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Tuberculosis Treatment Delay in Adults and Household Transmission to Children: A Community-based Study in a Setting with High Burden of Tuberculosis and HIV

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Declaration

I, Penelope Rose (RSXPEN002), hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Background

Tuberculosis (TB) control depends on interrupting transmission through rapid diagnosis and treatment initiation of infectious TB cases. With increasing delay in the diagnosis and treatment of pulmonary TB, disease is likely to progress, leading to progressive lung cavitation and increased sputum bacillary load, likely increasing TB transmission. This study investigated the effect of treatment delay in adult TB patients on the risk of TB infection and disease in child household contacts.

Methodology

Secondary analysis was performed using data from a community-based household contact investigation study. Cross-sectional analysis was conducted of baseline data collected at enrolment. Children aged three months to fifteen years with documented household exposure to an adult with TB were enrolled between December 2007 and June 2012. These children were screened for TB infection (Mantoux tuberculin skin test [TST] and two interferon-gamma release assays [IGRA]) and disease. Total treatment delay was measured in adult TB source cases as the time from cough onset until treatment initiation, with those reporting no cough serving as the reference category. Logistic regression models were used to evaluate the effect of total treatment delay in adults on the risk of TB infection in child household contacts, with TB disease evaluated as a secondary endpoint.

Results

In total 671 children were enrolled as household contacts of 290 adult TB source cases. In multivariate analysis, the odds of TST positivity increased with cough duration ≥4 weeks prior to TB treatment initiation (odds ratio (OR) = 1.77 [95% CI 1.02-3.09] for cough <4 weeks; OR = 2.74 [95% confidence interval (CI) = 1.39-5.40] for cough 4-12 weeks; OR = 2.39 [95% CI = 1.19-4.82] for cough >12 weeks, compared to non-coughing adult TB patients), child's age ≥5 years (OR = 4.51, [95% CI = 2.60-7.83]), sharing the same bedroom (OR = 2.17, [95% CI = 1.43-3.31]), more than one household TB contact (OR = 2.70, [95% CI = 1.35-

5.42]) and with household tobacco smoke exposure (OR = 2.10, [95% CI = 1.22-3.61]). Adult TB source case HIV status did not modify the association between cough duration and risk of infection in children. Results of analyses of TB infection indicated by IGRA positivity were consistent with TST results. Prevalent TB disease in child contacts was associated with source case sputum smear and culture positivity, additional household TB contacts and decreasing age of the child.

Conclusions

Delays of longer than four weeks from cough onset until TB treatment initiation were associated with increased risk of TB infection in child household contacts. These findings confirm the importance of reducing delays in TB diagnosis and treatment in adults to reduce transmission, ideally to less than four weeks. Although HIV co-infected TB patients are often considered less infectious, delayed treatment initiation remained associated with TB transmission, even amongst HIV co-infected adults with TB. In addition to the traditional risk factors for developing TB disease after infection, source case exposure factors also increased the risk of exposed children developing TB disease.

List of abbreviations

ART	Antiretroviral treatment
BCG	Bacille Calmette–Guérin
CI	Confidence interval
DFG	German Research Foundation
DNA	Deoxyribonucleic acid
DOTS	Directly observed treatment, short-course
ELISA	Enzyme-linked immunosorbent assay
HIV	Human immunodeficiency virus
IGRA	Interferon-gamma release assay
IPT	Isoniazid preventive therapy
M. tuberculosis	Mycobacterium tuberculosis
NIH	National Institutes of Health
NTP	National tuberculosis programme
NUFU	Norwegian Programme for Development, Research and Education
OR	Odds ratio
PCR	Polymerase chain reaction
RTHC	Road to health card
TB	Tuberculosis
TST	Tuberculin skin test
USA	United States of America
WHO	World Health Organization

A. PROTOCOL

Protocol synopsis

Control of the tuberculosis (TB) epidemic depends on timely diagnosis of all infectious TB cases and the rapid initiation of effective antituberculosis treatment. In South Africa transmission rates remain high and the patient diagnostic rate is low. In South African adults the median total treatment delay from symptom onset until starting treatment was 31 days. With increasing delay in treatment initiation, patients with pulmonary TB are more likely to be sputum smear positive and have lung cavitation, and therefore will be more likely to transmit TB. To date no study has investigated the association between delay in treatment initiation in adult source cases and the risk of TB infection or disease in child contacts in a setting with a high prevalence of both TB and human immunodeficiency virus (HIV). This study aims to investigate the association between delay in treatment initiation in adult source cases and the risk of TB infection and disease in child household contacts in a high TB and high HIV burden setting.

A cross-sectional study will be conducted involving secondary analysis of previously collected data. The data was collected prospectively as part of a cohort study that investigated the use of interferon-gamma release assays (IGRAs) for diagnosing tuberculosis (TB) infection and disease in HIV-infected and HIV-uninfected children. The main study was conducted in three impoverished urban communities in Cape Town, Western Cape, South Africa with a high prevalence of TB and HIV. Between December 2007 and June 2012 adult TB cases and their eligible child household contacts aged from three months to fifteen years were enrolled.

This study will investigate whether there is an association between the duration of total treatment delay (time from the onset of cough to the initiation of treatment) in adult TB source cases and the risk of infection in their child household contacts in a high TB and HIV burden setting. The hypothesis is that increasing delay in TB treatment initiation in adult source cases is associated with an increased risk of TB infection and TB disease in child household contacts.

Logistic regression models will be developed investigating TB infection and TB disease in children as dependent variables and total treatment delay experienced by adult source cases as the independent variable.

1. Background and rationale

Exposure to an infectious source case is necessary for tuberculosis (TB) transmission to occur. TB transmission depends on the number of new infectious TB cases occurring, the length of time cases remain infectious and the duration and closeness of contact with susceptible individuals.(1) Control of the TB epidemic depends on the timely diagnosis of new infectious TB cases and the rapid initiation of effective treatment.(2) As part of the World Health Organization's (WHO) DOTS (directly observed treatment, short course) strategy to achieve TB control worldwide, targets were set to achieve detection of 70% of new TB cases and cure 85% of cases.(3) In 2006 the Stop TB Strategy was introduced, which aimed to reduce the expanding global burden of TB by new strategies, including addressing co-infection with human immunodeficiency virus (HIV) and drug-resistant TB.(3)

In South Africa the annual TB incidence rate is estimated to be one of the highest in the world, at 1000 per 100000 population per year in 2012.(4) The annual risk of TB infection was reported to have increased from 4.1% in 1998 to 5.8% in 2005 in high burden communities in Cape Town, South Africa, indicating that TB transmission remains high and that TB control measures need to improve.(5) In a survey undertaken in Cape Town, South Africa, the prevalence of smear positive TB was 8-9/1000, higher than the national estimate of 5/1000.(6) The patient diagnostic rate of 0.30-0.38/person-year was low, suggesting that cases are not detected and treated sufficiently to interrupt transmission, including to children.(6)

At the onset of adult-type pulmonary TB disease, it is likely that cases are less infectious, but that with increasing time, disease progresses and infectiousness increases.(7) Delayed TB diagnosis and treatment initiation is associated with a significantly increased risk of pulmonary TB being smear positive and cavitatory, which likely increases TB transmission.(8) Delayed diagnosis ≥90 days has been associated with increased transmission to close adult contacts independently of other source case risk factors.(9) A dose-response relationship has been observed between the duration of total delay of smear-positive Chinese TB patients and latent TB infection in their household contacts with delays ≥30 days.(10) This study was conducted in a high TB burden setting, but only

included smear-positive cases and did not test TB patients or their household contacts for HIV.

Delays in the treatment of TB patients can be attributed both to the patient and the health system. The patient delay is the time from the onset of symptoms until the first contact with the health care service.(11,12) The health system delay is the time from a patient's first contact with the health care service until either a TB diagnosis is made or TB treatment is commenced.(11,12) The total delay is the time from the onset of symptoms until anti-TB treatment is initiated.(11) Significant total delays have been found between TB symptom onset and diagnosis or treatment initiation, due to both patient and health system delays.(11,12) In Cape Town, South Africa, the median duration of total delay was found to be 31 days, which was longer if patients initially consulted private health care practitioners or were HIV-infected.(13)

Children account for approximately 15% of the TB disease burden worldwide.(4,14) In South Africa children account for a similar proportion of total TB cases, estimated to be 13% in 2012.(15) A child's age and immune status are two of the most important factors which determine whether or not TB infection will progress to disease.(16) Young or HIV-infected children who are infected with TB have a higher risk of developing severe or disseminated forms of TB disease.(17,18) A systematic review and meta-analysis found that half of all child contacts had latent TB infection at the time of contact investigation in low and middle income countries.(19) Although isoniazid preventive therapy is recommended as standard of care for all children aged under five years or HIV-infected, who have had close contact with an adult TB case, this is poorly implemented in many settings, including in South Africa.(20) The lack of effective chemoprophylaxis means that the childhood TB burden is an accurate reflection of TB transmission within the community.

Well-quantified TB exposure, as measured by a TB contact score, has been demonstrated to measure a child's risk of TB infection well in a high burden setting such as South Africa.(21) Components of the score included maternal TB, sleep proximity, source case infectivity, duration of exposure and exposure to multiple cases. Four components – maternal TB and sleep exposure, infectivity of the index case, duration of exposure and multiple index cases

– predicted 68% of the variance in TB infection status. Exposure duration was only measured as average daily time of exposure and did not account for the duration of time the child was exposed before the source case initiated treatment.

To date no study has investigated the association between delay in TB treatment initiation in adult source cases and the risk of TB infection in child household contacts. Although a previous study has found a dose-response relationship with transmission from smear-positive patients to adult household contacts increasing significantly after 30 days, this study did not include smear-negative patients and did not analyse the effect of the HIV status of the source case.(10) In South Africa, as in many other sub-Saharan African countries, there is a high prevalence of HIV infection among TB patients, and it was estimated in 2012 that 63% of TB cases were co-infected with HIV.(4) Although HIV-infected TB patients are more likely to have smear-negative and extrapulmonary TB, and therefore possibly to be less infectious, the impact of the duration of delay in treatment initiation on TB transmission has not been well studied in relation to the HIV status of the source case.(22)

Interferon-gamma release assays (IGRAs) are immune-based diagnostic tests for TB that measure the interferon-gamma levels produced by T-lymphocytes incubated with antigens that are highly specific for *Mycobacterium tuberculosis* infection. There are two IGRA tests that are commercially available – Quantiferon-TB and T-SPOT.TB. The theoretical advantage of testing for TB infection using and IGRA is the theoretical greater specificity for TB compared to the Mantoux TST, which might have a false positive result following BCG vaccination or exposure to other mycobacteria. The TST is cheaper and more widely available. Using both markers of TB infection will enable a comparison of IGRA and Mantoux TST results.

The rationale of this study is to investigate the relationship between the duration of total treatment delay in adult TB source cases and the risk of TB infection and disease in child household contacts in a setting that has a high prevalence of both TB and HIV.

2. Hypotheses, Aims and Objectives

2.1 **Hypotheses**

The hypothesis of this study is that there is an association between the total treatment delay in adult TB source cases and the risk of infection in their child household contacts, with increasing delay in TB treatment initiation in adult source cases resulting in increased TB transmission rates and higher rates of infection among child household contacts. The HIV status of the adult TB source case will be investigated as a possible effect modifier of this association. Furthermore, it is hypothesised that increasing delay in TB treatment initiation in adult sources is associated with an increased risk of TB disease in child household contacts.

2.2 **Study aim**

This study aims to determine the association between the length of total treatment delay in adult TB cases and the risk of TB infection and disease in their child household contacts in a high TB and HIV burden setting.

2.3 **Objectives**

2.3.1 *Primary objective*

To determine the association between total treatment delay in adult TB source cases and the risk of TB infection, as measured by Mantoux tuberculin skin test (TST), in child household contacts.

2.3.2 *Secondary objectives*

2.3.2.1 To determine the association between total treatment delay in adult TB source cases and the risk of TB infection, as measured by interferon-gamma release assay (IGRA), in child household contacts.

2.3.2.2 To determine the association between total treatment delay in adult TB source cases and the risk of TB disease in child household contacts.

2.3.2.3 To investigate the effect of possible confounders and effect modifiers on the association between total TB treatment delay in adult TB source cases and the risk of TB infection or disease in child household contacts.

3. Methods

This study will perform secondary data analysis on data collected prospectively as part of a community-based household contact tracing cohort study that investigated the use of IGRAs for diagnosing TB infection and disease in HIV-infected and HIV-uninfected children.

3.1 **Study design**

A cross-sectional analysis will be conducted on baseline data collected at study enrolment.

3.2 **Study population and Sampling**

3.2.1 *Study population*

The main study was conducted in three impoverished urban communities in Cape Town, Western Cape, South Africa with a high prevalence of TB and HIV. The adult TB case notification rate was 671 per 100 000, and 315 per 100 000 in children aged 0-14 years in Cape Town in 2012 (personal communication, Judy Caldwell, Cape Town City Health Department). In the first two communities the HIV prevalence rate among adult TB cases was 16% in 2008 (unpublished data, Western Cape Department of Health), whereas in the third community 70% of all adult TB cases tested for HIV were found to be infected in 2009.(13)

3.2.2 *Method of sampling and eligibility criteria*

Between December 2007 and June 2012 children aged from three months to fifteen years, with and without known TB exposure, were recruited. Adult cases routinely started on TB treatment for either pulmonary or extrapulmonary TB at the three clinics in these communities were consecutively offered the opportunity to participate in the parent study, regardless of sputum status. Following informed consent, the adult source case was interviewed by trained study personnel and data collected both from the source case and the TB register. Visits to the households of adult TB source cases were conducted to enrol all eligible children living in the same household if the child's parent or legal guardian provided informed consent. All adult source cases and TB exposed children were enrolled within three months of diagnosis of the adult TB patient. Symptomatic adults living in all households were screened for TB, including sputum collection.

Exclusion criteria for children included a weight <5 kg, a documented haemoglobin <9 mg/dl, current TB treatment and where parental consent was not obtained. Children on

isoniazid preventive therapy (IPT) were not excluded. Enrolment was deferred if a tuberculin skin test (TST) had been placed during the preceding twelve weeks, if a live attenuated vaccine had been administered during the preceding six weeks, or if the child had an acute severe respiratory, diarrheal or neurological illness.

3.2.3 *Sample size*

The primary analysis of this study will be conducted using logistic regression where the dependent variable will be TB infection (as indicated by a positive Mantoux) and the independent variable, treatment delay, will be an ordered variable with fixed intervals of time for treatment delay. Further secondary analyses will be conducted using TB infection, as indicated by a positive IGRA test, and TB disease as the response variables. Sample size calculations were made based on the primary analysis.

Sample sizes were calculated using a simple approximation formula derived for detecting a linear trend in proportions.(23) nQuery Advisor (Statistical Solutions, Cork, Ireland) generated the sample size computations where a range of possible sample sizes was calculated using different estimated proportions for each treatment delay category based on the study data (Table 1).

A logistic regression model will be used in the final analysis. The sample size was adjusted for clustering of children in households by multiplying the design effect by the calculated nQuery sample sizes. The design effect was calculated using three different intraclass correlation coefficients (ICC) (0.10. 0.20 and 0.30). With a sample size of 234 child contacts, a 0.050 two-sided Chi-square test of trend in proportions based on the logistic model will have 80% power to detect a difference in proportions characterized by a Trend, C of 0.209 and a Variance term of 0.207 with an average proportion of 0.325. The available sample size is a total of 671 children, who were enrolled from 290 households.

3.3 **Study procedures**

Standard data collection tools were used to gather child-specific data regarding recent TB exposure from parents or primary care givers and TB source cases, and to extract routine data from the TB register. Data were collected regarding infectivity of the source case (sputum smear and culture status and disease site), proximity of the child to the index case (familial and caregiving relationship, sleep proximity), and duration of the child's exposure to the index case (hours of daily contact, weeks of extended household contact) through interviewing the child contact's parent or guardian. The number of TB cases within the household was enumerated. Household characteristics and socio-economic indicators were ascertained through an asset-based questionnaire and the total number of adults and children in the household enumerated.

TB infection

All children were screened at enrolment for TB infection through Mantoux TST and two IGRAs, the QuantiFERON-TB Gold (Cellistis, Carnegie, Victoria, Australia) and the T-SPOT.*TB* (Oxford Immunotec, Oxford, UK).

The Mantoux TST was performed by a trained study nurse injecting two tuberculin units (purified protein derivative RT-23, Statens Serum Institute, Copenhagen, Denmark) intradermally on the volar aspect of the left forearm. The largest transverse diameter of induration was read at 48-72 hours after administration, using the "ball-point" technique and callipers. A TST was not performed in children with a history of previous TST ulceration. The Mantoux TST was classified as being positive if the transverse induration measured 10mm or greater in HIV-uninfected children or 5mm or greater in HIV-infected children.

QuantiFERON-TB Gold and T-SPOT.TB results were performed using standard manufacturer's guidelines and defined as positive, negative or indeterminate using standard assay cut-offs recommended by the manufacturer.(24,25)

TB disease

All children were screened for TB disease, which was diagnosed through a combination of standard symptom screening, clinical evaluation, chest radiographic findings and mycobacterial culture of gastric aspirates or sputum. Antero-posterior and lateral chest radiographs were read by two blinded independent experts, using a standard international paediatric TB radiologic classification tool.(26) TB disease was classified as confirmed, probable, suspected, unlikely and not TB, based on international consensus guidelines.(27)

Total treatment delay

This was measured as the total duration of time in weeks the adult TB source case had been coughing before the date of initiation of TB treatment. The duration of cough was collected as an ordinal variable in the main study. Treatment delay was categorised into intervals of no cough reported, <4 weeks, 4-6 weeks, 6-12 weeks and >12 weeks. Child contacts of TB patients with no reported cough will provide the reference group for comparison.

Source case and contact details

Adult source case data recorded at enrolment include age, gender, HIV status, self-reported presence or absence of cough, duration of cough and current or past smoking habits. Data collected from the TB register include date of registration as a patient at the TB clinic, patient category[¶], type of TB disease (pulmonary or extrapulmonary), treatment start date and smear and culture results, including drug susceptibility test results where available. All data were collected and recorded in a standardized manner by trained research staff.

HIV and immune status

HIV rapid testing was performed on all children (Abbott Determine HIV-1/2 rapid test, Abbott diagnostics, Hoofdorp, The Netherlands). A positive rapid test was confirmed with ELISA (children aged > 18 months) and DNA polymerase chain reaction (children aged ≤ 18 months). The most recent CD4 count and percentage and HIV viral load were documented

[¶] Patient category: new, retreatment after cure, retreatment after completion, retreatment after failure, retreatment after interruption

from routine laboratory reports. HIV-infected children were assessed clinically and the stage of their HIV disease classified according to the WHO staging system.(28)

Anthropometric measures

All anthropometry was measured using standardized calibrated equipment by trained research staff. Electronic scales with taring capability and calibrated to 0.1kg were used to measure weight. Recumbent length was measured using an infant stadiometer in children aged under 18 months. Standing height using a wall-mounted stadiometer was measured in children 18 months or older. Both length and height were recorded to the last completed unit rather than the nearest unit. In order to correct for the systematic negative bias this practice introduces, half of the smallest measurement unit (0.05cm) was added to each measurement before analysis.

Age and gender

Age was recorded in years calculated at the date of enrolment from the date of birth. Gender was categorized as male or female at enrolment.

BCG vaccination status

A child was considered to have been vaccinated with BCG either if there was a typical BCG scar present on the right deltoid documented at enrolment or if there was documentation of the BCG vaccine having been administered at birth in the Road to Health Card (RTHC).

Household characteristics

Data on household socioeconomic status, as measured by household assets, were obtained from interviewing the child's parent or guardian at enrolment. The number of TB cases within the household was enumerated. Household characteristics and socio-economic indicators were ascertained through an asset-based questionnaire and the total number of adults and children in the household enumerated.

4. Variables

No additional measurements will be performed for this study. All data to be analysed have already been collected for the parent study. The dependent variables that will be analysed include TB infection and TB disease. For TB infection the Mantoux TST will be the primary outcome variable of interest. A secondary analysis of TB infection will be conducted, using either IGRA (QuantiFERON-TB Gold or T-SPOT.*TB*) being positive as indicative of TB infection. The results of these two analyses will be compared to determine if the findings differ between different markers of TB infection. A further secondary analysis will be conducted with TB disease as the outcome variable of interest. The independent variable in all analyses will be the total treatment delay. A summary of the variables to be analysed are listed in Appendix I at the end of the dissertation.

5. Data Capture and Handling

All data were collected by trained research staff using standardized study forms. Strict quality control procedures were followed by all staff involved in collecting or capturing data. All completed data forms were reviewed on-site for completeness before signing off for data capture. Any queries were resolved before data capture. All data were entered into an SQL database on a secure centralized server. Dual capture was performed with review of any discrepancies by a third data technician. All data were stored in password-protected electronic format. Before analysis, the data set will be thoroughly reviewed and cleaned. All variables will be checked for possible coding or other errors.

6. Statistical Analysis

Baseline demographic variables collected at enrolment will be summarised by descriptive statistics. Continuous data will be summarised by means and standard deviations for variables with a Normal distribution, or medians and interquartile ranges for non-normally distributed data. For categorical variables, frequencies and proportions will be summarised. Basic descriptive statistics, including unadjusted odds ratios will be calculated. Chi-squared or Fisher's exact test will be used to calculate the association between categorical variables. For ordinal variables, the Chi-squared test for trend will be used.

Logistic regression models will be developed using TB infection (as indicated by Mantoux TST or IGRA) and TB disease as dependent variables and total treatment delay as an independent variable. Total treatment delay will be treated as an ordinal variable to be able to assess for a dose-response relationship. Covariates of interest will be assessed for inclusion into the models and clinically important confounders will be included in the analysis. Possible confounders that are clinically important and will be investigated include adult source case and child contact age, gender, HIV status and intensity of contact. Adult source case HIV status will be investigated as a possible effect modifier. Adjustment will be made for the clustering of children who are from the same household. Results will be presented as adjusted odds ratios with 95% confidence intervals. All statistical analyses will be performed using STATA/IC 12.0 (StataCorp LP, College Station, Texas, USA).

7. Ethics

This study involves secondary analysis of previously collected data. The study from which data will be utilised was conducted according to the principles of the International Conference on Harmonisation Good Clinical Practice. Ethical approval was obtained from the research ethics committees of Case Western Reserve (IRB number: 04-07-31) and

Stellenbosch Universities (IRB numbers: N05/07/129 and N08/08/207) as well as the relevant local health authorities.

The dataset that will be used for this analysis does not contain any personal identifying details and participants are identified only by study numbers to ensure anonymity. All data that were collected as part of the study are stored in a password protected database.

Results from this study might contribute to improved knowledge and understanding of the association between treatment delay in TB source cases and risk of infection and disease in child household contacts. Because the children in the communities studied have a high burden of TB disease, this study will assist in generating knowledge that can be used to target interventions to reduce treatment delay in adults and reduce TB transmission to child household contacts.

The findings will be submitted in a manuscript for publication to a peer-reviewed journal. Feedback of the study findings will be given to the local health authorities.

8. Logistics

8.1 **Timeline for study completion**

Month	1	2	3	4	5	6	7
Protocol development							
Ethics submission							
Data analysis							
Write-up of thesis and manuscript							
Submission of final thesis							

8.2 **Budget**

Because the data have already been collected no significant costs will be incurred. The parent study was funded by the Norwegian Programme for Development, Research and Education (NUFU), National Institutes of Health (NIH, grant no 1R01AI076199-01A1) and German Research Foundation (DFG). Data will be analysed and a thesis compiled as part of a Masters in Public Health (MPH) dissertation by Penelope Rose whose salary is paid in full. The costs of dissemination, including publication, will be covered by these grants.

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B. LITERATURE REVIEW

1. Introduction

Tuberculosis (TB) is a major global public health problem, estimated to have caused disease in 8.6 million and death in 2 million people during 2012.(4) South Africa has one of the highest TB incidences in the world, of approximately 1000 per 100 000 population per year, and also the third highest TB burden in the world with 349 582 TB cases notified in 2012.(4) In addition, HIV-associated TB accounts for 62% of the total TB burden and 1% of children under five years of age have been notified as having TB.(4,29) Childhood TB is a sentinel event, reflecting recent transmission within a community, because more than 95% of children who develop TB infection will progress to disease within the first year after infection.(30,31) In the absence of effective chemoprophylaxis, the burden of childhood TB disease is therefore a good indicator of how successful a TB control programme is.

Tuberculosis is an airborne disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*). *M. tuberculosis* is transmitted through the air in droplet nuclei, which are infectious particles generated when a person with pulmonary or laryngeal tuberculosis coughs, sneezes, shouts, talks loudly or sings.(32) Droplet nuclei may remain suspended in the air for hours depending on environmental factors.(33) Transmission occurs when one or more of these droplet nuclei containing tubercle bacilli are inhaled and reach the alveoli of the lung in a susceptible individual. The *M. tuberculosis* bacilli are ingested by alveolar macrophages, where some survive and may multiply. The tubercle bacilli are either contained, resulting in latent TB infection, or continue to multiply, resulting in TB disease. Bacilli may also spread through the lymphatics or bloodstream to other parts of the body, such as the lymph nodes, brain, spine, bone or kidneys. Extrapulmonary TB disease may occur if bacilli are not contained at these sites.(31,34) Usually extrapulmonary forms of TB disease, without associated pulmonary TB, are not infectious.

Exposure to an infectious source case is necessary for TB transmission to occur. Control of the TB epidemic depends on the timely diagnosis of new infectious cases and the rapid initiation of effective treatment.(2) The risk of infection in exposed contacts depends predominantly on the infectiousness of the TB case, the duration and closeness of contact, the virulence of the microorganism and the susceptibility of the contact.(1,19,35) The risk

of disease following infection depends primarily on the contact's age, integrity of the immune system, the time since infection occurred and other comorbid conditions.(1)

The force of TB infection is defined as the proportion of individuals who were previously uninfected with TB and become infected each year. The main determinants are the prevalence of infectious TB patients and the number of secondary cases which each infectious patient generates. In Cape Town, South Africa the force of infection has been estimated to be between 4% and 8% per year, indicating that TB transmission remains high and that TB control measures need to improve.(5,29) Even small reductions in the force of infection due to improved TB control would lead to large benefits in reducing transmission over time.(29) The South African TB control strategy has focused on the effective management of TB patients identified through passive case-finding using the DOTS (directly observed treatment, short course) approach and more recently the "Stop TB" strategy.(3,36) As part of the DOTS strategy to achieve TB control worldwide, targets were set to achieve detection of 70% of new TB cases and cure of 85% of cases.(3)

Although effective case management is necessary for TB control, it is insufficient in settings where there is a high force of infection and high HIV prevalence because effective contact numbers are high and delays in diagnosis and treatment initiation result in continuing TB transmission.(29,37) In a survey undertaken in Cape Town, South Africa, the prevalence of smear positive and culture positive TB was higher than national estimates and the patient diagnostic rate low, suggesting that cases are not detected and treated sufficiently to interrupt transmission.(6) This means that in a high burden setting, such as South Africa, early diagnosis through intensified case-finding and rapid treatment initiation might have significant benefits to reduce transmission.

Delays in the treatment of TB patients may contribute to prolonged duration of exposure and increased transmission of TB.(7,38) The purpose of this literature review is to describe what is known about treatment delay and its impact on tuberculosis (TB) transmission, including household transmission to children and transmission from HIV co-infected TB patients. An overview of risk factors known to influence the likelihood of developing TB infection after exposure and TB disease after infection in children will be included. This is

relevant because these risk factors for infection and disease may be important confounders or mediators in the relationship between treatment delay and the development of TB infection and disease in child household contacts of adult TB source cases. In addition the impact of the HIV status of the source case on TB transmission will also be described, because this will be assessed as a possible effect modifier.

2. Literature search strategy

Electronic database searches were performed on 26 and 27 March 2015 of Pubmed, the Cochrane Library and Google Scholar. The specific searches conducted are listed in Table 1. Searches were not limited by language, date or type of article. Articles limited only to nosocomial or other congregate institutional settings of tuberculosis transmission were excluded. Abstracts of articles identified were screened for relevance and selected if they were possibly relevant and not a duplicate. These articles were read in full if the full article was in English and available. Further relevant articles were identified from consulting the reference lists of articles read. In addition textbooks and other relevant literature published by the International Union Against Tuberculosis and Lung Disease and the World Health Organization were also read and included in the literature review. Additional literature was identified by reviewing a colleague's personal collections of articles.

Table 1. Literature search strategy for electronic databases

Electronic database	Search strategy	Articles found (relevant)
Pubmed	1. (("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields]) OR TB[All Fields]) AND ("infection"[MeSH Terms] OR "infection"[All Fields])) AND delay[All Fields]	300 (12)
	2. ((((TB OR tuberculosis))) AND (("disease transmission, communicable") OR "disease transmission, infectious")) AND delay	48 (9)
	3. ((TB[All Fields] OR ("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields])) AND (("disease transmission, infectious"[MeSH Terms] OR ("disease"[All Fields] AND "transmission"[All Fields] AND "infectious"[All Fields]) OR "infectious disease transmission"[All Fields] OR ("disease"[All Fields] AND "transmission"[All Fields] AND "communicable"[All Fields])) OR "disease transmission, infectious"[All Fields])) AND (("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields]) OR ("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields]) OR ("Childhood"[Journal] OR "childhood"[All Fields]) OR ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]))	590 (35)
	4. (("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields]) AND ("transmission"[Subheading] OR "transmission"[All Fields])) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields])	1807 (12)
	5. (("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields]) AND ("transmission"[Subheading] OR "transmission"[All Fields])) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields])	509 (19)
Cochrane Library	Tuberculosis AND transmission	3 (0)
Google Scholar	1. tuberculosis AND treatment delay AND household transmission AND children	22 400 (23)
	2. tuberculosis transmission AND HIV co-infection	9070 (4)

3. Summary of literature

3.1 Delay in tuberculosis diagnosis and treatment

Rapid diagnosis and treatment initiation are essential for an effective TB control programme. Delayed diagnosis and treatment initiation is associated with a significantly increased risk of pulmonary TB being smear positive and cavitatory, which likely increases TB transmission.(8,30,39) This is important both because it impacts on the patient's own disease course and prognosis, and also because it is likely to result in increased transmission of infection. In many communities with a high TB incidence ongoing transmission leading to reinfection is the main contributor to the TB epidemic.(7)

Delay can be due to both patient health-seeking behaviour and health system factors.(7,38) The patient delay is the time from the onset of symptoms until the first contact with the health care service.(11,12) The health system delay is defined as the time from a patient's first contact with the health care service until either a TB diagnosis is made or TB treatment is commenced.(11,12) Health system delay can be further divided into the diagnostic delay, which is the time from first contact with health care services until a diagnosis is made, and the treatment delay, the time from when a diagnosis of TB is made until treatment is started.(40) The total delay is the time from the first onset of symptoms until anti-TB treatment is initiated.(11) Definitions vary between different studies, resulting in results not always being directly comparable. Symptom onset, which defines the beginning of patient delay, has been defined as either the onset of cough, or alternatively as any symptom onset.(41) The time of first contact with the healthcare system has also been variably defined to be the first contact with the national TB program, a western medicine healthcare provider, or any healthcare provider, sometimes including traditional healers.(41)

Significant total delays have been found due to both patient- and health system-related factors.(11,12) In Cape Town, South Africa, the median duration of total delay for adult TB patients was found to be 31 days, which was longer if patients initially consulted private health care practitioners or were HIV-infected.(13) A study of adult Ethiopian TB patients that estimated the infectious pool of TB from the duration of total delay found that treatment delay among newly diagnosed smear-positive TB patients made the largest contribution to the total infectious pool, with a median total delay for new patients of 95 days.(42) A study of Chinese pulmonary TB cases found that 95.3% of patients presented to the healthcare system a median of 58 days after symptom onset and that the proportion presenting sputum smear positive and with lung cavitation increased significantly with increasing delay.(8) Sputum smear-negative pulmonary disease can also be associated with a delay in diagnosis and treatment. A study of Zambian patients found that TB patients with sputum smear-negative pulmonary disease were 2.8 times more likely to experience delay.(43) A systematic review of delays in the diagnosis of pulmonary TB found that the mean total delay ranged from 25 to 185 days, with patient and health system delay contributing roughly equally.(12)

A systematic review of the causes of delay in tuberculosis diagnosis and treatment found that the main factor leading to delayed diagnosis and treatment was patients repeatedly visiting the same healthcare facility, receiving antibiotic treatment and therefore not accessing TB services.(41) Further risk factors for diagnostic delay included HIV co-infection, co-existence of any chronic cough or chronic lung disease, sputum smear-negative disease, extrapulmonary disease, living in a rural area, initial consultation with a non-NTP healthcare practitioner, poverty, female sex, alcohol or substance abuse, low educational level and factors related to knowledge and beliefs about TB were associated with increased diagnostic and treatment delays.(41) In a multi-country study conducted by the WHO in the Eastern Mediterranean Region, total delay was found to be unacceptably long, with mean delay ranging from one and a half to four months.(11) A systematic review and meta-analysis of factors associated with delayed TB diagnosis and treatment in sub-Saharan African countries found that both initial consultation with traditional healers and return travelling time to access care consistently predicted a longer patient delay.(44)

In a hospital-based study, HIV-coinfected South African TB patients had a median total delay of 28 days, with advanced HIV disease, unemployment, ethanol consumption, previously seeking treatment at another facility and overcrowding being risk factors that predicted longer delay before presentation to hospital.(45) A Brazilian study found that the median time to treatment initiation in HIV co-infected TB patients was 41 days and that delay was associated with presenting with nonspecific systemic complaints and having sputum smear negative pulmonary TB.(46)

Very few studies have attempted to quantify the effect of the duration of delay on the risk of transmission to exposed contacts. In Maryland, USA, delayed diagnosis ≥90 days was associated with increased transmission from adult pulmonary TB patients to close adult contacts independently of other source case risk factors.(9) This study was conducted in a low TB and low HIV prevalence setting. A further study found a dose-response relationship between the duration of total delay of smear-positive Chinese TB patients and latent TB infection in their household contacts, with a turning point at 30 days after which the risk of TB infection increased significantly.(10) This study was conducted in a high TB burden setting, but only included smear-positive cases and did not test either TB patients or their household contacts for HIV. No studies were found that specifically investigated the impact of the duration of treatment delay on the risk of TB infection and/or disease in children or that investigated the impact of treatment delay in a high HIV and high TB burden setting. A summary of selected studies investigating treatment delay is provided in Table 1.

A Cochrane review was conducted to investigate whether or not active case finding detects more TB cases than passive case finding among people in contact with TB patients. The conclusion of this review was that there have been no randomised controlled trials performed to investigate this question and that there is currently insufficient evidence.(47) It has been demonstrated that active case finding detects TB cases who are less symptomatic and more likely to be at an earlier stage of disease.(48) It would be important to know whether cases become more infectious over time and to quantify this to determine how rapidly cases need to be diagnosed and treated to reduce the risk of ongoing transmission in households and the community.

3.2 Risk factors for TB infection

The risk of a contact becoming infected with TB depends on the infectiousness of the TB source case, environmental factors including the closeness and duration of contact, microbial factors including virulence, and contact susceptibility.(1,19,35)

3.2.1 *Infectiousness of the source case*

The infectiousness of the source case is determined primarily by the anatomical site of disease, with the vast majority of transmission occurring from pulmonary TB cases. A patient's infectiousness is determined both by the ability to aerosolise tubercle bacilli and the bacillary load with the largest number of bacilli being found in pulmonary lesions with lung cavities.(49) Sputum smear status and grade, cough strength and frequency, the presence of lung cavitation and the initiation of effective treatment also impact on infectiousness.(1,35,49)

Early effective chemotherapy reduces the length of infectiousness and an untreated case will remain infectious longer than a treated case.(1,30,49) With effective treatment, most TB patients become non-infectious within two to three weeks.(50,51) Before effective antituberculosis treatment became available, infectious TB cases were estimated to infect on average ten people per year.(52) The number of bacilli found in the sputum provides an indication of the infectiousness of a case, with sputum smear positive patients being more infectious than smear negative and accounting for more transmission and a greater risk of infections among exposed contacts.(1,53–58) Between 60-80% of children exposed to a sputum smear-positive source case within a household for a prolonged time will become infected with TB, compared to 10-40% of children exposed to a sputum smear-negative source case.(35,59) The transmission from smear-negative TB patients is estimated to be approximately one fifth that of smear-positive TB patients.(60)

3.2.2 *Environmental factors including closeness of case-contact interaction*

The likelihood of TB transmission varies depending on the closeness and duration of contact with an infectious TB case.(61) Increased closeness of contact increases the risk of infection, in particular if the source case is the mother or primary caregiver.(21,55,57,62–65) The intensity of exposure is determined by both the duration of exposure and the number of infectious droplets in the surrounding air.(30) Dwelling size, number of occupants, childcare arrangements and sleeping arrangements all contribute to the likelihood of infection. Improved ventilation reduces the probability of infection of exposed individuals.(1) Transmission increases in poorly ventilated, overcrowded dwellings.(30,35,65,66) Population density varies between different countries, between urban and rural areas and between different dwellings. Increasing population density results in increased likelihood of exposure and infection among contacts of infectious TB cases even with a constant TB incidence.(1) Further environmental factors that influence transmission include the room volume, humidity and the presence of ultraviolet light.(1,35) Environmental tobacco smoke exposure increases the risk of TB infection.(56)

Well-quantified TB exposure, as measured by a TB contact score, has been demonstrated to measure a child's risk of TB infection well in a high burden setting such as South Africa.(21) Components of the score included maternal TB, sleep proximity, source case infectivity, duration of exposure and exposure to multiple cases. Four components – maternal TB and sleep exposure, infectivity of the index case, duration of exposure and multiple index cases – predicted 68% of the variance in TB infection status.

In low prevalence settings the household is the most important site of TB transmission from adults to children.(67,68) During early childhood most TB transmission occurs within the household, whereas older children have higher numbers of non-household contacts and are increasingly exposed to TB contacts outside the household.(69–72) Although TB transmission to young children occurs predominantly within the household, it may also occur in the community in high burden settings.(67,71,72) In a study modelling the risk of TB transmission to young children in a South African township, it was estimated that 75% of transmission occurred within the child's primary household.(72) In older children, most TB transmission occurs outside the household in congregate settings, such as the workplace,

school or crèche and public transport.(70,73–75) Intergenerational mixing, which is necessary to maintain a TB epidemic, occurs most frequently in households and when using public transport, with exposure times being shorter during transport usage.(70,73)

3.2.3 *Microbial factors*

Different TB strains have been found to differ in their virulence.(62,76) Due to the increased mobility of individuals, geographical isolation is less likely and the most virulent strains, such as the Beijing strain, have spread globally.(30) In a study in Cape Town, no association was found between *M. tuberculosis* genotype and within household transmission.(77)

Although drug-resistant cases might plausibly remain infectious and transmit TB for longer, no increase in infection rates has been found among child household contacts of drug-resistant TB and there is currently no convincing evidence that drug resistance per se alters the likelihood of TB transmission.(49) Drug-resistant TB can be as infectious as drug-susceptible strains and may be infectious for a longer period than drug-susceptible TB if there is a delay in initiating effective treatment.(49,78)

3.2.4 *Contact susceptibility factors*

Among children an increasing prevalence of infection occurs with increasing age.(35,58,79) It is likely that this is due to increasing exposure over time as children are exposed to more people outside their household. HIV has been found to have a variable effect on TB infection rates. Whereas in Kenya TB infection rates have increased with increasing HIV prevalence over time, in Tanzania the TB annual risk of infection remained unchanged despite increased HIV prevalence.(80,81) There is currently no evidence that HIV alters the risk of TB infection after exposure.(29)

Recent evidence suggests that BCG vaccination might protect against infection with TB, reducing the odds of infection by 40% and children who have not been vaccinated with BCG are at increased risk of TB infection.(56,82,83)

Higher rates of infection have been described among different racial or ethnic groups.(1,58) Although it is possible that host genetics might play a role in determining susceptibility to infection in some individuals, in most cases social and environmental factors confound any association observed at a population level and it is more likely that environmental rather than genetic factors explain any observed differences.(30)

3.3 Risk factors for TB disease

3.3.1 Age

Young children aged under three years are extremely susceptible to developing disease following infection with TB, with 50% of infants and 20-40% of children aged less than two years developing disease within a year of primary infection.(30,31,49,84,85) Children aged under five years are also more likely to develop disseminated forms of disease, such as miliary TB and tuberculous meningitis.(49,62,85,86) The risk of progression to disease is lower in children aged between five and ten years and increases again in adolescence.(62)

3.3.2 *Integrity of the immune system*

HIV is the single strongest risk factor for developing active TB disease.(35) HIV infection increases the risk of progression from TB infection to disease, with the risk of TB disease in HIV-infected individuals being strongly related to the CD4 count.(1,87) With progressive immunosuppression, TB disease is also more likely to be smear-negative or extrapulmonary.(35) Antiretroviral therapy reverses HIV-associated immunosuppression and can decrease the risk of TB disease developing.(29) In adults, HIV infection increases the likelihood of progression to disease from a 10% lifetime risk of developing disease after infection, to a 10% per annum risk of developing disease.(1,35). HIV-infected individuals are more likely to develop TB disease, both due to increased rates of reactivation of latent TB infection and due to new TB infections.(1,88) The relative risk of TB among HIV-infected infants has been found to be 24 times higher than among HIV-uninfected infants, likely due

to a combination of increased exposure to TB, increased risk of progression to disease as a result of immune suppression and a lack of protective effect of BCG vaccine.(62,89)

Any medical condition that leads to impairment of the innate or adaptive cellular immune system can lead to an increased risk of TB disease – including malnutrition, immunosuppressant therapy such as corticosteroids, diabetes mellitus, malignancies or renal failure.(1,38) Malnutrition may reduce cellular immunity, leading to the development of TB disease.(1,30,35,62,90,91) Deficiencies of protein or micronutrients, such as vitamin A, vitamin D and zinc, lead to impaired immunity and progression from TB infection to disease.(91,92) Although the risk of TB disease is higher in severe malnutrition, mild to moderate malnutrition may affect a larger proportion of a population, contributing to the high TB incidences seen in many populations.(92) Malnutrition may also lead to a poorer outcome of TB disease in children.(91)

Neonatal bacille Calmette-Guérin (BCG) vaccination provides some protection mainly against disseminated forms of TB during early childhood – such as miliary TB and tuberculous meningitis – but does not protect against pulmonary TB.(93,94)

3.3.3 *Other host factors*

The risk of developing disease is higher following recently acquired TB infection, with most children developing disease within the first year after infection, and diminishes with increasing time following infection.(49,62,95) Differences in disease incidence between different racial or ethnic groups have been reported, but associations are often confounded by socioeconomic status, immigration from a country with a different TB prevalence and other environmental factors.(1,96)

3.3.4 *Environmental factors*

Poverty is a known risk factor for developing TB disease.(62) Many of the known environmental and host risk factors for both *M. tuberculosis* infection and disease are

associated with poverty and low socioeconomic status.(96) In a South African study, lower individual, household and community-level socioeconomic status were associated with higher rates of TB disease, even after adjusting for known demographic and behavioural risk factors.(96) It is likely that the higher risk of TB disease among individuals and communities with a lower socioeconomic status is related to their greater exposure to risk factors associated with poverty, such as environmental tobacco smoke, malnutrition, overcrowding and air pollution.(96,97) Environmental tobacco smoke exposure is associated with a five times higher risk of developing TB disease following infection.(98)

3.3.5 *Source case factors*

The risk of progressing to disease has been reported to be greater if the source case is smear positive, compared to contacts of smear negative patients, but these results are controversial because a Mantoux tuberculin skin test was interpreted as positive with an induration of 5mm or greater, which would reduce the specificity and predictive value of the test.(1,99)

3.4 Influence of HIV on TB transmission

Although 44% of South African TB cases are co-infected with HIV, only 14% of smear-positive TB is HIV-related, suggesting that although the HIV epidemic has increased the TB case load, it might have had a lesser effect on TB transmission.(29) This is because a greater proportion of HIV-associated TB is smear-negative pulmonary or extrapulmonary TB and therefore likely to be less infectious. Different studies have produced different results regarding to what extent HIV co-infected TB patients differ in infectiousness from HIV-uninfected patients. Different studies have produced conflicting results regarding the difference in infectiousness of HIV-infected TB patients. Whereas some studies reported a higher rate of TB transmission from HIV-infected patients, other studies found that transmission rates were either similar or lower than those from HIV-uninfected patients.(22,100,101) More recently a study from Peru found that there was no significant difference in TB transmission from HIV-infected TB patients with a CD4 count >250 cells/μL and HIV-uninfected TB patients, but that HIV-infected patients with a CD4 count ≤250 cells/μL were half as likely to transmit TB to household contacts.(102) It is possible that

differential transmission depending on extent of immunosuppression might explain the different results obtained in previous studies.

In a study in Cape Town, South Africa, the risk of TB infection in TB exposed children was unrelated to the HIV status of the adult TB source case.(54) In a further study, the annual risk of infection was found to remain high at 4.1% among school-going children, but not to have increased despite an increase in the number of adult pulmonary TB cases, mostly due to an increase in HIV-associated TB cases.(103) Because most of the increase in TB cases is due to HIV-related TB, it was concluded that HIV-associated TB does not have a major influence on TB transmission from adults to children.

The peak TB notification rate occurs among young HIV-infected adults, resulting in increased exposure of both HIV-infected and HIV-uninfected children.(29,62,85,95,104) Children living in households affected by HIV are more likely to develop TB disease.(62) It is likely that the effect of HIV on TB transmission might vary depending on the type of TB (pulmonary or extrapulmonary, smear positive or negative) as well as the immune status (CD4 count and antiretroviral therapy status) of the HIV co-infected TB source case. A summary of selected studies on TB transmission from HIV co-infected patients is provided in Table 2.

4. Conclusions

Delayed diagnosis and treatment of pulmonary TB is associated with more advanced pulmonary TB disease, with a greater likelihood of sputum being smear positive and lung cavitation developing. These in turn are well recognised risk factors for TB transmission and infection of exposed contacts, including children living in the same household. To date no study has investigated and attempted to quantify the effect of delay in TB treatment initiation in adult source cases on the risk of TB infection in child household contacts. It is not known how rapidly adult TB cases need to be diagnosed and initiated on treatment to interrupt transmission, in particular in a setting of high burden of both TB and HIV. The aim of this study is to investigate the relationship between total treatment delay in adult TB

source cases and the risk of TB infection and disease in child household contacts in a high TB and high HIV burden setting, investigating also the role of the HIV status of the source case as a possible effect modifier. Although a cough duration of greater than two weeks is conventionally considered by health care workers as being suggestive of possible TB, determining how infectious symptomatic TB patients are, depending on the duration of their symptoms, will enable TB programs to plan turnaround times for investigation and treatment initiation that reduce the risk of ongoing transmission.

Table 1. Summary of selected studies in literature review of treatment delay

In text citation	Author, year	Setting	Population	Study Design	Outcomes	Key findings
31	Golub, 2006	Maryland, USA	Close contacts of adult TB patients	Prospective cohort study	TST	▪ Total treatment delay ≥90 days associated with 40% positive TSTs in HH contacts compared to 24% in delay >90 days ▪ Risk factors for TST positivity: black race, sputum smear positive source case, lung cavitation on CXR
21	WHO (Eastern Mediterranean), 2006	Egypt, Iran, Iraq, Pakistan, Somalia, Syria, Yemen	Newly diagnosed smear positive pulmonary TB cases	Cross sectional	Total treatment delay	▪ Both patient and health system factors contribute to delay ▪ Main causes of delay: sociodemographic (illiteracy, suburban residence), economic, stigma, time to reach health facility, seeking care from non-specialised individuals, visiting more than one health care provider before diagnosis ▪ Unacceptable delay in treatment of TB patients reported in all countries
32	Lin, 2008	Yunnan Province, China	HHH contacts of TB index cases and non-TB patients	Cross-sectional prevalence survey	TST	▪ Dose-response relationship between HH infection and delay in TB treatment. Older age, lung cavitation in index patient and sleeping in same bedroom increase risk of TST positivity ▪ After delay of 30 days, risk of TB infection increases significantly
26	Storla, 2010	Amhara region, Ethiopia	New, retreatment and	Cross sectional	Total treatment delay (days between	▪ Estimate of infectious pool can be calculated by recording treatment delay for

			treatment failure TB cases		symptom onset and start of TB treatment)	new, retreatment and treatment failure TB cases ▪ Treatment delay among new smear-positive TB cases contributes the greatest number of infectious days
25	Van Wyk, 2011	Cape Town, SA	Adult TB patients	Cross sectional	Total treatment delay (days between symptom onset and start of TB treatment)	▪ Median duration of total delay was 31 days ▪ Initial visit to non-National TB Control Programme facility was associated with total, health system and diagnostic delay ▪ HIV infection was associated with total and health system delay
19	Cheng, 2013	Shenzhen, China	All pulmonary TB cases	Retrospective cohort study	- Sputum smear positivity - Pulmonary cavitation	▪ Patients presented to health care system a median of 58 days after symptom onset ▪ Delayed diagnosis and treatment are associated with increased sputum smear positivity and increased pulmonary cavitation

Abbreviations: CXR=chest radiograph, DNA=deoxyribonucleic acid, HIV=human immunodeficiency virus, HH=household, RFLP=restriction fragment length polymorphism, SA=South Africa, TB=tuberculosis, TST=tuberculin skin test, USA=United States of America, WHO= World Health Organization

Table 2 Summary of selected studies in literature review of TB transmission from HIV-infected adult TB source cases

In text citation	Author, year	Setting	Population	Study Design	Outcomes	Key findings
86	Nunn, 1994	Nairobi, Kenya	HH contacts of HIV-positive and negative pulmonary TB cases	Prospective cohort	TST; active TB	▪ HIV-associated TB is not more infectious than TB occurring in HIV-negative patients
85	Carvalho, 2001	Rio de Janeiro, Brazil	Close contacts of HIV-positive and negative pulmonary TB patients	Prospective cohort	TST conversion	▪ HIV seropositivity in the TB case was associated with lower risk of TB infection among contacts (8% vs 26% of HIV-uninfected)- especially among HH contacts aged <15 years
89	Middelkoop, 2008	Cape Town, SA	School children aged 5-17 years	Cross sectional	TST	▪ Annual risk of infection was high at 4.1% and remained constant across age groups ▪ TB incidence in children remained constant from 1999 to 2005 despite increased incidence of adult TB ▪ HIV-associated TB is not a major influence on annual risk of infection in children
38	Middelkoop, 2009	Cape Town, SA	Children <15 years exposed to HIV-infected and HIV-uninfected adults with TB	Not specified (?retrospective cohort/cross sectional)	TST, TB notification	▪ Acquisition of TB infection was not associated with HIV status of the adult TB case to which the child was exposed ▪ Mean number of adult smear-positive cases per child for TB-uninfected, TB-infected and TB-diseased children were 1.0, 1.6 and 1.9 respectively
88	Huang, 2013	Lima, Peru	HH contacts of drug-sensitive TB patients	Cross-sectional	TST	▪ HH contacts of HIV-infected TB patients with CD4≤250 less likely to be infected with TB

						▪ No significant difference in risk of infection between contacts of HIV-infected TB patients with CD4>250 and HIV-uninfected TB patients

Abbreviations: CXR=chest radiograph, DNA=deoxyribonucleic acid, HIV=human immunodeficiency virus, HH=household, RFLP=restriction fragment length polymorphism, SA=South Africa, TB=tuberculosis, TST=tuberculin skin test, USA=United States of America, WHO= World Health Organization

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C. MANUSCRIPT

Tuberculosis Treatment Delay in Adults and Household Transmission to Children: a Community-based Study in a Setting with High Burden of TB and HIV

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Abstract

Background

Delayed diagnosis and treatment of pulmonary tuberculosis (TB) cases likely leads to disease progression, increased transmission and failed TB control.

Methodology

In a community-based cohort study between 2007 and 2012 children aged three months to fifteen years with household adult TB exposure were screened for TB infection (tuberculin skin test, TST; and interferon-gamma release assays, IGRA) and disease. Logistic regression analysis evaluated the effect of total delay – time from cough onset until treatment initiation - on TB infection risk in child contacts.

Results

671 children were enrolled as contacts of 290 adult TB source cases. In multivariate analysis, the odds of TST positivity increased with cough duration ≥4 weeks (odds ratio (OR) = 1.77 [95% CI 1.02-3.09] for cough <4 weeks; OR = 2.74 [95% CI = 1.39-5.40] for cough 4-12 weeks; OR = 2.39 [95% CI = 1.19-4.82] for cough >12 weeks); child's age ≥5 years (OR = 4.51, [95% CI = 2.60-7.83]); shared bedroom (OR = 2.17, [95% CI = 1.43-3.31]); ≥2 TB contacts (OR = 2.70, [95% CI = 1.35-5.42]); and household tobacco smoking (OR = 2.10, [95% CI = 1.22-3.61]). IGRA results were similar. The odds of TB disease in children increased with adult source case sputum smear and culture positivity, ≥2 household TB contacts and younger age in the child.

Conclusions

Our findings confirm the importance of reducing delay in TB diagnosis and treatment in adults, including HIV-coinfected TB patients, to reduce not only infection but also TB disease in child household contacts.

Introduction

Tuberculosis (TB) is a global public health problem, estimated to have caused disease in 9 million people, of whom 1.5 million died, in 2013.(4) South Africa has one of the highest global TB incidences with approximately 860 per 100000 population per year in 2013 and the third largest TB burden in the world, with 25% of the global burden of human immunodeficiency virus (HIV)-associated TB.(4,29)

Exposure to an infectious TB case is necessary for transmission to occur. TB control depends on interrupting transmission through rapid diagnosis and treatment initiation of infectious cases.(7,105) With increasing treatment delay, disease is likely to progress with pulmonary TB (PTB) patients developing progressive lung disease with higher sputum bacillary load, likely increasing transmission.(8,12) In South Africa transmission rates remain high and the diagnostic rate in adult TB low.(6,29) The annual risk of TB infection among young children in high-burden communities is high, mostly due to household exposure .(5,56,72,106)

Delays in the treatment of TB patients can be attributed both to the patient and the health system. The patient delay is the time from the onset of symptoms until the first contact with the health care service.(11,12) The health system delay is the time from a patient's first contact with the health care service until either a TB diagnosis is made or TB treatment is commenced.(11,12) The total delay is the time from the onset of symptoms until anti-TB treatment is initiated.(11) Significant total delays have been found between TB symptom onset and diagnosis or treatment initiation, due to both patient and health system delays.(11,12) In Cape Town, South Africa, the median duration of total delay was found to be 31 days, which was longer if patients initially consulted private health care practitioners or were HIV-infected.(13)

In North American patients, treatment delays ≥90 days were associated with a 2.34 times higher TB infection rate among close contacts.(9) In Chinese patients a dose-response relationship was observed between treatment delays over 30 days in adult smear-positive PTB patients and TB infection rates in household contacts.(10) Both studies were conducted

in low HIV prevalence settings. In South Africa, the median delay from symptom onset to starting TB treatment was 31 days, with increased delay in HIV-infected patients.(13) HIV-infected TB patients with immunosuppression are more likely to have smear-negative PTB or extrapulmonary TB (EPTB) and therefore might be less infectious, resulting in less transmission.(22,102,107)

There is limited data on the effect of treatment delay on TB transmission to child household contacts in settings with high TB and HIV prevalence. We hypothesized that there is a positive association between total treatment delay in adult TB source cases and the risk of infection in child household contacts. The primary objective of this study was to investigate the effect of the duration of total treatment delay in adult TB source cases on the risk of TB infection, measured by the Mantoux tuberculin skin test (TST), in child contacts.

Interferon-gamma release assays (IGRAs) are immune-based diagnostic tests for TB that measure the interferon-gamma levels produced by T-lymphocytes incubated with antigens that are highly specific for *Mycobacterium tuberculosis* infection. There are two IGRA tests that are commercially available – Quantiferon-TB and T-SPOT.TB. The theoretical advantage of testing for TB infection using and IGRA is the theoretical greater specificity for TB compared to the Mantoux TST, which might have a false positive result following BCG vaccination or exposure to other mycobacteria. The TST is cheaper and more widely available. Using both markers of TB infection will enable a comparison of IGRA and Mantoux TST results. Secondary analyses were conducted using interferon-gamma release assay (IGRA) to diagnose TB infection, and evaluating TB disease as the outcome.

Methods

Study Setting and Design

The study was conducted in three impoverished communities in Cape Town, South Africa from December 2007 through June 2012, with high burden of TB and HIV. The adult TB case

notification rate was 671 per 100 000, and 315 per 100 000 in children aged 0-14 years in Cape Town in 2012 (personal communication, Judy Caldwell, Cape Town City Health Department). This cross-sectional analysis was nested in a community-based cohort contact investigation study investigating the use of TST and IGRAs to detect TB infection and disease in HIV-infected and HIV-uninfected child household TB contacts.

Eligibility

Children aged three months to fifteen years with documented household TB exposure were enrolled by identifying adult source cases routinely started on TB treatment at local TB clinics. Household visits were conducted within three months of adult TB treatment initiation to enrol all eligible children living in the same household. Children were excluded with weight <5kg, haemoglobin <9mg/dl, current TB treatment or no parental and source case consent (and assent in children >7 years). Enrolment was deferred if the child had a TST during the preceding twelve weeks, a live attenuated vaccine during the preceding six weeks or an acute severe illness.

Study measures

All children were screened for TB infection through Mantoux TST and IGRAs, the Quantiferon-TB Gold (Cellistis, Carnegie, Victoria, Australia) and the T-SPOT.*TB* (Oxford Immunotec, Oxford, UK). The TST was performed by injecting two tuberculin units (purified protein derivative RT-23, Statens Serum Institute, Copenhagen, Denmark) intradermally on the volar left forearm. The largest transverse diameter of induration was read 48-72 hours later using the "ball-point" technique and callipers and measured in millimetres. TST positivity, the dependent variable, was classified as ≥10mm in HIV-uninfected children or ≥5mm in HIV-infected children.(31) Quantiferon-TB Gold and T- SPOT.*TB* results were defined as positive, negative or indeterminate using standard manufacturer assay cut-offs.(24,25) IGRA positivity was indicated by either IGRA being positive.

All children were screened for TB disease through symptom screening, clinical evaluation. Mantoux TST and IGRA. Those who had any suggestion of possible TB disease including symptoms or chest radiographic findings underwent mycobacterial culture of gastric aspirates. Chest radiographs were read by two blinded independent experts, using a

standard paediatric TB radiologic classification tool.(26) TB disease was classified as confirmed, probable, suspected, unlikely and not TB, based on international consensus guidelines.(27) A TB case was defined as any case of confirmed or probable TB. Prevalent TB disease was defined as TB disease diagnosed in child contacts within the first three months following enrolment. All children had HIV testing (Abbott Determine HIV-1/2) with positive or indeterminate test results confirmed with DNA PCR in children aged ≤18 months or ELISA in older children.

Total treatment delay was the main independent variable, measured as the total duration the source case reported from the start of coughing until TB treatment initiation. The duration of TB exposure was considered to be equivalent to the duration of cough reported by the source case. TB cases reporting no cough served as the reference category.

Children's demographic data, contact proximity (how physically close the child was to the source case within the household - i.e. whether the source case sleeps in the same bed, same room or same household) and duration of exposure to the source case were collected through interviewing the child's parent or guardian. BCG vaccination status was ascertained by documenting either a scar on physical examination or vaccination recorded in the child's road to health card (RTHC). Source cases provided data on their demographic and clinical status through study-administered questionnaire. Data on source case diagnosis, patient treatment category and treatment start date were obtained from the clinic TB register. Sputum samples were submitted in all adult source cases able to provide a sample.

Data and Statistical Analysis

Data were analysed using STATA/IC 12.0 (StataCorp LP, College Station, Texas, USA). Baseline variables were summarised using descriptive statistics. Chi-squared or Fisher's exact test were used to calculate univariate associations between categorical variables. For ordinal variables the Chi-squared test for trend was used. Logistic regression models were developed with the ordinal variable, cough duration, as the primary exposure of interest and TST positivity as the outcome. Variables associated with TST positivity in univariate analysis with a p-value <0.05 were assessed for inclusion in the multivariate model. Nested models including and excluding variables that were risk factors for TB infection were

compared sequentially one at a time using the likelihood ratio test. Additional variables that significantly improved the model, with a p-value <0.05, were included in the final model. Regression model standard errors were adjusted to account for household clustering. Further analyses were conducted for TB infection indicated by positive IGRA and for TB disease. Observations with missing data were excluded from the multivariate analysis.

Ethical approval was provided by the Human Research Ethics Committees of the Universities of Stellenbosch (Ref N05/07/129 and N08/08/207) and Case Western Reserve University (Ref 04-07-31) and additional approval by the University of Cape Town (Ref 303/2014).

Results

671 children (median age 63 months; IQR 33-107 months) were enrolled as household contacts of 290 adult TB source cases. 437 of 1092 enrolled in the larger study were excluded (241 neighbouring controls with no reported TB exposure; 180 HIV-infected children enrolled from antiretroviral therapy (ART) clinics; 16 had no TST result). All children were screened for TB, of whom 52 were identified as potential TB cases and 41 of these were diagnosed as having TB disease.

Of the child contact's adult TB source cases (median age 31.8 years; IQR 25.8-40.9), 410/633 (65%) were female and 197/605 (33%) HIV-infected, with 54/175 (31%) receiving ART at diagnosis. 567/592 (96%) source cases had PTB with or without EPTB; 364/613 (61%) were sputum smear positive, 25/314 (8%) smear negative but culture positive, 133/314 (42%) both smear and culture negative. 416/598 (70%) source cases were new TB cases and 96/598 (33%) retreatment cases. At treatment initiation 438/647 (69%) were coughing, including 4/25 (16%) with EPTB. 17/20 (85%) EPTB cases were HIV co-infected, compared to 157/554 (28%) PTB cases. Only 74/177 (42%) HIV-infected adults were smear-positive, compared to 281/399 (70%) of HIV-uninfected patients. The median cough

duration was 4-6 weeks (IQR 2-12 weeks). 62/655 (9%) children had more than one reported TB source case in addition to and concurrent with the index case who was the closest TB contact. Only 42 (6%) adult TB source cases could not produce a sputum sample.

The median age of child contacts was 5.3 years (IQR 2.8-8.9), 349/655 (53%) were female, 31/655 (5%) reported previous TB, 5/655 (1%) were HIV-infected and 571/655 (87%) had evidence of BCG vaccination. 61/655 (9%) households reported a death in the past year and 498/652 (76%) households reported at least one smoker. Unadjusted risk factors for child TST results are shown in Table 1, and IGRA results in Table 2.

Univariate TST and IGRA analysis

Increasing adult source case cough duration was associated with both TST and IGRA positivity in child household contacts, with a dose response effect. Additional source case risk factors associated with TST and IGRA positivity included PTB, sputum smear positive status, sputum culture positive status, sharing a bedroom, and having additional TB contacts. Household characteristics associated with TST positivity included tobacco smoke exposure, household death in the past year and living in a flat. Children's age ≥5 years increased the odds for TST and IGRA positivity. Although BCG vaccination appeared to be protective against infection, this was confounded by age since younger children, more likely to be TST negative, were also more likely to have the RTHC available as evidence of BCG vaccination, compared to older children.

HIV co-infection in the adult source case was associated with a 31% reduction in IGRA positivity in child contacts, but was not associated with TST positivity in child contacts. The adult TB source case being the primary caregiver was associated with IGRA positivity, but not with TST positivity. Children with weight-for-age z-score less than -2, prior TB treatment or with household tobacco smoke exposure were more likely to be IGRA positive, but these factors were not associated with TST positivity.

Multivariate TST analysis

The odds of TST positivity in child contacts was higher with cough duration of four weeks or more (OR = 1.77 [95% CI 1.02-3.09] for cough <4 weeks; OR = 2.74 [95% CI = 1.39-5.40] for cough 4-12 weeks; OR = 2.39 [95% CI = 1.19-4.82] for cough >12 weeks) after adjusting for the child's age, contact proximity, additional TB contacts, sputum smear positive status and household tobacco smoking. Associations were similar when potential mediators such as sputum smear status were excluded from the model. Source case HIV status was not an effect modifier even when results were stratified by CD4 count. The odds of TST positivity increased with age over five years (OR = 4.51, [95% CI = 2.60-7.83]), sharing a bedroom (OR = 2.17, [95% CI = 1.43-3.31]), more than one household TB contact (OR = 2.70, [95% CI = 1.35-5.42]) and with household tobacco smoking (OR = 2.10, [95% CI = 1.22-3.61]). Multivariate logistic regression results are summarised in Table 3. Complete TST analysis results are provided in Appendix C. The final multivariate model was applied to the full dataset only omitting observations with missing data in any of the variables included in the model. Complete results of the missing data analysis are provided in Appendix D. Model checking was performed and results are provided in Appendix E.

Multivariate IGRA analysis

Findings were very similar to the TST analysis, with the odds of IGRA positivity increasing with increasing duration of cough in the adult source case with a dose response effect (OR = 1.14 [95% CI 0.66-1.98] for cough <4 weeks; OR = 1.87 [95% CI = 0.99-3.56] for cough 4-12 weeks; OR = 3.23 [95% CI = 1.47-7.13] for cough >12 weeks).]). Source case HIV status was not an effect modifier even when stratified by CD4 count, despite being a significant risk factor in the univariate analysis and results were similar when the potential mediator, sputum smear status, was excluded from the model. The odds of IGRA positivity increased with age over five years (OR = 3.98, [95% CI = 2.29-6.93]), if the source case was the primary caregiver (OR = 2.14 [95% CI= 1.38-3.32]) and with household tobacco smoking (OR = 2.39, [95% CI = 1.38-4.16]). Multivariate logistic regression results are summarised in Table 5. Complete results of the IGRA analysis are provided in Appendix F.

TB disease analysis

TB disease in children was associated with adult source case duration of cough, sputum smear positive status, increasing sputum smear grade, sputum culture positive status, additional household TB contacts and was inversely related to the child's age. Results of the TB disease analysis are provided in Table 3 (and Appendix G).

Discussion

Treatment delay of four weeks or more in adults with TB is associated with an increased risk of TB infection and disease in child household contacts. Findings are consistent using different measures of TB infection, with a dose response effect demonstrated for IGRA positivity. Being HIV infected did not modify the effect of cough duration on TB transmission, implying that HIV-infected TB cases were as likely to have TB-infected children in their household despite being more likely to be sputum smear-negative. Although sputum smear positivity is a possible mediator of the effect of duration of treatment delay on the outcome TB infection in the child, results were not significantly different when sputum smear status was excluded from the final multivariate model. This implies that the duration of delay is an independent risk factor for TB transmission, regardless of sputum status.

The findings of this study, conducted in a high HIV prevalence setting, are consistent with those of Lin et al's findings that transmission to household contacts of smear-positive Chinese TB patients increased significantly with delays ≥30 days with a dose-response effect. These results differ from those of Golub's study in which only delay ≥90 days was associated with increased transmission among close contacts. These study findings suggest that active case finding is likely to reduce TB transmission by ensuring that new TB cases are diagnosed earlier thereby reducing delay and ongoing household transmission to child contacts.

Further interventions are needed to reduce both patient and health system delay, in order to reduce total delay. Increasing public awareness of the need to start TB treatment rapidly

might encourage individuals who are coughing to access healthcare earlier. Measures such as rapid diagnostic tests and improved turnaround time between submitting samples and health care providers receiving results will enable healthcare providers to diagnose TB more rapidly. Improving awareness among health care providers that reducing delay can decrease TB transmission and that TB treatment should ideally be commenced within four weeks of the onset of cough is also necessary.

Further measures to reduce TB transmission include limiting contact between children and infectious TB patients, including where possible sleeping in separate rooms. Smoking cessation programs will likely also lead to reduced TB transmission rates. Antiretroviral therapy (ART) is strongly associated with reduced TB incidence in HIV-infected adults and increased ART coverage at a population level has been shown to reduce TB incidence at a population level.

Whereas risk factors for TB infection are largely exogenous factors relating to source case infectivity, duration and intensity of exposure, risk of developing TB disease is mostly related to host factors, such as age, immunosuppression – especially HIV infection, nutritional status, BCG vaccination and time since infection.(1,108) A 1975 Canadian study found the risk of developing TB disease in both intimate and casual adult and child contacts was greater if the infection was caused by a sputum smear-positive case than a smear-negative case.(99) These results have been criticised because a 5 mm TST cut-off was used, reducing TST specificity and predictive value.(1) Whether or not source case bacteriological factors can also be risk factors for disease in contacts remains unresolved. These results indicate that the odds of TB disease in child contacts increased with adult source case sputum smear positivity and grade, sputum culture positivity and with additional TB contacts. This suggests that in addition to the traditional host risk factors, exposure factors may also increase the risk of TB disease. It is possible this might be due to more virulent mycobacterial strains causing more severe disease in adult TB cases, also resulting in infection in child contacts being more likely to progress to disease.

This was a cross sectional analysis of a larger cohort study, investigating prevalent risk factors and outcomes found at study enrolment. Comprehensive efforts were made to

recruit all TB-exposed child household contacts, with exposure characteristics documented in detail. Because the adult populations in this setting have a high prevalence of both TB and HIV, with 32.6% of the adult source cases co-infected, it was possible to assess the effect of HIV co-infection on the risk of TB transmission to child household contacts, not assessed in previous studies. An important limitation was that the exposure of interest, cough duration, depended on self-report and source case recall for measurement. This might result in nondifferential misclassification, which would tend to produce bias results towards the null and reduce the observed association. Other studies have also relied on self-reported cough duration to measure treatment delay and it has been reported that TB patients are mostly able to recall the timing of symptom onset with acceptable accuracy.(8,9,13,41)

In settings with a high HIV burden, delayed TB diagnosis and treatment initiation combined with a large number of exposed contacts result in high rates of ongoing transmission. Improved case finding with rapid treatment initiation may contribute significantly to controlling the TB epidemic.(29) These results suggest that diagnosing and initiating treatment in both HIV-infected and uninfected adult TB patients within four weeks of cough onset is likely to reduce transmission to child household contacts significantly, and also reduce children's risk of developing TB disease. In low resource settings contact tracing of adult PTB cases who are smear or culture positive will enable identification of children most at risk of TB disease and who will benefit most from isoniazid prophylactic therapy.

Conclusion

These results confirm the importance of reducing delays in diagnosing and starting treatment in adult TB patients to reduce TB infection and disease in children. Treatment should be initiated as early as possible, ideally within four weeks of cough onset. Although HIV-coinfected TB patients are often considered to be less infectious, HIV-infected TB patients were as likely to have TB-infected child household contacts.

Table 1. Univariate analysis: Adult source case, TB exposure, household and child contact risk factors for Mantoux TST positivity in child household contacts (n=655)

Variable	TST positive	TST negative	Total (percentage)	Unadjusted OR (95% CI)	P-value
Adult source case characteristics of child household contacts (n=655)					
Age of source case, in years (n=623)					
<25	67 (23.4%)	68 (20.2%)	135 (21.7%)	1	
25 to <35	106 (36.0%)	129 (38.3%)	232 (37.2%)	0.81 (0.53-1.24)	0.481
35 to <50	93 (32.5%)	110 (32.6%)	203 (32.6%)	0.86 (0.55-1.33)	
≥50	23 (8.0%)	30 (8.9%)	53 (8.5%)	0.78 (0.41-1.47)	
Gender of index case (n=633)					
Female	180 (62.1%)	230 (67.0%)	410 (64.8%)	1	
Male	110 (37.9%)	113 (33.0%)	223 (35.2%)	0.80 (0.58-1.11)	0.191
Duration of coughing, weeks (n=630)					
No cough	61 (21.1%)	131 (38.4%)	192 (30.5%)	1	
<4	91 (31.5%)	98 (28.7%)	189 (30.0%)	1.99 (1.31-3.03)	<0.001
4 to <12	91 (31.5%)	77 (22.6%)	168 (26.7%)	2.54 (1.65-3.90)	
≥12	46 (15.9%)	35 (10.3%)	81 (12.9%)	2.82 (1.65-4.82)	
HIV status (n=605)					
Negative	198 (71.2%)	210 (64.2%)	408 (67.4%)	1	
Positive	80 (28.8%)	117 (35.8%)	197 (32.6%)	0.73 (0.51-1.02)	0.066
CD4 count, if HIV-positive (n=170)					
≥ 200	40 (54.1%)	51 (53.1%)	91 (53.5%)	1	
<200	34 (46.0%)	45 (46.7%)	79 (46.5%)	1.04 (0.57-1.91)	0.904
Antiretroviral therapy, if HIV-positive (n=175)					
Yes	22 (30.1%)	32 (31.4%)	54 (30.9%)	1	
No	51 (69.9%)	70 (68.6%)	121 (69.0%)	0.94 (0.49-1.81)	0.861
Patient category (n=598)					
New	190 (69.1%)	226 (70.0%)	416 (69.6%)	1	
Retreatment after completion	6 (2.2%)	10 (3.1%)	16 (2.7%)	0.71 (0.25-2.00)	0.050
Retreatment after cure	68 (24.7%)	78 (24.2%)	146 (24.4%)	1.04 (0.71-1.51)	
Retreatment after failure	3 (1.1%)	8 (2.5%)	11 (1.8%)	0.45 (0.12-1.70)	
Retreatment after interruption	8 (2.9%)	1 (0.3%)	9 (1.5%)	9.52 (1.18-76.8)	
Disease site (n=592)					
Extrapulmonary	7 (2.5%)	18 (5.8%)	25 (4.2%)	1	
Pulmonary	272 (97.5%)	295 (94.3%)	567 (95.8%)	2.39 (0.93-6.87)	0.046
Sputum smear result (n=613)					
Negative	85 (30.4%)	148 (46.7%)	233 (39.0%)	1	
Positive	195 (69.6%)	169 (53.3%)	364 (61.0%)	2.01 (1.43-2.81)	<0.001
Sputum culture result (n=322)					
Negative	59 (36.1%)	99 (63.5%)	155 (49.8%)	1	
Positive	99 (63.9%)	57 (36.5%)	156 (50.2%)	3.07 (1.93-4.87)	<0.001
TB exposure characteristics of child contacts (n=655)					
Primary caregiver to child (n=644)	177 (60.4%)	247 (71.4%)	424 (66.4%)	1	0.003
No	116 (39.6%)	99 (28.6%)	215 (33.7%)	1.64 (1.18-2.28)	
Yes					
Contact proximity (n=637)					
Sleeps in same house	131 (44.6%)	196 (57.1%)	327 (51.3%)	1	0.005
Sleeps in same room	63 (21.4%)	51 (14.9%)	114 (17.9%)	1.85 (1.20-2.84)	
Sleeps in same bed	100 (34.0%)	96 (28.0%)	196 (30.8%)	1.56 (1.09-2.27)	
Number of additional household TB contacts (n=655)					
0	261 (86.7%)	332 (93.8%)	593 (90.5%)	1	
1	36 (12.0%)	20 (5.7%)	56 (8.6%)	2.29 (1.25-4.05)	0.009
2	4 (1.3%)	2 (0.5%)	6 (0.9%)	2.54 (0.46-14.0)	

Household characteristics of child contacts (n=655)					
Environmental tobacco smoke (n=652)					
No	54 (17.9%)	100 (28.5%)	154 (23.6%)	1	
Yes	247 (82.1%)	251 (71.5%)	498 (76.3%)	1.82 (1.25-2.65)	0.001
Type of residence (n=652)					
Main house	207 (68.8%)	248 (70.7%)	455 (69.8%)	1	
Yard house	63 (20.9%)	85 (24.2%)	148 (22.7%)	0.89 (0.61-1.29)	0.036
Flat	31 (10.3%)	18 (5.1%)	49 (7.5%)	2 06 (1.12-3.80)	
Child contact characteristics (n=655)					
Age in years (n=655)					
<2	32 (10.6%)	83 (23.5%)	115 (17.6%)	1	
2 to <5	71 (23.6%)	127 (35.9%)	198 (30.2%)	1.45 (0.88-2.39)	<0.001
≥5	198 (65.8%)	144 (40.7%)	342 (54.2%)	3.57 (2.25-5.65)	
Gender (n=655)					
Male	138 (45.8%)	168 (47.5%)	306 (46.7%)	1	
Female	164 (54.2%)	186 (52.5%)	349 (53.3%)	1.07 (0.78-1.45)	0.681
Prior TB treatment (n=655)					
No	283 (94.0%)	341 (96.3%)	624 (95.3%)	1	
Yes	18 (6.0%)	13 (3.7%)	31 (4.7%)	1.67 (0.80-3.46)	0.166
HIV status (n=655)					
Negative	298 (99.0%)	352 (99.4%)	650 (99.2%)	1	
Positive	3 (1.0%)	2 (0.6%)	5 (0.8%)	1.77 (0.29-0.67)	0.527
BCG, scar or documented (n=655)					
No	37 (10.5%)	37 (10.5%)	84 (12.8%)	1	
Yes	254 (84.4%)	317 (89.6%)	571 (87.2%)	0.63 (0.40-1.00)	0.049
Weight-for-age z-score (n=650)					
≥ -2	257 (85.4%)	319 (90.1%)	576 (87.9%)	1	
< -2	44 (14.6%)	35 (9.9%)	79 (12.1%)	1.56 (0.97-2.51)	0.065
Total	301 (46.0%)	354 (54.0%)	655 (100%)		

Table 2. Univariate analysis: Adult source case, TB exposure, household and child contact risk factors for IGRA positivity in child household contacts (n=638)

Variable	IGRA positive	IGRA negative	Total (percentage)	Unadjusted OR (95% CI)	P-value
Adult index case characteristics (n=638)					
Age of index case, in years (n=605)					
<25	71 (22.0%)	58 (20.6%)	129 (21.3%)	1	
25 to <35	122 (37.8%)	107 (37.9%)	229 (37.9%)	0.93 (0.60-1.44)	0.7275
35 to <50	106 (32.8%)	89 (31.6%)	195 (32.2%)	0.97 (0.62-1.52)	
≥50	24 (7.4%)	28 (9.9%)	52 (8.6%)	0.70 (0.86-1.73)	
Gender of index case (n=615)					
Female	206 (63.0%)	191 (66.3%)	397 (64.6%)	1	
Male	121 (37.0%)	97 (33.7%)	218 (35.5%)	0.86 (0.62-1.20)	0.3898
Duration of coughing, weeks (n=612)					
No cough	72 (22.1%)	108 (37.8%)	180 (29.4%)	1	
<4	96 (29.5%)	88 (30.8%)	184 (30.1%)	1.64 (1.08-2.48)	<0.001
4 to <12	99 (30.4%)	67 (23.4%)	166 (27.1%)	2.22 (1.44-3.41)	
≥12	59 (18.1%)	23 (8.0%)	82 (13.4%)	3.85 (2.18-6.78)	
HIV status (n=590)					
Negative	226 (72.0%)	176 (63.8%)	402 (68.1%)	1	
Positive	88 (28.0%)	100 (36.2%)	188 (31.2%)	0.69 (0.48-0.97)	0.0329
CD4 count, if HIV-positive (n=161)					
≥ 200	46 (56.8%)	42 (52.5%)	88 (54.7%)	1	
<200	35 (43.2%)	38 (47.5%)	73 (45.3%)	0.84 (0.45-1.57)	0.5845
Antiretroviral therapy, if HIV-positive (n=164)					
No	58 (72.5%)	54 (64.3%)	112 (68.3%)	1	
Yes	22 (27.5%)	30 (35.7%)	52 (31.7%)	0.68 (0.35-1.33)	0.2577
Patient category (n=581)					
New	207 (66.8%)	192 (70.9%)	399 (68.7%)	1	
Retreatment after completion	7 (2.3%)	8 (3.0%)	15 (2.6%)	0.81 (0.29-2.28)	0.0899
Retreatment after cure	84 (27.1%)	63 (23.3%)	147 (25.3%)	1.24 (0.84-1.81)	
Retreatment after failure	4 (1.3%)	7 (2.6%)	11 (1.9%)	0.53 (0.15-1.84)	
Retreatment after interruption	8 (2.6%)	1 (0.4%)	9 (1.6%)	7.42 (0.92-9.88)	
Disease site (n=574)					
Extrapulmonary	8 (2.5%)	15 (5.8%)	23 (4.0%)	1	0.044
Pulmonary	309 (97.5%)	242 (94.2%)	551 (96.0%)	2.40 (0.94-6.63)	
Sputum smear (n=581)					
Negative	94 (29.8%)	129 (48.7%)	223 (38.4%)	1	<0.001
Positive	222 (70.3%)	136 (51.3%)	358 (61.65)	2.24 (1.59-3.15)	
Sputum culture (n=302)					
Negative	59 (35.1%)	89 (66.4%)	148 (49.0%)	1	<0.001
Positive	109 (64.9%)	45 (33.6%)	154 (51.0%)	3.65 (2.26-5.90)	
TB exposure variables (n=638)					
Primary caregiver to child (n=621)					
No	203 (61.0%)	211 (73.3%)	414 (66.7%)	1	
Yes	130 (39.0%)	77 (26.7%)	207 (33.3%)	1.75 (1.25-2.47)	0.0011
Relationship to index case (n=622)					
Parent	162 (48.5%)	106 (36.7%)	268 (43.1%)	1	
Aunt or uncle	85 (25.5%)	96 (33.3%)	181 (29.1%)	0.58 (0.40-0.85)	0.0087
Other family	56 (16.8%)	45 (15.6%)	101 (16.2%)	0.81 (0.51-1.29)	
Other	31 (9.3%)	41 (14.2%)	72 (11.6%)	0.49 (0.29-0.84)	
Intensity of contact (n=620)					
Sleeps in same house	157 (46.9%)	157 (55.1%)	314 (50.7%)	1	0.1233
Sleeps in same room	68 (20.3%)	48 (16.8%)	116 (18.7%)	1.42 (0.92-2.18)	
Sleeps in same bed	110 (32.8%)	80 (28.1%)	190 (30.7%)	1.38 (0.96-1.98)	
Number of additional household TB contacts (n=637)					
0	298 (87.4%)	279 (94.3%)	577 (90.6%)	1	
1	39 (11.4%)	16 (5.4%)	55 (8.6%)	2.28 (1.25-4.18)	0.0096
2	4 (1.2%)	1 (0.3%)	5 (0.8%)	3.74 (0.42-3.71)	

Child household contact details (n=638)					
Age in years (n=638)					
<2	36 (10.5%)	69 (23.3%)	105 (16.5%)	1	
2 to <5	84 (24.6%)	111 (37.5%)	195 (30.6%)	1.45 (0.89-2.37)	<0.001
≥5	222 (64.9%)	116 (39.2%)	338 (53.0%)	3.67 (2.31-5.82)	
Gender (n=638)					
Female	142 (46.2%)	157 (45.9%)	299 (46.6%)	1	
Male	154 (53.9%)	185 (54.1%)	339 (53.4%)	1.09 (0.80-1.48)	0.6019
Prior TB treatment (n=637)					
No	315 (92.4%)	288 (97.3%)	603 (94.7%)	1	
Yes	26 (7.6%)	8 (2.7%)	34 (5.3%)	2.97 (1.32-6.67)	0.0045
HIV status (n=638)					
Negative	340 (99.4%)	294 (99.3%)	634 (99.4%)	1	
Positive	2 (0.6%)	2 (0.7%)	4 (0.6%)	0.86 (0.12-6.18)	0.8848
BCG, scar or documented (n=638)					
No	54 (15.8%)	32 (10.8%)	86 (13.5%)	1	
Yes	288 (84.2%)	264 (89.2%)	552 (86.5%)	0.65 (0.40-1.03)	0.068
Weight-for-age z-score (n=632)					
≥ -2	290 (84.8%)	269 (90.9%)	559 (87.6%)	1	
< -2	52 (15.2%)	27 (9.1%)	79 (12.4%)	1.79 (1.09-2.93)	0.021
Household characteristics (n=638)					
Household death in past year (n=637)					
No	308 (90.3%)	269 (90.9%)	577 (90.6%)	1	0.8106
Yes	33 (9.7%)	27 (9.1%)	60 (9.4%)	1.07 (0.63-1.82)	
Environmental tobacco smoke (n=634)					
No	64 (18.8%)	83 (28.3%)	147 (23.2%)	1	0.0045
Yes	277 (81.2%)	210 (71.7%)	487 (76.8%)	1.71 (1.18-2.48)	
Type of residence (n=635)					
Main house	235 (68.7%)	206 (70.3%)	441 (69.5%)	1	0.0580
Yard house	73 (21.4%)	72 (24.6%)	145 (22.8%)	0.89 (0.61-1.29)	
Flat	34 (9.9%)	15 (5.1%)	49 (7.7%)	1.99 (1.05-3.75)	
Total	342 (53.6%)	296 (46.4%)	638 (100%)		

Table 3 Multivariate analysis[1]: risk factors for TB infection, as indicated by Mantoux TST positivity or IGRA positivity, in child household TB contacts adjusted for household clustering with sputum smear status as a potential mediator:

	Mantoux TST (n=571)			IGRA (n=556)		
Variable	Adjusted OR	95% C.I.	P-value	Adjusted OR	95% C.I.	P-value
Duration of cough, (weeks)						
No cough	1			1		
<4	1.77	1.02-3.09	0.044	1.17	0.68-2.03	0.565
4-12	2.74	1.39-5.40	0.004	1.91	1.00-3.65	0.049
>12	2.39	1.19-4.82	0.014	3.01	1.39-6.51	0.005
Age of child contact, (years)						
<2	1			1		
2-5	1.68	0.97-2.91	0.064	1.53	0.90-2.61	0.118
>5	4.51	2.60-7.83	<0.001	4.35	2.55-7.42	<0.001
Contact proximity[2]						
Same house	1			1		
Same room	2.17	1.43-3.31	<0.001	1.75	1.15-2.65	0.009
Additional household TB contacts[21]						
0	1			1		
≥1	2.70	1.35-5.42	0.005	1.90	0.88-4.09	0.100
Household tobacco smoking						
No	1			1		
Yes	2.10	1.22-3.61	0.008	2.09	1.20-3.65	0.009
Sputum smear status						
Negative	1			1		
Positive	1.92	1.16-3.18	0.011	2.36	1.44-3.88	0.001

[1] Multivariate analysis performed using 607 observations with complete data for variables included in model

[2] Categories collapsed in regression analysis

Table 4. Risk factors for prevalent TB disease in child household contacts (n=668)

Variable	TB disease	No TB disease	Total (percentage)	Unadjusted OR (95% CI)	P-value
Adult index case characteristics (n=635)					
Age of index case, in years (n=635)	12 (28.6%)	123 (20.7%)	135 (21.3%)	1	0.2887
<25	14 (33.3%)	226 (38.1%)	240 (37.8%)	0.63 (0.28-1.42)	
25 to <35	10 (23.8%)	195 (32.9%)	205 (32.3%)	0.53 (0.22-1.25)	
35 to <50	6 (14.3%)	49 (8.3%)	55 (8.7%)	1.26 (0.45-3.53)	
≥50					
Gender of index case (n=645)					
Male	14 (33.3%)	213 (35.3%)	227 (35.2%)	1	0.7932
Female	28 (66.7%)	390 (64.7%)	418 (64.8%)	1.09 (0.56-2.12)	
Currently coughing (n=645)					
No	12 (28.6%)	185 (30.7%)	197 (30.5%)	1	0.7729
Yes	30 (71.4%)	418 (69.3%)	448 (69.5%)	1.11 (0.55-2.21)	
Duration of coughing, weeks (n=642)					
No cough	12 (28.6%)	182 (30.3%)	194 (30.2%)	1	0.4507
<4	9 (21.4%)	185 (30.8%)	194 (30.2%)	0.74 (0.30-1.79)	
4 to <12	15 (35.7%)	156 (26.0%)	171 (26.6%)	1.46 (0.66-3.21)	
≥12	6 (14.3%)	77 (12.8%)	83 (12.9%)	1.18 (0.43-3.26)	
HIV status (n=617)					
Negative	30 (75.0%)	386 (66.9%)	416 (67.4%)	1	0.2799
Positive	10 (25.0%)	191 (33.1%)	201 (32.6%)	0.67 (0.32-1.41)	
CD4 count, if HIV-positive (n=173)	4 (44.4%)	90 (54.9%)	94 (54.3%)	1	0.5416
≥ 200	5 (55.6%)	74 (45.1%)	79 (45.7%)	1.52 (0.39-5.87)	
<200					
Antiretroviral therapy, if HIV-positive (n=179)					
No	4 (44.4%)	118 (69.4%)	122 (68.2%)	1	0.1320
Yes	5 (55.6%)	52 (30.6%)	57 (31.8%)	2.84 (0.73-10.99)	
Patient category (n=609)					
New	26 (63.4%)	396 (69.7%)	422 (69.3%)	1	0.1713
Retreatment after completion	3 (7.3%)	13 (2.3%)	16 (2.6%)	3.51 (0.94-13.11)	
Retreatment after cure	10 (24.4%)	141 (24.8%)	151 (24.8%)	1.08 (0.51-2.30)	
Retreatment after failure	0 (0.0%)	11 (1.9%)	11 (1.8%)	-	
Retreatment after interruption	2 (4.9%)	7 (1.2%)	9 (1.5%)	4.35 (0.86-22.0)	
Disease site (n=574)					
Extrapulmonary	0 (0.0%)	25 (4.4%)	25 (4.1%)	-	-
Pulmonary	41 (100.0%)	538 (95.6%)	579 (95.9%)		
TB exposure variables (n=655)					
Hours per day of contact (n=663)					
<4	4 (9.3%)	110 (17.7%)	114 (17.2%)	1	0.4266
4-8	16 (37.2%)	224 (36.1%)	240 (36.2%)	1.96 (0.64-6.02)	
9-12	19 (44.2%)	249 (40.2%)	268 (40.4%)	2.10 (0.70-6.31)	
≥12	4 (9.3%)	37 (6.0%)	41 (6.2%)	2.97 (0.71-12.49)	
Sputum smear result (n=609)					
Negative	7 (17.5%)	229 (40.3%)	236 (38.8%)	1	0.0026
Positive	33 (82.5%)	340 (59.8%)	373 (61.3%)	3.18 (1.38-7.30)	
Sputum smear grade (n=561)					
Negative	5 (13.5%)	211 (40.3%)	216 (38.5%)	1	0.0098
Scanty	2 (5.4%)	27 (5.2%)	29 (5.2%)	3.08 (0.57-16.67)	
1+	8 (21.6%)	61 (11.6%)	69 (12.3%)	5.84 (1.84-18.53)	
2+	7 (18.9%)	59 (11.3%)	66 (11.8%)	4.94 (1.51-16.12)	
3+	15 (40.5%)	166 (31.7%)	181 (32.3%)	3.83 (1.36-10.75)	
Sputum culture result (n=315)					
Negative	3 (16.7%)	154 (51.9%)	157 (49.8%)	1	0.0025
Positive	15 (83.3%)	143 (48.2%)	158 (50.2%)	5.38 (1.53-18.99)	
Primary caregiver to child (n=651)	27 (64.3%)	404 (66.3%)	431 (66.2%)	1.09 (0.56-2.10)	0.7865
No	15 (35.7%)	205 (33.7%)	220 (33.8%)		
Yes					
Relationship to index case (n=652)	19 (45.2%)	261 (42.8%)	280 (42.9%)	1	0.7508
Parent	9 (21.4%)	176 (28.9%)	185 (28.4%)	0.70 (0.31-1.59)	
Aunt or uncle	8 (19.1%)	100 (16.4%)	108 (16.6%)	1.10 (0.47-2.59)	

Other family	6 (14.3%)	73 (12.0%)	79 (12.1%)	1.13 (0.43-2.93)	
Other					
Contact score, median (IQR) (n=668)	6 (5-8)	5 (4-7)	5 (4-7)	1.24 (1.05-1.46)	0.010
Intensity of contact (n=649)					
Sleeps in same house	21 (48.8%)	308 (50.8%)	329 (50.7%)	1	0.5409
Sleeps in same room	6 (14.0%)	115 (19.0%)	121 (18.6%)	0.77 (0.30-1.94)	
Sleeps in same bed	16 (37.2%)	183 (30.2%)	199 (30.7%)	1.28 (0.65-2.52)	
Number of additional household TB contacts (n=661)					
0	34 (79.1%)	570 (91.4%)	604 (90.6%)	1	0.0095
1	9 (20.9%)	48 (7.7%)	57 (8.6%)	3.14 (1.42-6.94)	
2	0 (0.0%)	6 (1.0%)	6 (0.9%)	-	
Child household contact details (n=655)					
Age in years (n=668)					
<2	15 (34.9%)	100 (16.0%)	115 (17.2%)	1	<0.001
2 to <5	19 (44.2%)	183 (29.3%)	202 (30.2%)	0.69 (0.34-1.42)	
≥5	9 (20.9%)	342 (54.7%)	351 (52.5%)	0.18 (0.07-0.41)	
Gender (n=668)					
Female	23 (53.5%)	333 (53.3%)	356 (53.3%)	1	0.9879
Male	20 (46.5%)	292 (46.7%)	312 (46.7%)	1.01 (0.54-1.87)	
Ethnicity (n=638)					
African/Black	5 (11.6%)	118 (18.9%)	123 (18.4%)	1	0.2076
Mixed race	38 (88.4%)	505 (80.8%)	543 (81.3%)	1.78 (0.68-4.61)	
Indian	0 (0.0%)	1 (0.2%)	1 (0.2%)	-	
White	0 (0.0%)	1 (0.2%)	1 (0.2%)	-	
Prior TB treatment (n=667)					
No	40 (93.0%)	592 (94.9%)	632 (94.8%)	1	0.6146
Yes	3 (7.0%)	32 (5.1%)	35 (5.3%)	1.39 (0.41-4.73)	
HIV status (n=638)					
Negative	42 (97.7%)	621 (99.4%)	663 (99.3%)	1	0.3111
Positive	1 (2.3%)	4 (0.6%)	5 (0.8%)	3.70 (0.40-33.81)	
BCG, scar or documented (n=668)	3 (7.0%)	86 (13.8%)	89 (13.3%)	1	0.216
No	40 (93.0%)	539 (86.2%)	579 (86.7%)	2.13 (0.64-7.03)	
Yes					
Weight-for-age z-score (n=662)					
More than -1	24 (55.8%)	393 (63.5%)	417 (63.0%)	1	0.3765
-1 to -2	11. (25.6%)	156 (25.2%)	167 (25.2%)	1.15 (0.55-2.41)	
Less than -2	8 (18.6%)	70 (11.3%)	78 (11.8%)	1.87 (0.81-4.33)	
Length-for-age z-score (n=661)					
More than -1	9 (20.9%)	203 (32.9%)	212 (32.1%)	1	0.202
-1 to -2	16 (37.2%)	209 (33.8%)	225 (34.0%)	1.73 (0.75-4.00)	
Less than -2	18 (41.9%)	206 (33.3%)	224 (33.9%)		
Weight-for-length z-score (n=458)	35 (83.3%)	391 (89.1%)	426 (88.6%)	1	0.5632
More than -1	6 (14.3%)	40 (9.1%)	46 (9.6%)	1.68 (0.66-4.23)	
-1 to -2	1 (2.4%)	8 (1.8%)	9 (1.9%)	1.40 (0.17-11.49)	
Less than -2					
Household characteristics (n=655)					
Household death in past year (n=667)					
No	41 (95.4%)	563 (90.2%)	604 (90.6%)	1	0.2245
Yes	2 (4.7%)	61 (9.8%)	63 (9.5%)	0.45 (0.11-1.91)	
Environmental tobacco smoke (n=664)					
No	6 (14.0%)	152 (24.5%)	158 (23.8%)	1	0.1240
Yes	37 (86.1%)	469 (75.5%)	506 (76.2%)	2.00 (0.83-4.83)	
Type of residence (n=635)					
Main house	27 (62.8%)	437 (70.3%)	464 (69.8%)	1	0.4999
Yard house	11 (25.6%)	140 (22.5%)	151 (22.7%)	1.27 (0.62-2.63)	
Flat	5 (11.6%)	45 (7.2%)	50 (7.5%)	1.80 (0.66-4.90)	
Housing structure (n=661)					
Tin shack	5 (11.9%)	95 (15.4%)	100 (15.1%)	1	0.2101
Prefab house	1 (2.4%)	4 (0.7%)	5 (0.8%)	4.75 (0.44-50.74)	
Brick house	24 (57.1%)	415 (67.0%)	439 (66.4%)	1.10 (0.41-2.95)	
Wendy house	12 (28.6%)	105 (17.0%)	117 (17.7%)	2.17 (0.74-6.39)	

Household electricity (n=635)					
No	1 (2.3%)	38 (6.1%)	39 (5.9%)	1	0.2512
Yes	42 (97.7%)	584 (93.9%)	626 (94.1%)	2.73 (0.37-20.40)	
Total	43 (6.4%)	625 (93.6%)	668 (100%)		

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D. APPENDICES

Appendix A. Ethics Committee Approvals

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

Room E52-24 Old Main Building
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Observatory 7925
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Website: www.health.uct.ac.za/research/humanethics/forms

12 May 2014

HREC REF: 303/2014

Prof L Myer
Public Health & Family Medicine
Falmouth Building

Dear Prof Myer

PROJECT TITLE: TUBERCULOSIS TREATMENT DELAY IN ADULTS AND HOUSEHOLD TRANSMISSION TO CHILDREN: A_COMMUNITY-BASED STUDY IN a SETTING WITH HIGH BURDEN OF TUBERCULOSIS AND HIV (Masters Candidate – Dr Penelope Rose)

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

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

Approval is granted for one year until the 30th May 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

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

We acknowledge that the Masters student, Dr Penelope Rose is also involved in this study.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

pp T Burgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 303/2014

S

Ethics Letter

18-Apr-2013

Ethics Reference #: N05/07/129
Title: The utility of inferon-gamma release assays in TB-HIV co-infected children (NUFU study).

Dear Professor Anneke Hesseling,

At a meeting of the Health Research Ethics Committee that was held on 17 April 2013, the progress report for the abovementioned project has been approved and the study has been granted an extension for a period of one year from this date.

Please remember to submit progress reports in good time for annual renewal in the standard HREC format.

Approval Date: 17 April 2013 Expiry Date: 17 April 2014

If you have any queries or need further help, please contact the REC Office 0219389207.

Sincerely,

REC Coordinator
Mertrude Davids
Health Research Ethics Committee 2

Verwysing
Reference
Isalathiso 2007/RP48

Navrae
Enquiries
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Fax: **+27 21 9389719**

Dear Dr Hasseling

The Utility of Interferon-Gamma Release Assays in TB-HIV co-infected Children

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that your research proposal has been approved for Site B Clinic (CHC and Ubuntu TB/HIV clinics), Khayelitsha. Please contact Dr Virginia Zweigenthal at vzweigen@pgwc.gov.za or 021 460 9257 to assist you with accessing the site and ensuring that the site is adequately prepared for your study.

Please inform us in writing when the research report will be available and quote the reference number above.

We look forward to hearing from you.

Yours sincerely

DR J CUPIDO
DEPUTY-DIRECTOR GENERAL
DISTRICT HEALTH SERVICES AND PROGRAMMES
DATE:

CC: Dr KC Cloete: CD: MDHS

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Appendix B. Author Instructions for Manuscript Submission

Thorax

Instructions for Authors

Editorial policy

Thorax seeks to publish significant advances in scientific understanding which are likely to impact on clinical practice. Articles concerning clinical topics, critical care, and those on basic mechanisms with application to clinical material, will be welcomed. We aim to cover all areas of respiratory medicine (epidemiology, paediatrics, immunology, sleep, pharmacology, pathology, surgery and critical care) through publishing original papers, editorials, reviews, audit/research/guideline/sytematic review updates, case based discussions and images. The priorities are originality and excellence. All submissions are subject to peer review. All papers that are potentially acceptable undergo statistical analysis.

Submissions to Thorax if favorably peer reviewed, are discussed at the weekly editorial committee prior to decision. We aim to ensure a fair and independent peer review system and to publish articles which follow the highest ethical standards concerning research conduct.

How we handle papers

Incoming manuscripts are checked by the staff, and if they conform to the Journal style, are assigned to the Editors in Chief. Note please: we are toughening up, and if your manuscript is too long or has too many references it will be returned unrefereed for you to edit; terseness not Tolstoy, please. Manuscripts that are reviewed positively are discussed by the Gang of Four at the weekly Hanging Committee. After Hanging Committee discussion, the decision may be to reject, or, if there are any numerical data at all in the manuscript, a statistical review is obtained, and a final decision taken when this review has been received. We have the statistical reviews in series not parallel because of cost and scarcity of precious statistical time. If your manuscript is rejected, of course you may appeal, and the appeal will be handled by whichever one of the EICs did not handle the original manuscript unless there is a conflict of interest. But please, only appeal if you feel there are significant errors of fact made during the initial process, and point them out to us. Editorial priority (aka whims) is inevitably arbitrary and does change as new manuscripts are accepted. All authors (including ourselves) allocate the highest priority to their own work, and feel editors who disagree were not merely conceived out of wedlock but have an IQ beginning with a minus sign. This assessment may be true, but expressing it will not get a decision over-turned.

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During submission you will be asked whether or not you agree to pay for the colour print publication of your colour images. This service is available to any author publishing within this journal for a fee of £250 per article. Authors can elect to publish online in colour and black and white in print, in which case the appropriate selection should be made upon submission.

What you can expect from us

We are getting typically between 100 and 180 manuscripts a month, and many tough priority decisions have to be made, and acceptance rate is just over 10% - sorry! The editorial process has been speeding up. We hope to get our first decision to you within 30 days. However, this is not always possible particularly around holiday periods.

The word count excludes the title page, abstract, tables, acknowledgements and contributions and the references. If you are not a native English speaker there is a professional editing service available.

Original Research

Full papers should follow the basic structure of abstract, introduction, methods, results, discussion, references, and tables and figures as appropriate. They should not normally exceed 250 words for the abstract, 3000 words for the content and include no more than 35 references. There is an online data repository for extra information, tables, figures and appendices. Please include an initial one sentence response to each of the following questions: what is the key question; what is the bottom line; and why read on? Failure to do this will result in the manuscript being returned unrefereed, and the answers to these questions will carry weight in the review process. These will be published as a text box at the beginning of the article

Word count: up to 3000 words
Structured abstract: up to 250 words
Key questions: One sentence response to each of the following questions: what is the key question; what is the bottom line; and why read on?
Tables/illustrations: Images submitted should be those which uniquely display the data and not repetition of information available either in the text or as a table. Figures are not limited, but must be thoroughly justified
References: up to 35

Case based discussions

The case report on which the discussion will be based should not exceed 1500 words with one table or illustration, and up to 5 references; in most cases, we expect the report to be significantly shorter. An abstract is not nescessary. It might be easier to reference guideline statements rather than source papers in the reference list. We will consider more references if authors can show significant contributions and/or give compelling or specific reasons. We do ask that authors indicate that they have obtained patient consent. We are interested in cases that raise interesting diagnostic or management issues. All readers will recall unusual cases that have made a deep impact on them or taught them an important lesson. Often they will not be our best cases - we learn most from our mistakes. Don't be afraid to share the message with others; these are just the sort of cases we are interested in. More traditional case reports of cases that offer important insights into pathogenesis (i.e. adverse or unexpected beneficial effects of new treatments, new and unlikely associations) will be considered but only as a letter (see below).

We prefer the following formats for case based discussions; all have stood the test of time:

1. A dialogue between a junior doctor(s) and an experienced clinician. All participants should be authors. Pertinent aspects of the history, examination and investigations should be presented by the junior clinician in chronological order such that it mimics the actual clinical presentations. After every presentation the experienced clinician will discuss likely diagnosis and key missing information. This information will then be presented and the case should unravel naturally in much the same way it did in reality, ideally with one or two important take home messages.

2. A response to a referral note (Dear Chest Clinic) which clearly sets out the diagnostic and management approach. Most will be commissioned. We are interested in expert views on optimum management of that case. We would like you to outline what you regard as best management in a reasonably sized and equipped District General Hospital. Don't be afraid to ask for tests or treatments that are not readily available but do be prepared to justify clearly why you regard this test or treatment as essential.

3. Lesson of the month. A description of two or three cases from which an important lesson is learnt.

Ideally the key investigation could be included as an image. The quality of the image must be at least 600dpi and in TIFF, JPEG, GIF, Powerpoint or EPS format.

Word count: up to 1500 words
Structured abstract: not required
Tables/illustrations: up to 1
References: up to 5

Pulmonary Puzzles

This category is for unusual cases that make an educational point. Since the aim of these articles is to stimulate the reader to think about the case, the title should be ambiguous and not give away the final diagnosis immediately.

Pulmonary Puzzles will appear in two parts and should be submitted via the website identified as such. The first part should contain a very brief clinical introduction to a case (maximum 250 words) followed by an image and a question designed to stimulate the reader to think about what the image shows. The legend should not indicate the diagnosis but should simply describe the nature of the image. The second part (maximum 250 words) will appear later in the issue and should contain the answer. The answer should include a brief description of the key diagnostic features of the image, the outcome, and a teaching point. Pulmonary Puzzles will not include more than 5 references. The quality of the image must be at least 600dpi and in TIFF, JPEG, GIF, Powerpoint or EPS format. We do ask that authors indicate that they have obtained patient consent.

Images in Thorax

Our Images in thorax section consists of a case report of 100 words, a few learning points, a maximum of two figures, and two references. The images can be radiological, pathological or both. Thorax will cover the cost of printing pathological images in colour. We recommend an author limit of 5, but we can consider more if authors can show significant contributions and/or give compelling or specific reasons. We do ask that authors indicate that they have obtained patient consent.

Journal club

For information on being an author for Journal club please contact Dr Jennifer Quint (jennifer.quint@lshtm.ac.uk).

Opinion

This is an unstructured section allowing contributors to highlight issues for debate. These could be in any relevant subject area. These articles will be commissioned but we are happy to consider unsolicited articles submitted via ScholarOne. Please aim for 1500 words and less than 15 references. An abstract is not neccesary. We are particularly interested in hearing from colleagues who are retired or nearing retirement. Is there anything you would like to get off your chest? Manuscripts that make an important contribution to controversial areas of practice or health policy or legitimately question established dogma are particularly welcome. Please feel free to discuss your proposal with the Editors in advance of submission.

Word count: up to 1500 words
Tables/illustrations: no specific limit
References: up to 15

Basic science for the Chest Physician

These brief reviews of important recent advances in basic science relevant to the Chest Physician will be solicited but we will consider unsolicited articles submitted via ScholarOne. We would like 1000-1500 words, less than 5 references and an excellent figure. The goals of the article should be to: explain the science to the clinician, assuming no prior knowledge; and highlight the key clinically important findings.

Word count: up to 1500 words
Tables/illustrations: up to 1
References: up to 5

Audit, research and guideline updates

We are happy to consider important audit findings with national or international implications, brief descriptions of the protocol of forthcoming important research projects and brief updates to guideline documents. Summaries of important systematic reviews can be submitted as Cochrane's Corner manuscripts. We would like a breif abstract, up to 1500 words, 5 references and either a figure or table.

Word count: up to 1500 words
Unstructured abstract: up to 100 words
Tables/illustrations: up to 1
References: up to 5

Reviews

Although usually commissioned, we do occasionally accept unsolicited review articles on important and topical subjects with a particular focus on recent advances. Before submitting a review, we ask that you send the editors a brief outline (no more than 500 words) indicating the importance and novelty of the subject, and why you are qualified to write it. A one-page CV highlighting relevant work in the field from each proposed author will need to be attached. These will be peer reviewed. An invitation to submit will in no way guarantee acceptance. We ask reviewers to ensure that they include up-to-date and relevant references, including papers published by Thorax. Reviews should not normally exceed 4000 words and 75 references.

Word count: up to 4000 words
Structured abstract: up to 500 words
Tables/illustrations: no specific limit
References: up to 75

Letter to the Editor (original research and case reports)

Research letters in Thorax are welcome and should be submitted via ScholarOne. These should not normally exceed 500 words, with a brief abstract, one table or figure and no more than 5 references. Any additional submission information including methodology,

data and tables can be placed in the on-line repository facility on the Thorax website. We prefer case reports in the Case-based discussion format (see above). We publish very occasional case reports in the research letter format but these cases must be exceptional and illuminating on mechanisms of disease rather than rare or obscure.

Correspondence

Letters in response to articles published in Thorax are welcome and should be submitted via ScholarOne. Correspondence must reach us by the end of the following calendar month (eg. by the end of July, for letters referring to articles in the June print issue) and be a maximum of 400 words, with one figure or table and no more than 5 references. As for research letters, authors may also make use of the on-line repository facility for supplemental data.

Editorial

Editorials are normally commissioned and relate to original research papers. The aim is to critically discuss the paper, highlight important issues and put them into perspective and identify areas where more information is needed. The Editors may occasionally accept uncommissioned articles of this type, but it is suggested this is discussed with the Editors prior to submission. The word count should be up to 1500 words and 20 references.

Word count: up to 1500
Structured abstract: not required
Tables/illustrations: up to 2
References: up to 20

HOT off the Breath

The editors welcome and will fast track articles on really hot topics. These should be discussed in advance with the Editors in Chief. They will be peer-reviewed, and clear justification as to why the article should not go through the normal processes should be given.

Supplements

BMJ journals are willing to consider publishing supplements to regular issues. Supplement proposals may be made at the request of:

1. The journal editor, an editorial board member or a learned society may wish to organise a meeting, sponsorship may be sought and the proceedings published as a supplement.
2. The journal editor, editorial board member or learned society may wish to commission a supplement on a particular theme or topic. Again, sponsorship may be sought.

3. BMJ itself may have proposals for supplements where sponsorship may be necessary.
4. A sponsoring organisation, often a pharmaceutical company or a charitable foundation, that wishes to arrange a meeting, the proceedings of which will be published as a supplement.

In all cases, it is vital that the journal's integrity, independence and academic reputation is not compromised in any way.

When contacting us regarding a potential supplement, please include as much of the information below as possible.

- Journal in which you would like the supplement published
- Title of supplement and/or meeting on which it is based
- Date of meeting on which it is based
- Proposed table of contents with provisional article titles and proposed authors
- An indication of whether authors have agreed to participate
- Sponsor information including any relevant deadlines
- An indication of the expected length of each paper Guest Editor proposals if appropriate

For further information on criteria that must be fulfilled, download the supplements guidelines (PDF).

Plagiarism detection

BMJ is a member of CrossCheck by CrossRef and iThenticate. iThenticate is a plagiarism screening service that verifies the originality of content submitted before publication. iThenticate checks submissions against millions of published research papers, and billions of web content. Authors, researchers and freelancers can also use iThenticate to screen their work before submission by visiting www.ithenticate.com.

Appendix C. Additional TST analysis results: univariate and multivariate with analysis of possible mediators

Complete results of the TST univariate and multivariate analyses are provided in Tables 7 and 8 respectively below. Further to the results already presented in the main body of the manuscript, in univariate analysis, adult source case current cough (OR=2.25 [95% CI = 1.58-3.21]) was strongly associated with TST positivity in the child household contact. There was a borderline association between patient category (new or retreatment after completion, cure, failure or interruption) and TST positivity, but the numbers in most categories were small. There was no association with the number of hours per day of contact with the adult source case, child's ethnicity, type of housing structure or household electrification. Although the sputum smear grade was associated with TST positivity, there was no clear dose response effect. The weight-for-age z-score was borderline associated with TST positivity, but there was no association with either length-for-age or weight-for-length z-score.

The contact score was strongly predictive of TST positivity (OR=1.29 [95% CI = 1.18-1.40]). This is a score which quantifies the extent of exposure to TB and is based on ten questions, with the score ranging from zero for no TB contact to a maximum of ten.(21) For each one point increase in score the odds of TST positivity increased by 29%.

In univariate analysis, having evidence of BCG vaccination was associated with a reduced risk of TB infection, but this association was confounded by the child's age as demonstrated in Table 6 below. Younger children are more likely to have their RTHC present when the child is seen by a health care provider, as evidenced by 115 (99.1%) of children aged <2 years and 202 (97.5%) of children aged 2-5 years having evidence of BCG vaccination, compared to only 268 (76.4%) of children >5 years. Because increasing age is associated with increased risk of TB exposure and increasing risk of TB infection, the apparent protective effect of BCG vaccination that is found is as a result of confounding by the child's age.

Table 5. BCG vaccination status by child's age

BCG vaccination status	Child's age <2 years	2-5 years	>5 years	Total
Evidence of vaccination	114 (99.1%)	197 (97.5%)	268 (76.4%)	579 (86.7%)
No evidence of vaccination	1 (0.9%)	5 (2.5%)	83 (23.7%)	89 (13.3%)
Total	115 (100%)	202 (100%)	351 (100%)	668 (100%)

The final multivariate model is almost unchanged when sputum smear status, a possible mediator of the effect of delay on TB infection, is removed from the model. This suggests that the effect of delay is only partly mediated by sputum positivity and that treatment delay is also an independent risk factor for TB transmission. In both models there is increased TST positivity when the adult source case has a cough of less than four weeks duration compared to not having a cough, with increasing TST positivity with a cough duration greater than four weeks.

Table 6. Univariate analysis: risk factors for Mantoux tuberculin skin test (TST) positivity in child household contacts (n=655)

Variable	Mantoux TST positive	Mantoux TST negative	Total (percentage)	Unadjusted OR (95% CI)	P-value
Adult source case characteristics of child household contacts (n=655)					
Age of source case, in years (n=623)					
<25	67 (23.4%)	68 (20.2%)	135 (21.7%)	1	0.481
25 to <35	106 (36.0%)	129 (38.3%)	232 (37.2%)	0.81 (0.53-1.24)	
35 to <50	93 (32.5%)	110 (32.6%)	203 (32.6%)	0.86 (0.55-1.33)	
≥50	23 (8.0%)	30 (8.9%)	53 (8.5%)	0.78 (0.41-1.47)	
Gender of index case (n=633)					
Female	180 (62.1%)	230 (67.0%)	410 (64.8%)	1	0.191
Male	110 (37.9%)	113 (33.0%)	223 (35.2%)	0.80 (0.58-1.11)	
Currently coughing (n=647)					
No	63 (21.7%)	132 (38.5%)	195 (30.8%)	1	<0.001
Yes	227 (78.3%)	211 (61.5%)	438 (69.2%)	2.25 (1.58-3.21)	
Duration of coughing, weeks (n=630)	61 (21.1%)	131 (38.4%)	192 (30.5%)	1	<0.001
No cough	91 (31.5%)	98 (28.7%)	189 (30.0%)	1.99 (1.31-3.03)	
<4	91 (31.5%)	77 (22.6%)	168 (26.7%)	2.54 (1.65-3.90)	
4 to <12	46 (15.9%)	35 (10.3%)	81 (12.9%)	2.82 (1.65-4.82)	
≥12					
HIV status (n=605)					
Negative	198 (71.2%)	210 (64.2%)	408 (67.4%)	1	0.066
Positive	80 (28.8%)	117 (35.8%)	197 (32.6%)	0.73 (0.51-1.02)	
CD4 count, if HIV-positive (n=170)	40 (54.1%)	51 (53.1%)	91 (53.5%)	1	0.904
≥ 200	34 (46.0%)	45 (46.7%)	79 (46.5%)	1.04 (0.57-1.91)	
<200					
Antiretroviral therapy, if HIV-positive (n=175)					
Yes	22 (30.1%)	32 (31.4%)	54 (30.9%)	1	0.861
No	51 (69.9%)	70 (68.6%)	121 (69.0%)	0.94 (0.49-1.81)	
Patient category (n=598)					
New	190 (69.1%)	226 (70.0%)	416 (69.6%)	1	0.050
Retreatment after	6 (2.2%)	10 (3.1%)	16 (2.7%)	0.71 (0.25-2.00)	
completion	68 (24.7%)	78 (24.2%)	146 (24.4%)	1.04 (0.71-1.51)	
Retreatment after cure	3 (1.1%)	8 (2.5%)	11 (1.8%)	0.45 (0.12-1.70)	
Retreatment after failure	8 (2.9%)	1 (0.3%)	9 (1.5%)	9.52 (1.18-76.8)	
Retreatment after interruption					
Disease site (n=592)					
Extrapulmonary	7 (2.5%)	18 (5.8%)	25 (4.2%)	1	0.046
Pulmonary	272 (97.5%)	295 (94.3%)	567 (95.8%)	2.39 (0.93-6.87)	
TB exposure characteristics of child contacts (n=655)					
Hours per day of contact (n=651)	46 (15.3%)	68 (19.4%)	114 (17.5%)	1	0.274
<4	104 (34.7%)	132 (37.6%)	236 (36.3%)	1.16 (0.74-1.83)	
4-8	128 (42.7%)	132 (37.6%)	260 (36.9%)	1.43 (0.92-2.24)	
9-12	22 (7.3%)	19 (5.4%)	41 (6.3%)	1.71 (0.83-3.51)	
≥12					
Sputum smear result (n=613)					
Positive	195 (69.6%)	169 (53.3%)	364 (61.0%)	2.01	<0.001
Negative	85 (30.4%)	148 (46.7%)	233 (39.0%)	(1.43-2.81)	
Sputum smear grade (n=574)					
Negative	85 (32.3%)	130 (45.1%)	215 (39.0%)	1	0.021
Scanty	15 (5.7%)	14 (4.9%)	29 (5.3%)	1.64 (0.75-3.57)	
1+	40 (15.2%)	26 (9.0%)	66 (12.0%)	2.35 (1.34-4.14)	
2+	31 (11.8%)	31 (10.8%)	62 (11.3%)	1.53 (0.87-2.70)	
3+	92 (35.0%)	87 (30.2%)	179 (32.5%)	1.62 (1.08-2.41)	
Sputum culture result (n=322)					
Negative	59 (36.1%)	99 (63.5%)	155 (49.8%)	1	<0.001
Positive	99 (63.9%)	57 (36.5%)	156 (50.2%)	3.07 (1.93-4.87)	
Primary caregiver to child (n=644)	I 177 (60.4%)	247 (71.4%)	424 (66.4%)	1	0.003
No	116 (39.6%)	99 (28.6%)	215 (33.7%)	1.64 (1.18-2.28)	
Yes					

Relationship to index case (n=640)	146 (49.7%)	127 (36.7%)	273 (42.7%)	1	<0.001
Parent	67 (22.8%)	116 (33.5%)	183 (28.6%)	0.50 (0.34-0.74)	
Aunt or uncle	54 (18.4%)	51 (14.7%)	105 (16.4%)	0.92 (0.59-1.45)	
Other family	27 (9.2%)	52 (15.0%)	79 (12.3%)	0.45 (0.27-0.76)	
Other					
Contact score, median (IQR) (n=655)	6 (5-7)	5 (4-6)	5 (4-7)	1.287 (1.18-1.40)	<0.001
Contact proximity (n=637)					
Sleeps in same house	131 (44.6%)	196 (57.1%)	327 (51.3%)	1	0.005
Sleeps in same room	63 (21.4%)	51 (14.9%)	114 (17.9%)	1.85 (1.20-2.84)	
Sleeps in same bed	100 (34.0%)	96 (28.0%)	196 (30.8%)	1.56 (1.09-2.27)	
Number of additional household TB contacts (n=655)					
0	261 (86.7%)	332 (93.8%)	593 (90.5%)	1	0.009
1	36 (12.0%)	20 (5.7%)	56 (8.6%)	2.29 (1.25-4.05)	
2	4 (1.3%)	2 (0.5%)	6 (0.9%)	2.54 (0.46-14.0)	
Child characteristics (n=655)					
Age in years (n=655)					
<2	32 (10.6%)	83 (23.5%)	115 (17.6%)	1	<0.001
2 to <5	71 (23.6%)	127 (35.9%)	198 (30.2%)	1.45 (0.88-2.39)	
≥5	198 (65.8%)	144 (40.7%)	342 (54.2%)	3.57 (2.25-5.65)	
Gender (n=655)					
Male	138 (45.8%)	168 (47.5%)	306 (46.7%)	1	0.681
Female	164 (54.2%)	186 (52.5%)	349 (53.3%)	1.07 (0.78-1.45)	
Ethnicity (n=899)					
African/Black	50 (16.6%)	68 (19.2%)	118 (18.0%)	1	0.246
Mixed race	249 (82.7%)	286 (80.8%)	535 (81.7%)	1.26 (0.85-1.86)	
Indian	1 (0.3%)	0 (0.0%)	1 (0.2%)	-	
White	1 (0.3%)	0 (0.0%)	1 (0.2%)	-	
Prior TB treatment (n=655)					
No	283 (94.0%)	341 (96.3%)	624 (95.3%)	1	0.166
Yes	18 (6.0%)	13 (3.7%)	31 (4.7%)	1.67 (0.80-3.46)	
HIV status (n=655)					
Negative	298 (99.0%)	352 (99.4%)	650 (99.2%)	1	0.527
Positive	3 (1.0%)	2 (0.6%)	5 (0.8%)	1.77 (0.29-10.67)	
BCG, scar or documented (n=655)	37 (10.5%)	37 (10.5%)	84 (12.8%)	1	0.049
No	254 (84.4%)	317 (89.6%)	571 (87.2%)	0.63 (0.40-1.00)	
Yes					
Weight-for-age z-score (n=650)					
More than -1	187 (62.3%)	224 (64.0%)	411 (63.2%)	1	0.073
-1 to -2	70 (23.3%)	95 (27.1%)	165 (25.4%)	0.88 (0.61-1.27)	
Less than -2	43 (14.3%)	31 (8.9%)	74 (11.4%)	1.66 (1.01-2.74)	
Length-for-age z-score (n=886)					
More than -1	97 (32.3%)	113 (32.3%)	210 (32.3%)	1	0.927
-1 to -2	104 (34.7%)	117 (33.4%)	221 (34.0%)	1.04 (0.71-1.51)	
Less than -2	99 (33.0%)	120 (34.3%)	219 (33.7%)	0.96 (0.66-1.41)	
Weight-for-length z-score (n=472)	164 (85.4%)	254 (90.7%)	418 (88.6%)	1	0.188
More than -1	24 (12.5%)	21 (7.5%)	45 (9.5%)	1.77 (0.95-3.28)	
-1 to -2	4 (2.1%)	5 (1.8%)	9 (1.9%)	1.24 (0.33-4.68)	
Less than -2					
Household characteristics of child contacts (n=655)					
Household death in past year (n=655)					
No	264 (87.7%)	330 (93.2%)	594 (90.7%)	1	0.016
Yes	37 (12.3%)	24 (6.8%)	61 (9.3%)	1.93 (1.12-3.30)	
Environmental tobacco smoke (n=652)					
No	54 (17.9%)	100 (28.5%)	154 (23.6%)	1	0.001
Yes	247 (82.1%)	251 (71.5%)	498 (76.3%)	1.82 (1.25-2.65)	
Type of residence (n=652)					
Main house	207 (68.8%)	248 (70.7%)	455 (69.8%)	1	0.036
Yard house	63 (20.9%)	85 (24.2%)	148 (22.7%)	0.89 (0.61-1.29)	
Flat	31 (10.3%)	18 (5.1%)	49 (7.5%)	2 06 (1.12-3.80)	
Housing structure (n=649)					
Tin shack	39 (13.0%)	56 (16.0%)	95 (14.6%)	1	0.680

Prefab house	3 (01.0%)	2 (0.6%)	5 (0.8%)	2.15 (0.34-13.50)	
Brick house	204 (68.2%)	230 (65.7%)	434 (66.9%)	1.27 (0.81-2.00)	
Wendy house	53 (17.7%)	62 (17.7%)	115 (17.7%)	1.23 (0.71-2.13)	
Household electricity (n=652)					
Yes	285 (94.7%)	332 (94.6%)	617 (94.6%)	1	0.956
No	16 (5.3%)	19 (5.4%)	35 (5.4%)	1.02 (0.51-2.02)	
Total	301 (46.0%)	354 (54.0%)	655 (100%)		

Table 7 Multivariate analysis[1]: risk factors for TST positivity in child household TB contacts adjusted for household clustering with sputum smear status as a potential mediator:

	Model excluding possible mediator n=610			Model including possible mediator n=571		
Variable	Adjusted OR	95% C.I.	P-value	Adjusted OR	95% C.I.	P-value
Duration of cough, (weeks)						
No cough	1			1		
<4	2.31	1.40-3.81	0.001	1.77	1.02-3.09	0.044
4-12	3.21	1.72-5.97	<0.001	2.74	1.39-5.40	0.004
>12	2.82	1.39-5.71	0.004	2.39	1.19-4.82	0.014
Age of child contact, (years)						
<2	1			1		
2-5	1.78	1.07-2.97	0.027	1.68	0.97-2.91	0.064
>5	4.78	2.87-7.95	<0.001	4.51	2.60-7.83	<0.001
Contact proximity[2]						
Same house	1			1		
Same room	1.94	1.31-2.87	0.001	2.17	1.43-3.31	<0.001
Additional household TB contacts[22]						
0	1			1		
≥1	3.11	1.55-6.24	0.001	2.70	1.35-5.42	0.005
Household tobacco smoking						
No	1			1		
Yes	2.07	1.23-3.48	0.006	2.10	1.22-3.61	0.008
Sputum smear status						
Negative				1		
Positive	-	-	-	1.92	1.16-3.18	0.011

[2] Multivariate analysis performed using 607 observations with complete data for variables included in model

[2] Categories collapsed in regression analysis

Appendix D. Analysis of missing data: Mantoux TST multivariate logistic regression

The final multivariate model was applied to the full dataset only omitting observations with missing data in one or more of the variables included in the model. The prevalence of TB infection as indicated by Mantoux TST positivity was somewhat lower in those who had missing data (34.5%) compared to those without missing data (47.6%). Observations with missing data did not differ with respect to adult TB source case age or gender, or to the child's age, gender or ethnicity. Although HIV-infected adult source cases and those reporting absence of cough were more likely to have missing data, the data missing was a sputum result. When the sputum result was omitted, there was no association between the duration of cough or the adult source case's HIV status and having missing data. It is likely that TB patients who were not coughing, or HIV-coinfected TB adults who had extrapulmonary forms of TB, were unable to produce a sputum sample, resulting in missing data. Results of the missing data analysis are presented in Table 14.

Table 8. Missing data analysis

Adult TB source case factors	Missing data	No missing data	Total	P-value
Age (years) (n=635)				
<25	13 (17.6%)	122 (21.8%)	135 (21.3%)	0.409*
25 to <35	35 (47.3%)	205 (36.5%)	240 (37.8%)	
35 to <50	24 (32.4%)	181 (32.3%)	205 (32.3%)	
≥50	2 (2.7%)	53 (9.5%)	55 (8.7%)	
Gender (n=645)				
Male	29 (39.2%)	198 (34.7%)	227 (35.2%)	0.444
Female	45 (60.8%)	373 (65.3%)	418 (64.8%)	
HIV status (n=617)				
Negative	38 (52.1%)	378 (69.5%)	416 (67.4%)	0.003
Positive	35 (48.0%)	166 (30.5%)	201 (32.6%)	(0.396#)
Duration of cough (weeks) (n=642)				
No cough				
<4	33 (46.5%)	161 (28.2%)	194 (30.2%)	0.028*
4 to <12	13 (18.3%)	181 (31.7%)	194 (30.2%)	(0.655#)
≥12	19 (26.8%)	152 (26.6%)	171 (26.6%)	
	6 (8.5%)	77 (13.5%)	83 (12.9%)	
Child contact factors				
Age (years) (n=668)				
<2	20 (20.6%)	95 (16.6%)	115 (17.2%)	0.742*
2 to <5	25 (25.8%)	177 (31.0%)	202 (30.2%)	
≥5	52 (53.6%)	299 (52.4%)	351 (52.5%)	
Gender (n=668)				
Male	43 (44.3%)	269 (47.1%)	312 (46.7%)	0.464
Female	54 (55.7%)	302 (52.9%)	356 (53.3%)	
Ethnicity (n=666)				
African/Black	13 (28.3%)	110 (17.7%)	123 (18.5%)	0.076
Mixed race	33 (71.7%)	510 (82.3%)	543 (81.5%)	
Total	97	571	668	

*Chi-squared test for trend

#if sputum status not included as missing data

Appendix E. Model checking

The Pearson Chi-square goodness of fit statistic indicates that the variables contribute significantly to the logistic regression model ($\chi 2 = 92.59$, $p=0.7594$).

The plots of standardized Pearson residuals and standardised deviance residuals against leverage and estimated logistic probability in Figure 1 indicate that there are some outliers with high leverage. Outliers were also identified by identifying observations with either a squared standardised deviance residual or dx2 residual of 4.0 or higher. These are plotted and presented in Figure 2. These observations were evaluated and no unusual or implausible values were found.

The final plot of Figure 2 indicates outliers weighted by influence (dbeta) in order to identify influential points. There were 37 observations identified. Of these, 12 observations were children who had a negative Mantoux TST despite having prolonged close contact with at least one strongly smear positive PTB case who reported a prolonged duration of cough. A further 25 observations were children who were Mantoux TST positive but with either less contact proximity with an adult PTB case, or contact with an adult who reported a shorter duration of cough. None of these observations were excluded from the final model.

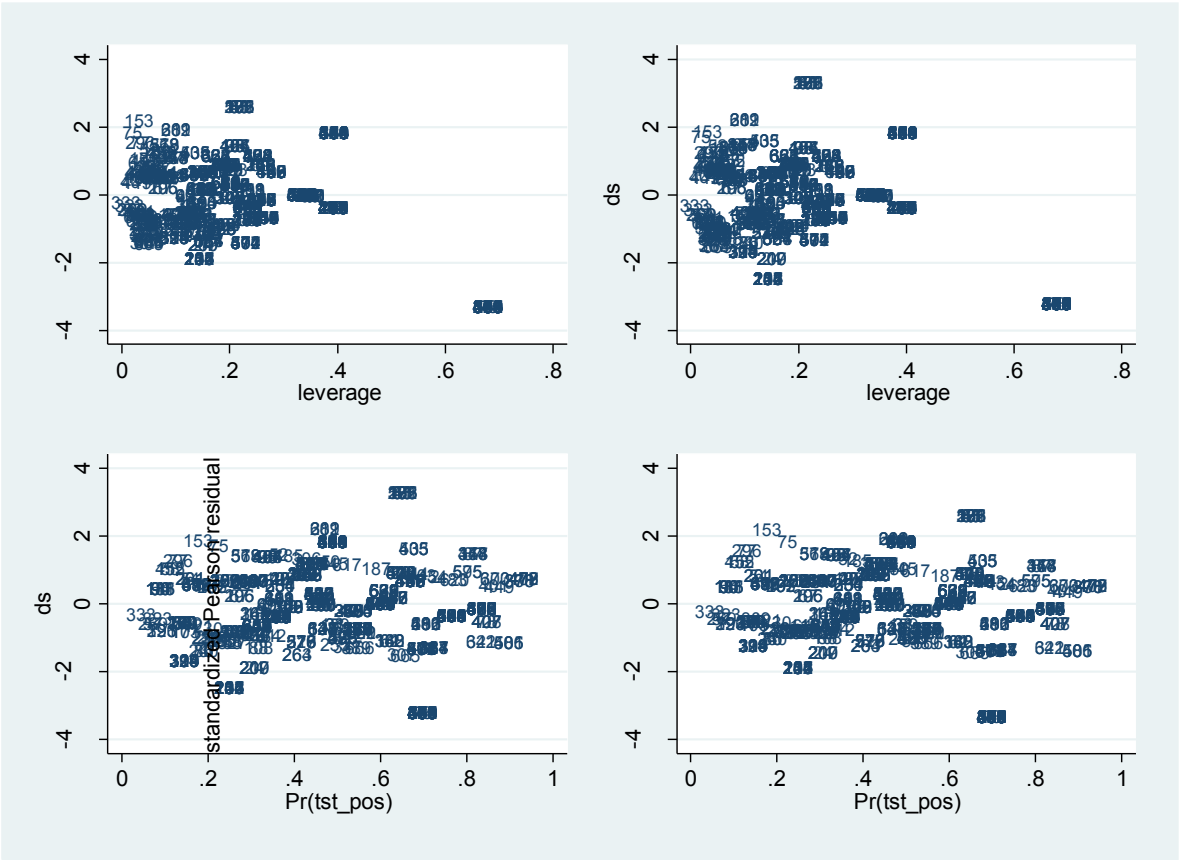

Figure 1. Plots of residuals against leverage and estimated logistic probability

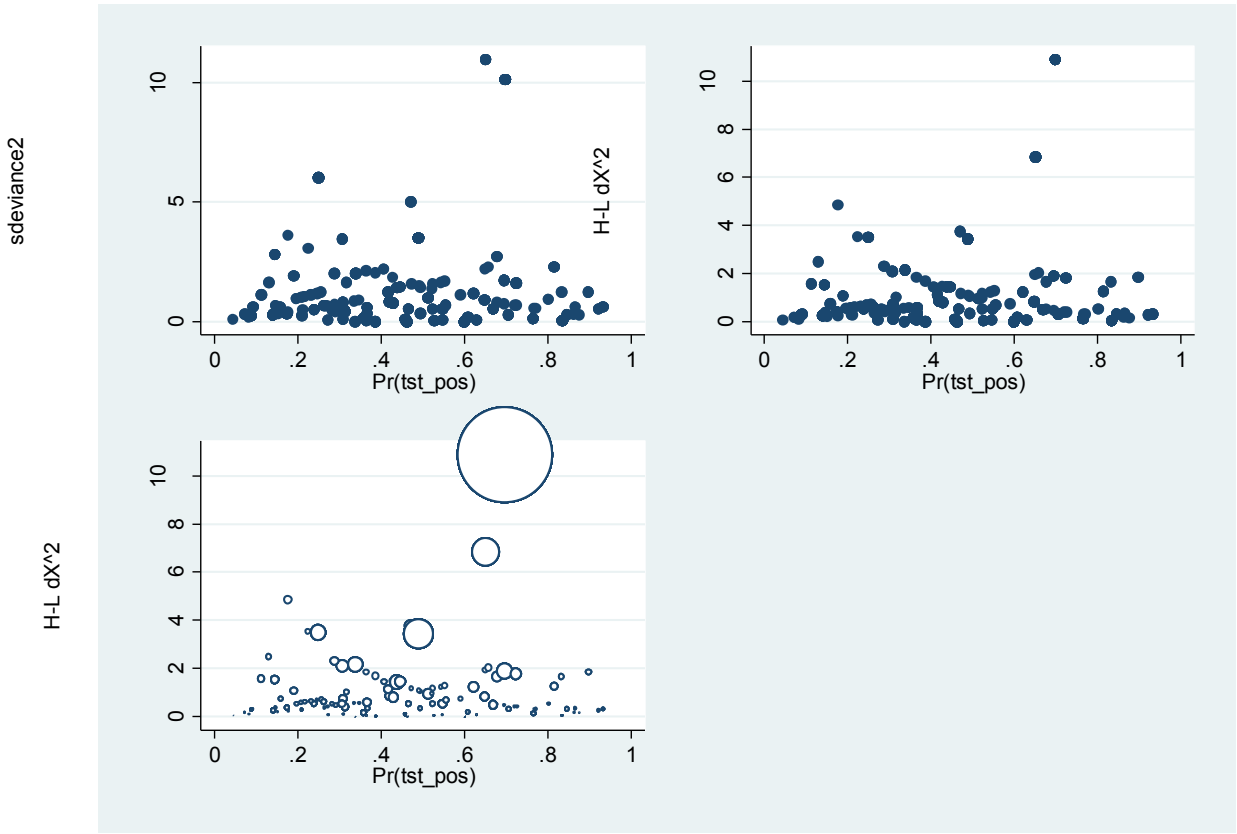

Figure 2. Plots of squared standardized deviance, dx2 residuals and dx2 (weighted by dbeta) against the estimated logistic probability

Appendix F. Secondary analysis 1: Interferon-gamma release assay (IGRA) analysis

Because the Mantoux TST has limited sensitivity and specificity in diagnosing TB infection, IGRAs were developed as more specific diagnostic tests. These blood tests measure the interferon-gamma produced by T-lymphocytes that are incubated with antigens specific to *Mycobacterium tuberculosis*. IGRAs are more expensive tests and less widely available than the Mantoux TST. Because two IGRA tests – Quantiferon-TB Gold and T-SPOT.*TB* –were performed as part of the parent study and the results were available for analysis, a further subanalysis was conducted to evaluate TB infection in child household contacts, as indicated by IGRA positivity. For the purposes of this subanalysis, IGRA positivity indicates either IGRA test being positive. Agreement between the two IGRA results was in the vast majority of cases very good (Kappa statistic 0.8286, p<0.001), as indicated in Table 9. Agreement between Mantoux TST and IGRA was good (Kappa statistic 0.7745, p<0.001), as indicated in Table 10.

Table 9. IGRA results

T-spot TB results	Quantiferon results		
	Positive	Negative	Total
Positive	174	10	184
Negative	26	213	239
Total	200	223	423

Table 10. Mantoux TST and IGRA results:

TST results	IGRA positive results		
	Positive	Negative	Total
Positive	278	15	293
Negative	56	278	334
Total	334	293	627

The results of this subanalysis are mostly consistent with the finding of the analysis of TB infection as indicated by Mantoux TST positivity. In univariate analysis (Table 11), IGRA positivity in the child household contact was associated with both the adult source case

reporting current cough (OR = 2.15 [95% CI = 1.51-3.06]) and the duration of cough, also with a dose-response effect (OR = 1.64 for cough <4 weeks, 95% CI = 1.08-2.48; OR = 2.22 [95% CI = 1.44-3.41] for cough 4-12 weeks; OR = 3.85 [95% CI = 2.18-6.78] for cough >12 weeks, compared to index cases who did not report coughing). HIV co-infection in the adult source case was associated with a 31% reduction in IGRA positivity (OR = 0.69, 95% CI = 0.48-0.97). IGRA positivity was also associated with disease site (OR = 2.40 [95% CI = 0.94-6.63] for PTB compared to EPTB), sputum smear status (OR = 2.24 [95% CI = 1.59-3.15] for sputum smear positive compared to negative TB), sputum culture status (OR = 3.65 [95% CI = 2.26-5.90] for culture positive compared to negative), the source case being the primary caregiver to the child (OR = 1.75, 95% CI = 1.25-2.47) and the number of household TB contacts (OR = 2.28 [95% CI = 1.25-4.18] for one; OR = 3.74 [95% CI = 0.96-33.71] for two, compared to no additional TB contacts). Contact proximity was not associated with IGRA positivity (OR = 1.42 [95% CI = 0.92-2.18] in contacts sleeping in the same room, OR = 1.38 [95% CI = 0.96-1.98]), which is different to TST positivity, which was strongly associated with contact proximity.

The child contact's age was a risk factor for IGRA positivity (OR = 3.67 [95% CI = 2.31-5.82] for children aged ≥5 years) and weight-for-age z-score less than -2 (OR = 2.01 [95% CI = 1.18-3.41). Unlike TST positivity, IGRA positivity was associated with prior TB treatment (OR = 2.97 [95% CI = 1.32-6.67] for children previously treated for TB compared to those not previously treated). Household tobacco smoke exposure was associated with IGRA positivity (OR = 1.71 [95% CI = 1.18-2.48] for environmental tobacco smoke exposure compared to none). Unlike TST positivity, having a household death in the past year was not associated with IGRA positivity.

In multivariate analysis, presented in Table 12, the findings were consistent with the results of the TST analysis, except that contact proximity and additional TB contacts were not associated with IGRA positivity in the final model and the adult source case being the primary caregiver was (OR = 2.14 [95% CI= 1.38-3.32]). The risk of IGRA positivity increased with increasing duration of cough prior to TB treatment initiation in the adult source with a dose response effect (OR = 1.14 [95% CI 0.66-1.98] for cough <4 weeks; OR = 1.87 [95% CI = 0.99-3.56] for cough 4-12 weeks; OR = 3.23 [95% CI = 1.47-7.13] for cough >12 weeks, compared to index cases not reporting cough) and the results were similar when the

potential mediator, sputum smear status, was excluded from the model. The risk of IGRA positivity increased with age over five years (OR = 3.98, [95% CI = 2.29-6.93]), if the source case was the primary caregiver (OR = 2.14 [95% CI= 1.38-3.32]) and with household tobacco smoking (OR = 2.39, [95% CI = 1.38-4.16]). HIV status of the source case was not an effect modifier of the association between adult TB source case duration of cough and risk of infection in child household contacts in the final model, although it was a significant risk factor in the univariate analysis.

Overall the results of the subanalysis conducted with a more sensitive and specific indicator of TB infection – IGRA positivity – are consistent with the findings of the primary analysis with TB infection in the child indicated by Mantoux TST positivity.

Table 11. Risk factors for IGRA positivity in child household contacts (n=638)

Variable	IGRA positive	IGRA negative	Total (percentage)	Unadjusted OR (95% CI)	P-value
Adult index case characteristics (n=637)					
Age of index case, in years (n=605)	71 (22.0%)	58 (20.6%)	129 (21.3%)	1	0.7275
<25	122 (37.8%)	107 (37.9%)	229 (37.9%)	0.93 (0.60-1.44)	
25 to <35	106 (32.8%)	89 (31.6%)	195 (32.2%)	0.97 (0.62-1.52)	
35 to <50	24 (7.4%)	28 (9.9%)	52 (8.6%)	0.70 (0.86-1.73)	
≥50					
Gender of index case (n=615)					
Female	206 (63.0%)	191 (66.3%)	397 (64.6%)	1	0.3898
Male	121 (37.0%)	97 (33.7%)	218 (35.5%)	0.86 (0.62-1.20)	
Currently coughing (n=615)					
No	73 (22.3%)	110 38.2%	183 (29.8%)	1	<0.001
Yes	254 (77.7%)	178 (61.8%)	432 (70.2%)	2.15 (1.51-3.06)	
Duration of coughing, weeks (n=612)					
No cough	72 (22.1%)	108 (37.8%)	180 (29.4%)	1	<0.001
<4	96 (29.5%)	88 (30.8%)	184 (30.1%)	1.64 (1.08-2.48)	
4 to <12	99 (30.4%)	67 (23.4%)	166 (27.1%)	2.22 (1.44-3.41)	
≥12	59 (18.1%)	23 (8.0%)	82 (13.4%)	3.85 (2.18-6.78)	
HIV status (n=590)					
Negative	226 (72.0%)	176 (63.8%)	402 (68.1%)	1	0.0329
Positive	88 (28.0%)	100 (36.2%)	188 (31.2%)	0.69 (0.48-0.97)	
CD4 count, if HIV-positive (n=161)	46 (56.8%)	42 (52.5%)	88 (54.7%)	1	0.5845
≥ 200	35 (43.2%)	38 (47.5%)	73 (45.3%)	0.84 (0.45-1.57)	
<200					
Antiretroviral therapy, if HIV-positive (n=164)					
No	58 (72.5%)	54 (64.3%)	112 (68.3%)	1	0.2577
Yes	22 (27.5%)	30 (35.7%)	52 (31.7%)	0.68 (0.35-1.33)	
Patient category (n=581)					
New	207 (66.8%)	192 (70.9%)	399 (68.7%)	1	0.0899
Retreatment after	7 (2.3%)	8 (3.0%)	15 (2.6%)	0.81 (0.29-2.28)	
completion	84 (27.1%)	63 (23.3%)	147 (25.3%)	1.24 (0.84-1.81)	
Retreatment after cure	4 (1.3%)	7 (2.6%)	11 (1.9%)	0.53 (0.15-1.84)	
Retreatment after failure	8 (2.6%)	1 (0.4%)	9 (1.6%)	7.42 (0.92-59.88)	
Retreatment after interruption					
Disease site (n=574)					
Extrapulmonary	8 (2.5%)	15 (5.8%)	23 (4.0%)	1	0.044
Pulmonary	309 (97.5%)	242 (94.2%)	551 (96.0%)	2.40 (0.94-6.63)	
TB exposure variables (n=655)					
Hours per day of contact (n=633)	54 (15.9%)	53 (18.1%)	107 (16.9%)	1	0.1947
<4	122 (35.9%)	113 (38.6%)	235 (37.1%)	1.06 (0.67-1.67)	
4-8	137 (40.3%)	115 (39.3%)	252 (39.8%)	1.17 (0.74-1.84)	
9-12	27 (7.9%)	12 (4.1%)	39 (6.2%)	2.21 (1.01-4.81)	
≥12					
Sputum smear result (n=581)					
Negative	94 (29.8%)	129 (48.7%)	223 (38.4%)	1	<0.001
Positive	222 (70.3%)	136 (51.3%)	358 (61.65)	2.24 (1.59-3.15)	
Sputum smear grade (n=536)					
Negative	88 (30.0%)	118 (48.6%)	206 (38.4%)	1	<0.001
Scanty	16 (5.5%)	12 (4.9%)	28 (5.2%)	1.79 (0.81-3.97)	
1+	41 (14.0%)	24 (9.9%)	65 (12.1%)	2.29 (1.29-4.07)	
2+	38 (13.0%)	23 (9.5%)	61 (11.4%)	2.22 (1.23-3.98)	
3+	110 (37.5%)	66 (27.2%)	176 (32.8%)	2.23 (1.48-3.37)	
Sputum culture result (n=302)					
Negative	59 (35.1%)	89 (66.4%)	148 (49.0%)	1	<0.001
Positive	109 (64.9%)	45 (33.6%)	154 (51.0%)	3.65 (2.26-5.90)	
Primary caregiver to child (n=621)	203 (61.0%)	211 (73.3%)	414 (66.7%)	1	0.0011
No	130 (39.0%)	77 (26.7%)	207 (33.3%)	1.75 (1.25-2.47)	
Yes					

Relationship to index case (n=622)	162 (48.5%)	106 (36.7%)	268 (43.1%)	1	0.0087
Parent	85 (25.5%)	96 (33.3%)	181 (29.1%)	0.58 (0.40-0.85)	
Aunt or uncle	56 (16.8%)	45 (15.6%)	101 (16.2%)	0.81 (0.51-1.29)	
Other family	31 (9.3%)	41 (14.2%)	72 (11.6%)	0.49 (0.29-0.84)	
Other					
Contact score, median (IQR) (n=638)	6 (5-7)	5 (4-6)	5 (4-7)	1.27 (1.16-1.38)	<0.001
Intensity of contact (n=620)					
Sleeps in same house	157 (46.9%)	157 (55.1%)	314 (50.7%)	1	0.1233
Sleeps in same room	68 (20.3%)	48 (16.8%)	116 (18.7%)	1.42 (0.92-2.18)	
Sleeps in same bed	110 (32.8%)	80 (28.1%)	190 (30.7%)	1.38 (0.96-1.98)	
Number of additional household TB contacts (n=637)					
0	298 (87.4%)	279 (94.3%)	577 (90.6%)	1	0.0096
1	39 (11.4%)	16 (5.4%)	55 (8.6%)	2.28 (1.25-4.18)	
2	4 (1.2%)	1 (0.3%)	5 (0.8%)	3.74 (0.42-33.71)	
Child household contact details (n=655)					
Age in years (n=638)					
<2	36 (10.5%)	69 (23.3%)	105 (16.5%)	1	<0.001
2 to <5	84 (24.6%)	111 (37.5%)	195 (30.6%)	1.45 (0.89-2.37)	
≥5	222 (64.9%)	116 (39.2%)	338 (53.0%)	3.67 (2.31-5.82)	
Gender (n=638)					
Female	142 (46.2%)	157 (45.9%)	299 (46.6%)	1	
Male	154 (53.9%)	185 (54.1%)	339 (53.4%)	1.09 (0.80-1.48)	0.6019
Ethnicity (n=638)					
	53 (15.5%)	58 (19.6%)	111 (17.4%)	1	0.185
African/Black	287 (83.9%)	238 (80.4%)	525 (82.3%)	1.32 (0.88-1.99)	
Mixed race	1 (0.3%)	0 (0.0%)	1 (0.2%)	-	
Indian	1 (0.3%)	0 (0.0%)	1 (0.2%)	-	
White					
Prior TB treatment (n=637)					
No	315 (92.4%)	288 (97.3%)	603 (94.7%)	1	0.0045
Yes	26 (7.6%)	8 (2.7%)	34 (5.3%)	2.97 (1.32-6.67)	
HIV status (n=638)					
Negative	340 (99.4%)	294 (99.3%)	634 (99.4%)	1	0.8848
Positive	2 (0.6%)	2 (0.7%)	4 (0.6%)	0.86 (0.12-6.18)	
BCG, scar or documented (n=638)	54 (15.8%)	32 (10.8%)	86 (13.5%)	1	0.068
No	288 (84.2%)	264 (89.2%)	552 (86.5%)	0.65 (0.40-1.03)	
Yes					
Weight-for-age z-score (n=632)					
More than -1	208 (61.2%)	192 (65.8%)	400 (63.3%)	1	0.0250
-1 to -2	82 (24.1%)	77 (26.4%)	159 (25.2%)	0.98 (0.68-1.42)	
Less than -2	50 (14.7%)	23 (7.9%)	73 (11.6%)	2.01 (1.18-3.41)	
Length-for-age z-score (n=632)					
More than -1	112 (32.9%)	91 (31.2%)	203 (32.1%)	1	0.8660
-1 to -2	113 (33.2%)	102 (34.9%)	215 (34.0%)	0.90 (0.61-1.32)	
Less than -2	115 (33.8%)	99 (33.9%)	214 (33.9%)	0.94 (0.64-1.39)	
Weight-for-length z-score (n=458)	191 (85.7%)	214 (91.1%)	405 (88.4%)	1	0.1911
More than -1	27 (12.1%)	18 (7.7%)	45 (9.8%)	1.68 (0.90-3.15)	
-1 to -2	5 (2.2%)	3 (1.3%)	8 (1.8%)	1.87 (0.44-7.92)	
Less than -2					
Household characteristics (n=655)					
Household death in past year (n=637)					
No	308 (90.3%)	269 (90.9%)	577 (90.6%)	1	0.8106
Yes	33 (9.7%)	27 (9.1%)	60 (9.4%)	1.07 (0.63-1.82)	
Environmental tobacco smoke (n=634)					
No	64 (18.8%)	83 (28.3%)	147 (23.2%)	1	0.0045
Yes	277 (81.2%)	210 (71.7%)	487 (76.8%)	1.71 (1.18-2.48)	
Type of residence (n=635)					
Main house	235 (68.7%)	206 (70.3%)	441 (69.5%)	1	0.0580
Yard house	73 (21.4%)	72 (24.6%)	145 (22.8%)	0.89 (0.61-1.29)	
Flat	34 (9.9%)	15 (5.1%)	49 (7.7%)	1.99 (1.05-3.75)	
Housing structure (n=631)					

	43 (12.7%)	45 (15.4%)	88 (14.0%)	1	0.7493
Tin shack	2 (0.6%)	2 (0.7%)	4 (0.6%)	1.05 (0.14-7.76)	
Prefab house	234 (69.0%)	191 (65.4%)	425 (67.4%)	1.28 (0.81-2.03)	
Brick house	60 (17.7%)	54 (18.5%)	114 (18.1%)	1.16 (0.67-2.03)	
Wendy house					
Household electricity (n=635)					
No	16 (4.7%)	16 (5.5%)	32 (5.0%)	1	0.6537
Yes	326 (95.3%)	277 (94.5%)	603 (95.0%)	1.18	
Total	342 (53.6%)	296 (46.4%)	638 (100%)		

Table 12. Multivariate analysis[1]: risk factors for IGRA positivity in child household TB contacts adjusted for household clustering with sputum smear status as a potential mediator

	Model excluding possible mediator n=601			Model including possible mediator n=564		
Variable	Adjusted OR	95% C.I.	P-value	Adjusted OR	95% C.I.	P-value
Duration of cough, (weeks)						
No cough	1			1		
<4	1.71	1.04-2.79	0.034	1.17	0.68-2.03	0.565
4-12	2.49	1.36-4.55	0.003	1.91	1.00-3.65	0.049
>12	3.75	1.67-8.42	0.001	3.01	1.39-6.51	0.005
Age of child contact, (years)						
<2	1			1		
2-5	1.72	1.05-2.84	0.032	1.53	0.90-2.61	0.118
>5	4.71	2.87-7.73	<0.001	4.35	2.55-7.42	<0.001
Contact proximity[2]						
Same house	1			1		
Same room	1.49	1.01-2.20	0.044	1.75	1.15-2.65	0.009
Additional household TB contacts[23]						
0	1			1		
≥1	2.26	1.04-4.89	0.038	1.90	0.88-4.09	0.100
Household tobacco smoking						
No	1			1		
Yes	2.03	1.19-3.47	0.009	2.09	1.20-3.65	0.009
Sputum smear status						
Negative	-	-	-	1		
Positive				2.36	1.44-3.88	0.001

[3] Multivariate analysis performed using 607 observations with complete data for variables included in model

[2] Categories collapsed in regression analysis

Appendix G. Secondary analysis 2: Prevalent TB disease: univariate analysis

Whereas risk factors for being infected with TB are largely exogenous factors relating to the infectivity of the source case and duration and intensity of exposure, the risk of developing disease is mostly related to host factors, such as age, immunity – including HIV status, nutritional status, BCG vaccination and the time since becoming infected.(1) Although a 1975 Canadian study found that the risk of developing disease following infection in intimate and casual adult and child contacts was greater if the infection was caused by a sputum smear-positive case than a sputum smear-negative case, the results of this study have been criticised because the TST was considered to be positive if the diameter of induration exceeded 5mm, which would reduce its specificity and predictive value.(1,99) Whether or not source case bacteriological factors can also be risk factors for the development of disease remains unresolved.

In this subanalysis, prevalent TB disease diagnosed within the first three months of enrolment into the parent study was associated with adult source case sputum smear positivity (OR = 3.18 [95% CI = 1.38-7.30]), sputum smear grade of positivity (OR = 5.84 [95% CI = 1.84-18.53] for grade 1+, OR = 4.94 [95% CI = 1.51-16.12] for grade 2+ and OR = 3.83 [95% CI = 1.36-10.75] for grade 3+ compared to sputum smear negative status) and sputum culture positivity (OR = 5.38 [95% CI = 1.53-18.99]). Prevalent TB disease was also associated with the number of additional household TB contacts (OR = 3.14 [95% CI = 1.42-6.94]). The child's age was also associated with prevalent TB disease, with decreasing risk of disease with increasing age (OR = 0.69 [95%CI = 0.34-1.42] for children aged 2 to <5 years, OR = 0.18 [95% CI = 0.07-0.41] for children aged ≥5 years, compared to children aged <2 years). The contact score, which measures the extent of exposure to TB, is also strongly associated with prevalent disease (OR = 1.24 [95%CI = 1.05-1.46]) with each unit increase in score out of ten associated with a 24% increase in odds of disease.

These results suggest that in addition to the traditional risk factors for the development of TB disease after infection – host age, nutrition, immune status and time since infection – exposure factors can also be risk factors for the development of TB disease.

Table 13. Risk factors for prevalent TB disease in child household contacts (n=668)

Variable	TB disease	No TB disease	Total (percentage)	Unadjusted OR (95% CI)	P-value
Adult index case characteristics (n=635)					
Age of index case, in years (n=635)	12 (28.6%)	123 (20.7%)	135 (21.3%)	1	0.2887
<25	14 (33.3%)	226 (38.1%)	240 (37.8%)	0.63 (0.28-1.42)	
25 to <35	10 (23.8%)	195 (32.9%)	205 (32.3%)	0.53 (0.22-1.25)	
35 to <50	6 (14.3%)	49 (8.3%)	55 (8.7%)	1.26 (0.45-3.53)	
≥50					
Gender of index case (n=645)					
Male	14 (33.3%)	213 (35.3%)	227 (35.2%)	1	0.7932
Female	28 (66.7%)	390 (64.7%)	418 (64.8%)	1.09 (0.56-2.12)	
Currently coughing (n=645)					
No	12 (28.6%)	185 (30.7%)	197 (30.5%)	1	0.7729
Yes	30 (71.4%)	418 (69.3%)	448 (69.5%)	1.11 (0.55-2.21)	
Duration of coughing, weeks (n=642)					
No cough	12 (28.6%)	182 (30.3%)	194 (30.2%)	1	0.4507
<4	9 (21.4%)	185 (30.8%)	194 (30.2%)	0.74 (0.30-1.79)	
4 to <12	15 (35.7%)	156 (26.0%)	171 (26.6%)	1.46 (0.66-3.21)	
≥12	6 (14.3%)	77 (12.8%)	83 (12.9%)	1.18 (0.43-3.26)	
HIV status (n=617)					
Negative	30 (75.0%)	386 (66.9%)	416 (67.4%)	1	0.2799
Positive	10 (25.0%)	191 (33.1%)	201 (32.6%)	0.67 (0.32-1.41)	
CD4 count, if HIV-positive (n=173)	4 (44.4%)	90 (54.9%)	94 (54.3%)	1	0.5416
≥ 200	5 (55.6%)	74 (45.1%)	79 (45.7%)	1.52 (0.39-5.87)	
<200					
Antiretroviral therapy, if HIV-positive (n=179)					
No	4 (44.4%)	118 (69.4%)	122 (68.2%)	1	0.1320
Yes	5 (55.6%)	52 (30.6%)	57 (31.8%)	2.84 (0.73-10.99)	
Patient category (n=609)					
New	26 (63.4%)	396 (69.7%)	422 (69.3%)	1	0.1713
Retreatment after completion	3 (7.3%)	13 (2.3%)	16 (2.6%)	3.51 (0.94-13.11)	
Retreatment after cure	10 (24.4%)	141 (24.8%)	151 (24.8%)	1.08 (0.51-2.30)	
Retreatment after failure	0 (0.0%)	11 (1.9%)	11 (1.8%)	-	
Retreatment after interruption	2 (4.9%)	7 (1.2%)	9 (1.5%)	4.35 (0.86-22.0)	
Disease site (n=574)					
Extrapulmonary	0 (0.0%)	25 (4.4%)	25 (4.1%)	-	-
Pulmonary	41 (100.0%)	538 (95.6%)	579 (95.9%)		
TB exposure variables (n=655)					
Hours per day of contact (n=663)					
<4	4 (9.3%)	110 (17.7%)	114 (17.2%)	1	0.4266
4-8	16 (37.2%)	224 (36.1%)	240 (36.2%)	1.96 (0.64-6.02)	
9-12	19 (44.2%)	249 (40.2%)	268 (40.4%)	2.10 (0.70-6.31)	
≥12	4 (9.3%)	37 (6.0%)	41 (6.2%)	2.97 (0.71-12.49)	
Sputum smear result (n=609)					
	7 (17.5%)	229 (40.3%)	236 (38.8%)	1	0.0026
Negative	33 (82.5%)	340 (59.8%)	373 (61.3%)	3.18 (1.38-7.30)	
Positive					
Sputum smear grade (n=561)					
Negative	5 (13.5%)	211 (40.3%)	216 (38.5%)	1	0.0098
Scanty	2 (5.4%)	27 (5.2%)	29 (5.2%)	3.08 (0.57-16.67)	
1+	8 (21.6%)	61 (11.6%)	69 (12.3%)	5.84 (1.84-18.53)	
2+	7 (18.9%)	59 (11.3%)	66 (11.8%)	4.94 (1.51-16.12)	
3+	15 (40.5%)	166 (31.7%)	181 (32.3%)	3.83 (1.36-10.75)	
Sputum culture result (n=315)					
Negative	3 (16.7%)	154 (51.9%)	157 (49.8%)	1	0.0025
Positive	15 (83.3%)	143 (48.2%)	158 (50.2%)	5.38 (1.53-18.99)	

Primary caregiver to child (n=651)	27 (64.3%)	404 (66.3%)	431 (66.2%)	1.09 (0.56-2.10)	0.7865
No	15 (35.7%)	205 (33.7%)	220 (33.8%)		
Yes					
Relationship to index case (n=652)	19 (45.2%)	261 (42.8%)	280 (42.9%)	1	0.7508
Parent	9 (21.4%)	176 (28.9%)	185 (28.4%)	0.70 (0.31-1.59)	
Aunt or uncle	8 (19.1%)	100 (16.4%)	108 (16.6%)	1.10 (0.47-2.59)	
Other family	6 (14.3%)	73 (12.0%)	79 (12.1%)	1.13 (0.43-2.93)	
Other					
Contact score, median (IQR) (n=668)	6 (5-8)	5 (4-7)	5 (4-7)	1.24 (1.05-1.46)	0.010
Intensity of contact (n=649)					
Sleeps in same house	21 (48.8%)	308 (50.8%)	329 (50.7%)	1	0.5409
Sleeps in same room	6 (14.0%)	115 (19.0%)	121 (18.6%)	0.77 (0.30-1.94)	
Sleeps in same bed	16 (37.2%)	183 (30.2%)	199 (30.7%)	1.28 (0.65-2.52)	
Number of additional household TB contacts (n=661)					
0	34 (79.1%)	570 (91.4%)	604 (90.6%)	1	0.0095
1	9 (20.9%)	48 (7.7%)	57 (8.6%)	3.14 (1.42-6.94)	
2	0 (0.0%)	6 (1.0%)	6 (0.9%)	-	
Child household contact details (n=655)					
Age in years (n=668)					
<2	15 (34.9%)	100 (16.0%)	115 (17.2%)	1	<0.001
2 to <5	19 (44.2%)	183 (29.3%)	202 (30.2%)	0.69 (0.34-1.42)	
≥5	9 (20.9%)	342 (54.7%)	351 (52.5%)	0.18 (0.07-0.41)	
Gender (n=668)					
Female	23 (53.5%)	333 (53.3%)	356 (53.3%)	1	0.9879
Male	20 (46.5%)	292 (46.7%)	312 (46.7%)	1.01 (0.54-1.87)	
Ethnicity (n=638)					
African/Black	5 (11.6%)	118 (18.9%)	123 (18.4%)	1	0.2076
Mixed race	38 (88.4%)	505 (80.8%)	543 (81.3%)	1.78 (0.68-4.61)	
Indian	0 (0.0%)	1 (0.2%)	1 (0.2%)	-	
White	0 (0.0%)	1 (0.2%)	1 (0.2%)	-	
Prior TB treatment (n=667)					
No	40 (93.0%)	592 (94.9%)	632 (94.8%)	1	0.6146
Yes	3 (7.0%)	32 (5.1%)	35 (5.3%)	1.39 (0.41-4.73)	
HIV status (n=638)					
Negative	42 (97.7%)	621 (99.4%)	663 (99.3%)	1	0.3111
Positive	1 (2.3%)	4 (0.6%)	5 (0.8%)	3.70 (0.40-33.81)	
BCG, scar or documented (n=668)	3 (7.0%)	86 (13.8%)	89 (13.3%)	1	0.216
No	40 (93.0%)	539 (86.2%)	579 (86.7%)	2.13 (0.64-7.03)	
Yes					
Weight-for-age z-score (n=662)					
More than -1	24 (55.8%)	393 (63.5%)	417 (63.0%)	1	0.3765
-1 to -2	11. (25.6%)	156 (25.2%)	167 (25.2%)	1.15 (0.55-2.41)	
Less than -2	8 (18.6%)	70 (11.3%)	78 (11.8%)	1.87 (0.81-4.33)	
Length-for-age z-score (n=661)					
More than -1	9 (20.9%)	203 (32.9%)	212 (32.1%)	1	0.202
-1 to -2	16 (37.2%)	209 (33.8%)	225 (34.0%)	1.73 (0.75-4.00)	
Less than -2	18 (41.9%)	206 (33.3%)	224 (33.9%)		
Weight-for-length z-score (n=458)	35 (83.3%)	391 (89.1%)	426 (88.6%)	1	0.5632
More than -1	6 (14.3%)	40 (9.1%)	46 (9.6%)	1.68 (0.66-4.23)	
-1 to -2	1 (2.4%)	8 (1.8%)	9 (1.9%)	1.40 (0.17-11.49)	
Less than -2					
Household characteristics (n=655)					
Household death in past year (n=667)					
No	41 (95.4%)	563 (90.2%)	604 (90.6%)	1	0.2245
Yes	2 (4.7%)	61 (9.8%)	63 (9.5%)	0.45 (0.11-1.91)	
Environmental tobacco smoke (n=664)					
No	6 (14.0%)	152 (24.5%)	158 (23.8%)	1	0.1240
Yes	37 (86.1%)	469 (75.5%)	506 (76.2%)	2.00 (0.83-4.83)	
Type of residence (n=635)					

Main house	27 (62.8%)	437 (70.3%)	464 (69.8%)	1	0.4999
Yard house	11 (25.6%)	140 (22.5%)	151 (22.7%)	1.27 (0.62-2.63)	
Flat	5 (11.6%)	45 (7.2%)	50 (7.5%)	1.80 (0.66-4.90)	
Housing structure (n=661)					
Tin shack	5 (11.9%)	95 (15.4%)	100 (15.1%)	1	0.2101
Prefab house	1 (2.4%)	4 (0.7%)	5 (0.8%)	4.75 (0.44-50.74)	
Brick house	24 (57.1%)	415 (67.0%)	439 (66.4%)	1.10 (0.41-2.95)	
Wendy house	12 (28.6%)	105 (17.0%)	117 (17.7%)	2.17 (0.74-6.39)	
Household electricity (n=635)					
No	1 (2.3%)	38 (6.1%)	39 (5.9%)	1	0.2512
Yes	42 (97.7%)	584 (93.9%)	626 (94.1%)	2.73 (0.37-20.40)	
Total	43 (6.4%)	625 (93.6%)	668 (100%)		

Appendix H. Household clustering

Table 14. Household clustering: number of child contacts per household

Number of child contacts per household	Number of observations	Total
1	100	100
2	90	180
3	49	147
4	37	148
5	8	40
6	3	18
7	1	7
8	1	8
9	0	0
10	2	20
		668

The extent of clustering at a household level is presented in Table 15, indicating the number of child contacts per household within the study.

Appendix I. Variables for analysis

Code	Name	Scale	Units	Possible Values
Adult source case				
indexcase_age	Age of index case	Continuous	Years	0-100
indexcase_gender	Gender	Binary	-	Male, female
indexcase_hiv_pos	HIV status	Binary	-	Positive, negative
indexcase_cd4_count	CD4 count, if HIV positive	Continuous	-	0-1500
indexcase_art	Antiretroviral therapy (ART), if HIV positive	Binary	-	On ART, not on ART
cough_clean	Coughing	Binary	-	Yes, No
cough_dur_clean	Total duration of coughing	Ordinal	Weeks	0, <4, 4-6, 6-12, >12
daily_hours	Hours per day of contact	Ordinal	Hours	<4, 5-8,9-12, >12
final_smear	Sputum smear	Binary	-	Positive, negative
final_smear_grade	Sputum smear grade	Nominal	-	Negative, scanty, 1+, 2+, 3+
final_culture	Sputum culture	Binary	-	Positive, negative
indexcase_patient_category	Patient category	Nominal	-	New, RAC/RT, RC, RF, RI, unknown
dzsite	Disease site	Binary	-	Pulmonary, extrapulmonary
Child contact				
age	Age of child	Continuous	Years	0-16
gendercode	Gender	Binary	-	Male, female
tb_contact_rel_cat	Relationship to adult source case	Nominal	-	Parent, aunt or uncle, other family, other
tb_contact_primarycare	Source case is primary caregiver	Binary	-	Yes, No

Code	Name	Scale	Units	Possible Values
contact_intens	Intensity of source case contact	Nominal	-	Sleeps in same bed, same bedroom, same house or different house
tb_prior_treatment	Previous TB	Binary	-	Yes, No
waz	Weight-for-age z-score	Continuous	-	-10 to +10
haz	Height-for-age z-score	Continuous	-	-20 to +20
whz	Weight-for-height z-score	Continuous	-	-10 to +10
child_hiv_baseline	HIV status	Binary	-	Positive, negative
child_birth_BCG	BCG documented	Binary	-	Yes, no
child_bcg_scar	BCG scar	Binary	-	Yes, no
tst_clean_baseline	TST result	Continuous	mm	0-40
tst_pos	TST result	Binary	-	Positive, negative
igra_pos	IGRA positive	Nominal	-	Positive, negative
Household				
child_tb_contact_number	No of TB contacts	Continuous	-	0-10
hhmember_die	Household death in past year	Binary	-	Yes, no
HH_current_smoke	Environmental tobacco smoke exposure	Binary	-	Yes, No
house	Type of residence	Nominal	-	Main house, yard house, Flat
structure	Housing structure	Nominal	-	Tin shack, Prefab house, Brick house, Container, Wendy house, Other
electricity	Household electricity	Binary	-	Yes, no

TST=tuberculin skin test, IGRA=interferon-gamma release assay