Absent	33	20

The median age of the children was 48 months with a range from six months to 13 years. Children aged less than five years numbered 84 (52.5%). Males were slightly more than females at 92 out of 160 (57.5%). Moderate to severe malnutrition was detected in 13 (8%) of the children showing that the majority of the children were in good nutritional status. A BCG scar was seen in 80% of the children which is in keeping with the rates in the expanded programme on immunization.

Chart 1. Results of HIV Screening of Children



HIV screening was offered for all children. Parents of 127 children (79%) gave consent for HIV testing. In this group 122 (96%) of 127 children were HIV negative and five children (4%) were HIV positive. One child under eighteen months of age was positive by PCR. The test was not done in 20% of the children because of lack of consent from the parent or guardian.

Table 6. Clinical Features of the Children- Symptoms Reported

Symptom Reported	Number	Percentage
Cough > two weeks	110	69
Persistent fever > two weeks	36	22.5
Weight loss/ poor weight gain	22	13.8
No symptoms	45	28

Cough for more than two weeks was reported in 110 children or 69% of the children. Fever was reported in 36 children (22.5%) and weight loss in 22 children (14%). Children that had all three suggestive symptoms were 22 (13.8%). Only one child had had measles infection in the month before examination. Within the group of children recruited 45 (28%) had no complaints.

Table 7. Clinical Features of the Children- Signs

Clinical Feature Noted	Number	Percentage
Lymphadenopathy (enlarged painless cervical)	3	1.9
Hepatomegally	1	0.6
Ascites	1	0.6
Non-specific respiratory signs	19	12
Gibbus/ arthropathy	1	0.6
No signs	138	86

On examination 22 (13.8%) children were found to have signs suggestive of tuberculosis. The majority of children i.e. 138 of 160 (86%) screened did not present with any suggestive clinical features of TB. Signs of pulmonary tuberculosis were seen in 18 children, TB adenitis in four children, one child with TB peritonitis and one child with Potts' disease. One child had features both of PTB and TB adenitis.

Lymphadenopathy suggestive of TB adenitis was seen in three children. None of the children reported marked tenderness in the areas of lymphadenopathy. Features of pneumonia were found in 19 children; which included tachypnoea in eight children (5%), crepitations in 19 children (12%) and rhonchi in ten children (6%). Severe pneumonia as

shown by lower chest wall indrawing was found in two children (1.2%). The children were referred to the paediatric filter clinic in Kenyatta for treatment awaiting the outcome of investigations. Both children with severe pneumonia were started on anti-TB medication after their results were available. One child reported an occasional back pain that was not taken seriously till the chest x-ray noted a lesion on the mid-thoracic spine. Further views of the region showed 'moth-eaten lesion' in the body of T 7. On further history the mother who was on treatment for PTB revealed she also had a similar lesion and her treatment had been extended by another three months. The child was referred to the Orthopaedic clinic for follow-up and was subsequently started on treatment. One child presented with generalized lymphadenopathy, hepatomegally and ascites. The parent declined ascitic tap and the child was followed up from the paediatric filter clinic in Kenyatta. The child was eventually started on treatment for TB after radiological investigations. No child presented with features suggestive of tuberculous meningitis in this study.

Table 8. Suggestive Radiological Features of TB

Radiological Features	Number	Percentage
Hilar/Paratracheal nodes	19	12
Miliary seeding	1	0.6
Pleural effusion	1	0.6
Fibrosis	3	1.9
Non-specific features	11	7
Normal findings	125	78

Features suggestive of pulmonary TB on X-ray were seen in 26 children (16%), including two HIV-positive children. The most common x-ray finding within the group was unilateral adenopathy in 19 children (73%). The child with Potts' disease required a further x-ray of the mid thoracic spine to define the lesion well.

1. TUBERCULOSIS INFECTION

A Tuberculin skin test was done on 159 children. The frequency of tuberculosis infection was 61 out of the 159 children (38.4%), based on the cut-off points as defined before. This gives a **prevalence of 38%** (31%-46% 95% C.I.) in child contacts of open TB. In this group the TST was positive in two HIV-positive children and five children with moderate to severe malnutrition, including one child with HIV as shown in table 9.

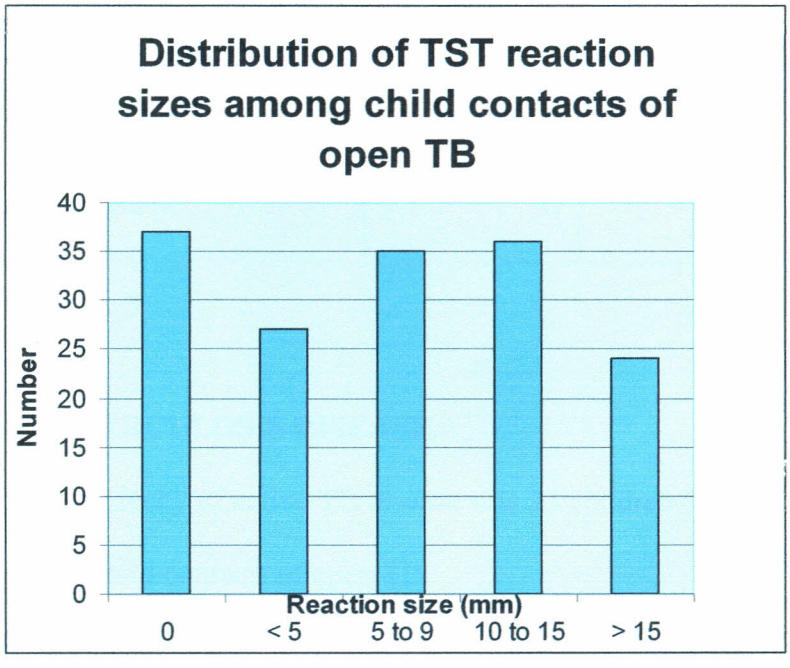
Table 9. Proportion of Children with HIV and Malnutrition in the TST Positive children.

Characteristic N=61	**TB Infection**
HIV negative (TST ≥ 10mm)	46 (75%)
HIV positive (TST ≥ 5mm)	2 (3%)
HIV status unknown (TST ≥ 10mm)	13 (22%)
WH z score ≥ -1.99 (TST ≥ 10mm)	55 (90%)
WH z score ≤ -2 (TST ≥ 5mm)	6 (10%)

The children came from a total of 47 families (57%) of the 82 families screened. In these families 23 source contacts were male and 24 were female. In nine families (11%) two

children were infected and in one family (1.2%) three children were infected. Of these families source contacts were female in four families and males in six families. The children lived with guardians of different ages, but approximately half i.e. 30 children (49%) lived with adult source patients within the ages of 25 to 34 years. Distribution of TST was as follows:

Chart 2. Tuberculin Skin Test Reaction Sizes.



An exploratory analysis for association between various characteristics and TB infection was done using the chi square method. (see Table 10) The analysis was speculative as the study was not powered or designed to evaluate associations. The factor that may have had the greatest impact was living in a house that had three or more persons (p value 0.051). Whereas a high proportion of children, 45 or 74%, lived in houses that had one to two rooms, or used charcoal or kerosene as cooking fuel this did not show strong influence on

infection in the children. Age less than five years was also not a significant factor in this group.

Table 10. Association of TB Infection with Different Factors.

Element of exposure	TB infection N=61	No TB N=98	Odds ratio (95% C.I.)	p value
No. of rooms in house ≤2	46	54	2.50 (1.17-5.39)	0.010
No. of children in house ≥3	43	55	1.95 (0.94-4.07)	0.051
Fuel: charcoal/kerosene	46	63	1.70 (0.79-3.71)	0.14
Age ≤5 years	37	61	0.98 (0.48-1.98)	0.94

2. TUBERCULOSIS DISEASE.

The frequency of active TB disease was **33** children **(20.6%)** (15%-28% at 95% C.I.) out of 160 child contacts of open TB.

Table 11. Features of Tuberculosis Disease in Children

Diagnostic Criteria	Number
Clinical features* + CXR suggestive + TST positve	18 (55%)
CXR suggestive + TST positive (no clinical features)	14 (42%)
Clinical features + CXR suggestive (TST not positive)	1(3%)
TOTAL	33(100%)

* Clinical features = suggestive symptoms +\- suggestive signs as defined in criteria.

In this group all except one child had a positive TST. All the children had suggestive radiology findings and 18 children (55%) had several features suggestive of TB. Thus slightly over a third of child contacts of open TB had infection, and more than half of these had progressed in their illness to active disease.

Table 12. Distribution of Active TB disease according to Age, HIV Status and Nutritional Status.

Characteristic N=33	**TB Active Disease**
HIV negative	22 (67%)
HIV positive	2 (6%)
HIV status unknown	9 (27%)
WH z score ≥ -1.99	30 (91%)
WH z score ≤ -2	3 (9%)
Age < 5 years	17 (52%)
Age > 5 years	16 (48%)

Children who were HIV positive had a relatively higher rate of infection than the HIV negative and HIV unknown status counterparts. [2/5 (40%), 22/122 (18%), 9/33 (27%)] The proportion of children with active disease was equally balanced among those with moderate to severe malnutrition and those without. [3/13(23%), 30/147(20%)]. Similarly almost equal numbers of those aged less than five years and those over five years were shown. [17/84 (20%), 16/76 (21%)]. However the numbers of children did not allow for definitive conclusions to be made in these groups.

The children came from 28 different families i.e. 34% of all the families. Three families (4%) had two children with active tuberculosis infection. The source contact was male in 17 families and female in 11 families. The source contact was aged between 25 to 24 years for 21 cases (64%). Features of household crowding were present as shown by a high number of children who lived in houses with one to two rooms (26 or 79%), and had three or more persons living in their houses (21 or 64%). Table 13 shows an exploratory analysis of possible factors that may have influenced active TB. The most important factor was the use of charcoal/kerosene as cooking fuel (p 0.002). As with TB infection age less than five years was not a significant factor.

Table 13. Factors Associated with Active TB Disease.

Element of Exposure	**TB Disease & Infection** N=33	**Infected/No Active Disease** N=28	**Odds Ratio** (95% C.I.)	**p value**
No. of rooms in house ≤2	26 (57%)	20 (43%)	1.49 (0.40-5.59)	0.51
≥3	7 (47%)	8 (53%)		
No. of children in house ≥3	21 (58%)	15 (42%)	1.52 (0.48-4.82)	0.43
<3	12 (48%)	13 (52%)		
Fuel: charcoal/ kerosene- yes	30(65%)	16(35%0	7.50 (1.61-39)	0.002
no	3(20%)	12(80%)		
Age ≤5 years	21(57%)	16(43%)	1.31 (0.41-4.18)	0.61
>5 years	12(50%)	12(50%)		

N.B. Percentages expressed as a fraction of their row values

All children found to have active tuberculosis were referred back to the source adult's treatment centre to start their own treatment and follow-up. The child with Pott's disease is on follow-up at the Orthopaedic clinic in Kenyatta Hospital for further management.

DISCUSSION

Tuberculosis infection is common among child contacts of open tuberculosis with over one-third (38%) of child contacts of adult TB patients in this study presenting with evidence of TB infection. This is in keeping with other contact studies that have found from one-fifth to one-half of all child contacts will manifest with a positive tuberculin skin test. [25.8% - 47%, (4,9, 10, 39)]. The majority of these studies were done in groups of children aged from three months to 15 years. These children were similar in age to the children screened in this study aged from six months to 13 years. Salazer-Vergara looking at child contacts, of up to 15 years in age, of patients attending a TB clinic in the Phillipines found a higher rate of transmission at 69%.(5) The reason for this was not ascertained. The children came from 47 different households thus 57% of families in this study were affected. This suggests a significant level of transmission within households. Some families had multiple children infected with ten families having more than one child infected. In the HIV infected children two out of five (40%) had a positive TST. The TST was able to elicit skin reactions in both the HIV infected and uninfected children. The TST was also positive in six out of 13 children (46%) with moderate to severe malnutrition. The test thus was a useful tool for detecting TB infection in these children. The study from Gambia also found a high TST positivity in the malnourished children (OR: 2.93; 95% CI: 0.56–15.42 for the cutoff point of 5 mm and OR: 3.09; 95% CI: 0.45–21.32 for the cutoff point of 10 mm).(9) Children with HIV infection had higher proportions of infection and active disease than their non-HIV infected counterparts. (active disease in 40% HIV infected, 18% non-HIV infected) However the numbers of children found to HIV in this group were small as only five children were HIV positive.

HIV appears to increase the risk of acquiring TB infection and also the risk of progression to active illness. This has been documented by Bhat et al. (15)

Active TB disease was found in 33 children (21%). This is expected as shown by other studies elsewhere. [5 - 34% (7, 8, 10)]. All of these studies were prospective studies that picked up an increasing number of active cases over time. This study however has demonstrated that even at a point prevalence the rate of active illness in these children was significant. Of the children with active disease both of the TST positive HIV infected children also showed signs of active disease. For children with moderate to severe malnutrition three out of 13 (23%) had features of active disease. There was an almost equal proportion of cases in children aged less than five years and those aged over five years. This was unexpected as younger children are more susceptible to TB because of immature immune mechanisms.(3) The age of five years to 12 years is usually referred to as the golden age of tuberculosis in that infections are less frequent in this group. Salazer-Vergara found age over five years as a significant risk factor of transmission of TB from adults to child contacts.(5) Other studies did not find an association between age of the child and tuberculosis infection or active disease. However the findings in this study suggest that TB infection and disease are a real problem even at this age.

An exploratory analysis was attempted in the group for association between various characteristics and TB infection and active illness. These remain purely exploratory as the study was not powered or designed to evaluate associations. While no firm conclusions can be drawn from the associations found, they have opened up areas that would benefit from further research with a larger cohort of children. There were factors suggestive of household overcrowding in the group. The median number of rooms per house was two and 74% of children infected and 79% of those with features of active

The World Health Organization recommends screening of child contacts using clinical features as well as the tuberculin skin test and radiology. Clinical features were applied as described in the WHO manual.(42) Thus while several children presented with complaints that could be found in children with TB (e.g. cough more than two weeks in 110 children or 69%), only 22 children (13.8%) had symptoms that were suggestive of TB and a similar number with clinical signs suggestive of TB. Using clinical features alone in screening children may be misleading as cough is a common complaint from parents of the children and may lead to an over-diagnosis of TB. Other symptoms like fever and poor weight gain also were non-specific. The TST has its limitations but was able to give results that were comparable to those obtained in other studies. Radiological features may also be subject to inter-observer variation but the use of independent reporting by two different radiologists reduced this to a minimum.

The study confirms that there is a high prevalence of infection found in child contacts of open TB. Thus there is a need for contact screening and follow-up of these children. The study may have benefited many of these who would have come to attention with advanced illness.

The findings of the study will be distributed to the various health centres and hospitals and to the policy makers. In generating awareness of the magnitude of the problem it is hoped that arrangements will be made to avail all that is needed for contact screening at local treatment centres.

One study limitation was the lack of longitudinal follow up for the children. The studies that have carried out long term follow-up for children document new cases picked up with time. [(8, 10)] One other study limitation was that it was difficult to attribute the high rates of infection and disease to the source contact alone. This is more so for the

children aged over five years, most of who go to school and thus may be in contact with other sources of TB. The cost of screening procedures which included the cost of the TST and X-rays, transport costs incurred by the parents and missing school days for the children, was a problem in this study. Fortunately all the parents and guardians in this group expressed a strong desire to have their children screened and returned with the child for follow-up.

CONCLUSIONS

1. Tuberculosis Infection was present in 38% of child contacts of adults with open Tuberculosis.
2. Active Tuberculosis Disease was present in 21% of child contacts of adults with open Tuberculosis.
3. Among children with infection, 54% had Active Tuberculosis Disease.

RECOMMENDATIONS

A prospective study to evaluate long term outcomes in child contacts of TB patients should be instituted.

A clear contact screening policy for health workers including the use of INH prophylaxis needs to be drawn up and implemented. Health workers would benefit from training on the previously mentioned policy. Contact screening would be made much easier if the facilities such as radiology and trained personnel would be made available at the sites of treatment.

REFERENCES

1. World Health Organisation,2006. Tuberculosis fact sheet.

www.who.int/mediacentre/factsheets/fs104/en.

2. National Leprosy and Tuberculosis Program,Kenya, 2006. National Tuberculosis and Leprosy Guidelines. National TB control Program Kenya, P.O. Box 20781, Nairobi.

3. American Thoracic Society, Diagnostic Standards and Classification of Tuberculosis in Adults and Children

   Am. J. Respir. Crit. Care Med., 2000, 161, 1376-1395

4. Tornee S, Kaekungwal J, Fungladda W, et al. 2005. The association between environmental factors and tuberculosis infection among household contacts. Southeast Asian J Trop Med Public Health. 36 Suppl 4:221-4.

5. Salazar-Vergara RM, Sia IG, Tupasi TE, et al. 2003 : Tuberculosis infection and disease in children living in households of Filipino patients with tuberculosis: a preliminary report. Int J Tuberc Lung Dis. 2003; 7(12 Suppl 3):S494-500.

6. Madhi F, Fuhrman C, Monnet I, et al. Transmission of tuberculosis from adults to children in a Paris suburb. Pediatr Pulmonol. 2002; 34(3):159-63.

7. Gessner BD, Weis N S, Nolan C M. Risk factors for pediatric tuberculosis infection and disease after household exposure to adult index cases in Alaska. J Pediatr. 1998;132(3 Pt 1):509-13.

8. Beyers N, Gie R P, Schaaf H S, et al.: A prospective evaluation of children under the age of 5 years living in the same household as adults with recently diagnosed pulmonary tuberculosis. Int J Tuberc Lung Dis. 1997;1(1):38-43.

9. Lienhardt C, Sillah J, Fielding K, et al. Risk factors for tuberculosis infection in children in contact with infectious cases in the Gambia, West Africa. Pediatrics.2003;111(5 Pt 1):e608-14.

10. Sinfield R, Nyirenda M, Haves S, Molyneux EM, Graham SM. Risk factors for TB infection and disease in young childhood contacts in Malawi. Ann Trop Paediatr. 2006 Sep;26(3):205-13.

11. Behrman,R.E. et al. Nelson Textbook of Pediatrics, 17th Edition. 2004.

12. Brailey ME. Tuberculosis in white and negro children. II. The epidemiologic aspects of the Harriet Lane study. Cambridge, MA: Harvard University Press, 1958.

13. American Lung Association.2005. Pediatric tuberculosis fact sheet. http://www.lungusa.org/site

14. Nolan RJ Jr. Childhood tuberculosis in North Carolina: a study of the opportunities for intervention in the transmission of tuberculosis to children. Am J Public Health 1986;76:26-30.

15. Bhat GJ, Diwan VK, Chintu C,et al. HIV, BCG and TB in children: a case control study in Lusaka, Zambia. : J Trop Pediatr. 1993;39(4):219-23.

16. Narayan S, Mahadevan S, Serane VT: Keith Edwards score for diagnosis of tuberculosis. Indian J Pediatr. 2003;70(6):467-9.

17. Van Rheenen P.: The use of the paediatric tuberculosis score chart in an HIV-endemic area. Trop Med Int Health. 2002;7(5):435-41.

18. CDC,2003. Guidelines for using the QuantiFERON®-TB test for diagnosing latent Mycobacterium tuberculosis infection. MMWR 2003;52 (No. RR-2):15--8.

19. Roth A, Sodemann M, Jensen H, et al: Vaccination technique, PPD reaction and BCG scarring in a cohort of children born in Guinea-Bissau 2000–2002 Vaccine Volume 23, Issue 30 , 2005, Pages 3991-3998

20. W Hoskyns: Paediatric tuberculosis. Postgraduate Medical Journal 2003;79:272-278

21. Zar HJ, Hanslo D, Apolles P, et al. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. Lancet. 2005;365:130–134

22. World Health Organisation,2006. Frequently asked questions on Tuberculosis and HIV, 2006. http://www.who.int/tb/hiv/faq/en/index.html

23. Goletti D, Carrara S, Vincenti D, et al. Accuracy of an immune diagnostic assay based on RD1 selected epitopes for active tuberculosis in a clinical setting: a pilot study. Clin Microbiol Infect. 2006;12(6):544-50.

24. Chapman AL, Munkata M, Wilkinson KA, et al. Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of Mycobacterium tuberculosis-specific T cells. AIDS. 2002;16(17):2285-93.

25. World Health Organisation, 2006. Tuberculosis fact sheet,TB and Children. www.searo.who.int/en/section10/section2097/section2106_10681.htm.

26. Okello D, Floyd K, Adatu F, et al.2003. Cost and cost-effectiveness of community-based care for tuberculosis patients in rural Uganda. : Int J Tuberc Lung Dis. 2003;7(9 Suppl 1):S72-9.

27. MacIntyre CR, Plant AJ, Hendrie D. Shifting the balance between in-patient and out-patient care for tuberculosis results in economic savings. : Int J Tuberc Lung Dis. 2001;5(3):266-71.

28. Costa JG, Santos AC, Rodrigues LC,et al. 2005. Tuberculosis in Salvador, Brazil: costs to health system and families. Rev Saude Publica. 2005;39(1):122-8. Epub 2005 Jan 11.

29. Khalilzadeh S, Masjedi H, Hosseini M, Safavi A, Masjedi MR. Transmission of Mycobacterium tuberculosis to households of tuberculosis patients: a comprehensive contact tracing study. Arch Iran Med. 2006;9(3):208-12.

30. Verma M, Chhatwal J, Aneja R. Tuberculin sensitivity in low birth weight and malnourished children. Indian Pediatr. 1995;32(3):354-7.

31. American Thoracic Society. Diagnostic Standards and Classification of Tuberculosis. American Review of Respiratory Disease Vol. 142, No. 3, 1990 pp. 725-735

32. Tuberculin Survey in Botswana, 1996. http://www.cdc.gov/mmwr/preview/mmwrhtml/00049310.htm

33. Almeida LM, Barbieri MA, Da Paixao AC, et al. Use of purified protein derivative to assess the risk of infection in children in close contact with adults with tuberculosis in a population with high Calmette-Guerin bacillus coverage. Pediatr Infect Dis J. 2001;20(11):1061-5.

34. Berkel GM, Cobelens FG, de Vries G, et al. Tuberculin skin test: estimation of positive and negative predictive values from routine data. Int J Tuberc Lung Dis. 2005;9(3):310-6.

35. Chintu C, Bhat G, Luo C, et al. Seroprevalence of human immunodeficiency virus type 1 infection in Zambian children with tuberculosis. Pediatr Infect Dis J. 1993;12(6):499-504

36. Lawn SD, Bekker LG, Middelkoop K, et al. Impact of HIV infection on the epidemiology of tuberculosis in a peri-urban community in South Africa: the need for age-specific interventions. Clin Infect Dis. 2006;42(7):1040-7.

37. A C Hesseling, A E Westra, H Werschkull, et al. Outcome of HIV infected children with culture confirmed tuberculosis. Archives of Disease in Childhood 2005;90:1171-1174.

38. Mukadi YD, Wiktor SZ, Coulibaly IM, et al. Impact of HIV infection on the development, clinical presentation, and outcome of tuberculosis among children in Abidjan, Cote d'Ivoire. AIDS. 1997;11(9):1151-8.

39. M. Singh, M.L. Mynak, L. Kumar, et al. Prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. Arch. Dis. Child. 2005; 90; 624-628.

40. Stanley Lemeshow, David W. Hosmer Jr, Janelle Klar, Stephen K Lwanga. Adequacy of sample size in health studies. Wiley. 1990.

41. World Health Organization, A manual for Management of severe malnutrition: A guide for physicians and other senior health workers. Chapter 3: Evaluation of the severely malnourished child, pp 4-5.

42. Guidance for national tuberculosis programmes on the management of tuberculosis in children. World Health Organization. Section 1: Diagnosis of TB in children, pp 4-8.

APPENDIX 1

QUESTIONAIRRE

Number _____

Hospital Unit – TB clinic _____

Ward _____

ADULT PATIENT

1. Name _____
2. Age (yrs) _____
3. Sex Male _____ Female _____
4. Marital status single_____ married_____ separated_____ divorced_____
5. Education status None_____ primary_____ secondary_____ college/university_____
6. Mobile Contact _____
7. Symptoms present Duration of symptoms (days/months)

i) Cough Yes _____ No _____ _____

ii) Fever Yes _____ No _____ _____

iii) Sweats Yes _____ No _____ _____

iv) Weight Loss Yes _____ No _____ _____

v) Other (specify) _____ _____

8. Date of positive sputum smear for AAFB (dd/mm/yyyy) _____

9. Any child living in your household Yes_____ No _____

If yes proceed to Qtn 10 below. If no is not eligible for study.

10. No. of household members living with the patient for at least last 6 weeks. (from eldest to youngest person)

No.	Age	Sex	Relation to index	Duration of stay
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				

11. Date when treatment started (dd/mm/yyyy) _____

12. Screened for HIV Yes _____ No _____

13. Results of HIV Test

Negative _____ Positive _____ Don't know _____

14. Occupation of client _____

15. Any other family member with TB Yes_____ No _____.

If Yes please specify how many _____

16. Area of residence

Slum _____ Middle Class _____

Upper _____ Other _____

17. Type of house

Mud _____ Wood _____ Mabati _____ Stone _____

Type of Toilet

Pit Latrine _____ Flush, Shared _____ Flush, Own _____

18. No. of rooms in the house _____

19. No. of windows in the house _____

20. No. of cigarette smokers in the house _____

21. Fuel cooking in the house

Electricity _____ Gas _____ Charcoal/Wood _____

Kerosene _____ Other(specify) _____

CHILD DETAILS

Number: _____(001A, 001B, etc)

1. Name _____

2. Age Years _____ Months _____

3. Sex Male _____ Female _____

4. Date of BCG vaccination. (dd/mm/yyyy) _____

5. Scar confirmed Yes _____ No _____

6. Repeat vaccination. Yes _____ No _____

7. History of

Duration (days)

a. Cough Yes _____ No _____ _____

b. Fever Yes _____ No _____ _____

c. Weight loss or FTT Yes ____ No _____ _____

d. Change in temperament, fit or coma Yes _____ No _____

e. Measles or chicken pox in last 2 weeks Yes_____ No _____

PHYSICAL EXAMINATION

1. Height (cm) _____ Length (cm) _____

2. Weight (kg) _____

3. General exam

a) Pallor Yes _____ No _____

b) Lymphadenopathy Yes _____ No _____

i. Site Cervical _____ Axillary's _____

Other (specify) _____

ii. Matted Yes _____ No _____

iii. Mobile Yes _____ No _____

c) Oral thrush Yes _____ No _____

d) Temperature (00.0 degrees C) _____

4. Respiratory examination

a) Respiratory rate (breaths/min) _____

b) Chest indrawing Yes _____ No _____

c) Crepitations/rhonchi Yes _____ No _____

5. Cardiovascular examination

a) Pulse rate (beats/min) _____

b) Heart sounds Normal _____ Abnormal _____

6. Abdominal examination

a) Hepatomegally Yes _____ No _____

b) Splenomegally Yes _____ No _____

c) Ascites Yes_____ No _____

7. Nervous systems examination

a) Alert, responds to the environment Yes _____ No _____

b) Neck supple Yes _____ No _____

c) Kernig's sign Positive _____ Negative _____

d) Features of Meningitis Yes _____ No _____

e) LP results _____

8. Musculoskeletal

a) Gibbus Yes _____ No _____

b) Joint Swelling Yes _____ No _____

9. Other findings (specify) _____

10. Clinical signs & symptoms suggestive of TB disease Yes_____ No _____

If yes, type of TB

PTB Yes _____ No _____

TB adenitis Yes _____ No _____

TB Spine Yes _____ No _____

TB Meningitis Yes _____ No _____

Other (specify) _____

MANTOUX (TST) TEST DONE Yes _____ No _____

Measurement _____mm

HIV SCREENING (rapid test)

Negative _____ Positive _____ Not Done _____

(PCR for children less than 18 months

Negative _____ Positive _____ Not Done _____

ELISPOT analysis

Negative _____ Positive _____ Not Done _____

CXR findings

Suggestive of TB _____

Not Suggestive of TB _____

SPUTUM CULTURE RESULTS

Positive for *Mycobacterium tuberculosis* _____

Negative for *Mycobacterium tuberculosis* _____

Not Done _____

APPENDIX 2

CONSENT FOR THE STUDY

Dear Sir/ Madam

I am carrying out a study to investigate the spread of tuberculosis from adults who have the disease to children living in their households. I would wish to recruit any children living with you in the house from the time that your illness started to the present time. Once in the study the children will undergo several investigations which will include a chest x-ray and a Mantoux(Tuberculin skin test) test.

- The Chest x-ray has a minimal amount of radiation and is generally considered safe for children of all ages. The x-ray will be useful to show presence or absence of disease in your child.
- The Mantoux test works on the principle that any person exposed to the bacteria causing tuberculosis can show a reaction if challenged again with proteins similar to those of the tuberculosis bacteria. Thus a small amount of these proteins, not the bacteria, are put into the skin. Two to three days later after the body has had time to process the bacteria, the skin test site is reviewed to measure the reaction. The test is generally considered safe. A few children may have strong reactions that can be managed safely.
- The ELISpot test also checks for the body's reaction to the tuberculosis bacteria. This requires that a small amount of blood be removed from the child and taken to the laboratory for assessment.
- HIV screening will be done with your permission. The HIV virus causes the body's immune system, which is supposed to defend it from diseases, to malfunction. Children exposed to both HIV and tuberculosis need screening for both diseases and may require treatment for one or both diseases.
- The tests administered are safe and do not pose a serious risk to the child. Other investigations as deemed necessary may also be performed, with your permission.

The study may be able to detect early tuberculosis disease. Any child found to be diseased will be placed on treatment. Children with a signs of infection but who do not have the disease currently will also be placed on treatment for at least 3 months. Tuberculosis is curable with treatment available from this hospital and other centers.

If you have no objection to your child being included in the study, please indicate by signing below:-

Parent/Guardian Name
Child Name
Signature

Date

Witness
Signature
Date

Thank you for your co-operation.
Dr. J. Muiva.

APPENDIX 3

Keith-Edwards score

Features	Points Awarded	Score
Positive sputum smear	7	
Contact wiyh a person with suspected or confirmed TB	2	
Tuberculin test 15mm or more (in unvaccinated child)	3	
Enlarged painless lymph nodes, sinus present	3	
Night sweats unexplained fever, no response to malaria treatment	2	
Abnormal chest X-ray	2	
Malnutrition not improving after 4 weeks of treatment	3	
Angle deformity of spine	4	
Firm, non fluid, non traumatic swelling of joint	3	
Unexplained abdominal swelling or Ascites	3	
Change in temperament, fits or coma	3	
Total Score		

A score equal to or above 7 should be treated as disease. 4-6 TB is probable, 0-3 TB unlikely.

APPENDIX 4

WHO guidelines for diagnosis of tuberculosis in children.

Suspect TB in a child

- Who is ill, with a history of contact with a suspect or confirmed case of pulmonary TB;
- Who does not return to normal health after measles or whooping cough;
- With loss of weight, cough, fever who does not respond to antibiotic therapy for acute respiratory disease;
- With abdominal swelling, hard painless mass and free fluid;
- With painless firm or soft swelling in a group of superficial lymph nodes;
- With signs suggesting meningitis or disease in the central nervous system.

APPENDIX 5. Procedure for the Tuberculin skin test.

Administration of a TST

Universal precautions will be followed with the client seated comfortably, resting his/her exposed arm on a firm, well lighted surface, the site will be cleaned and allowed to dry completely.

Using a single-dose, disposable tuberculin syringe and a 1-2 inch, 26 or 27 gauge needle with a short bevel a little more than 0.1 mL of PPD solution will be drawn into the TB syringe. After tapping it lightly to remove air and then expelling one drop it will be double-checked to ensure that a full 0.1 mL(i.e. 5U TU) remains in the syringe.

Areas on the skin that are red or swollen and visible veins will be avoided.

The usual injection site is on the anterior surface of the forearm, about four inches below the elbow. The skin will be stretched taut with the non-dominant hand. The syringe will be inserted parallel to (almost resting on) the surface, the needle inserted, bevel up, so that the tip of the needle is visible just below the surface of the skin.

The contents of the syringe will be injected slowly raising a firm, white wheal about 6-10 mm in diameter at the injection site immediately.

If the injected PPD leaks out onto the skin and no wheal appears, the needle was too shallow. If the wheal is shallow and diffuse, the needle was too deep. In either case, a second injection will be administered at least two inches from the first site and the second injection site will be circled with a pen.

A drop of blood may be seen after withdrawing the needle. This is normal. The patient will be given a small gauze swab to dab gently over the site (no deep pressure) and reassured. This will avoid squeezing out the tuberculin thereby disrupting the test.

The needle and syringe will be placed in a puncture-resistant container.

Instructions to Patient

Do not rub or scratch the site of the TST test.

Keep area clean.

No restrictions with respect to diet, type of activities.

Return in 48 to 72 hours for reading.

Reading a TST

The TST will be read 48 to 72 hours after being applied. However, if a person presents more than 72 hours after the TST was applied and the test result is greater than 10 mm, this test shall be considered positive. If a person presents after 72 hours and the result is less than 10 mm, the test is invalid and must be repeated. The TST will be read by the primary investigator or assistant who will have been trained in reading TSTs.

The reading shall be made in good light, with the person's forearm slightly flexed at the elbow. The presence or absence of induration shall be documented. Erythema or redness will not be measured. The development of erythema does not indicate infection.

Induration will be determined by inspecting the arm from a side view against the light as well as by direct light and by palpating the arm with a gentle stroke of the finger.

If induration is present, the diameter will be measured across the width of the forearm, (e.g., measure the width at right angles to the long axis of the forearm). A pen to help mark the beginning and end points of induration will be used then a non-stretch tape measure to measure the size of induration between the pen points applied. The size of induration will be recorded in millimetres. If the measurement falls between demarcations on the tape, the smaller of the two numbers will be used. If the participant has no induration, the result will be recorded as 0 mm.

Positive result:

- HIV non-infected/ within 2 SD weight-for-height or length: Mantoux induration >/equal to 10mm
- HIV-infected/ weight-for-height or length less than or equal to 3SD: Mantoux induration >/equal to 5mm