PREDICTING COPREVALENT AND INCIDENT TUBERCULOSIS DISEASE AMONGST HOUSEHOLD CONTACTS OF TUBERCULOSIS CASES

by

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(Under the Direction of Christopher Whalen)

ABSTRACT.

Problem: Globally tuberculosis incidence is decreasing by approximately 1 – 2% per year. If these trends continue 2050 global targets for tuberculosis control will not be met. Supplementary interventions are needed to supplement current control strategies. Household contact tracing has been widely recommended but not implemented in low-income, high-burden settings. **Goal**: Expand the evidence-base on the effectiveness of household contact tracing of tuberculosis cases and make the use of household contact tracing more efficient for National Tuberculosis Programs in low-income, high-burden settings. **Methods**: We conducted four separate studies using separate outcomes and methodologies. First, we conducted a systematic review and meta-analysis of studies that measured either latent or active tuberculosis in both household contacts of tuberculosis cases and unexposed controls. We compared prevalence rates in these two groups across studies. In the three subsequent studies, we used data from the Kawempe Community Health study set in Kampala Uganda. In aim 2, we derived a

predictive risk score to identify household contacts most at risk for coprevalent tuberculosis disease. In the third aim, we investigated risk factors for incident tuberculosis disease amongst household contacts. In the fourth aim, we attempted to validate two clinical algorithms, the World Health Organization's symptom-based algorithm and the Chan Risk Score, to detect coprevalent and incident tuberculosis disease in child household contacts. **Results**: In Aim 1, household contacts were 9.8 (95% CI, 4.0–24.0) times more likely to have coprevalent tuberculosis disease compared to unexposed control groups. In Aim 2, we created two proposed scores that would minimize the number of contacts screened but found over 80% of contacts. In Aim 3, HIV-infection, young age, cavitary status of the index case, and past active tuberculosis disease in contacts were strong risk factors for incident tuberculosis disease. In Aim 4, the WHO symptom-based algorithm was high efficient at finding coprevalent and incident diseased children however the Chan Risk Score validated poorly. **Conclusions**: Household contact tracing is a highly effective tuberculosis case finding tool that must be used to supplement current tuberculosis control. New tools that optimize household contact tracing, such as predictive risk scores and symptomatic algorithms may entice National Tuberculosis Programs in low-income, high-burden settings to use this intervention.

INDEX WORDS: tuberculosis, Mycobacterium tuberculosis, transmission dynamics, HIV, human immunodeficiency virus, Uganda, contact tracing, infectious disease contact tracing, household contact tracing, tuberculosis control.

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CHAPTER 1: INTRODUCTION

Public Health Impact.

Tuberculosis is an ancient disease that has plagued humans for over 3000 years [1,2]. Despite the disease's longevity, efforts to eliminate or control the disease have been difficult and largely unsuccessful. In 2014, tuberculosis became the deadliest infectious disease globally with approximately 1.5 million deaths due to the disease [3]. Although tuberculosis is fully preventable and treatable, there were nine million new cases of tuberculosis globally in 2013 according to the World Health Organization [3]. Tuberculosis predominantly affects low-income countries and impoverished populations and is considered a "disease of poverty" [4].

Comorbidity between tuberculosis and other diseases also has a strong global impact on tuberculosis incidence and burden. Of all global cases, 360,000 individuals are coinfected with both tuberculosis and human immunodeficiency virus (HIV) [3]. Patients infected with HIV and latent tuberculosis infection are a group of high importance for tuberculosis control because they carry a substantial increased risk of progressive primary disease and reactivation tuberculosis disease [5,6]. Furthermore, HIV-infected patients have a substantially higher risk of death when tuberculosis disease progression occurs [7,8]. Post-mortem studies show that mortality due to tuberculosis among HIV-infected adult patients is between 30 – 40% [9]. The vast majority of these coinfected cases are in sub-Saharan Africa, where approximately 41% of tuberculosis cases also have HIV [3].

Global Tuberculosis Control.

For the past 25 years, tuberculosis control has been based on passive finding of diseased cases followed by effective treatment [10]. This predominantly relies on patient behavior to seek health care after becoming symptomatic. The World Health Organization has invested heavily both monetarily and intellectually into their plan of directly observed therapy, short course (DOTS), which attempts to enhance and strengthen the effectiveness of passive case finding in the health care system. After implementation of DOTS globally in 1994 [11], prediction models by global experts projected large scale reductions in tuberculosis incidence in the realm of 10 – 25% per year [12,13]. Recent reports in tuberculosis incidence, however, have been disappointing. Currently, global tuberculosis incidence is lowering at approximately 1% per year, much lower than anticipated [14]. Alarmingly, in sub-Saharan Africa, tuberculosis incidence is still increasing at approximately 3% per year despite high levels of monetary investment and research. Furthermore, over 30% of tuberculosis cases, approximately three million cases, remain undetected globally through current tuberculosis control methods and continuously transmit the disease to their social network [3,15]. These recent reports are concerning and have led to calls for supplementary tuberculosis control measures that aim to reduce *M. tuberculosis* transmission [16-19]. Active case finding, through household contact investigations of tuberculosis index cases have been proposed as a potential method to supplement current tuberculosis control [5,6,20-22].

Household Contact Investigation.

Household contact investigations involve the systematic screening for tuberculosis infection and/or disease of all members of homes where a case is

present. Examination of contacts makes sense since the household is an easily identifiable and common location for tuberculosis transmission. For this reason contact investigations have been a classic epidemiological paradigm used to study the epidemiology and transmission of tuberculosis [23,24]. Household investigations, however, have primarily been used by researchers to study the disease and invariably are used as a supplementary tuberculosis control method by national tuberculosis programs despite high yield of both infection and disease [25]. Reasons for limited use of contact tracing as a supplementary measure to tuberculosis control is multifactorial. Poor implementation of household contact investigations as a control measure persists even when they are included in the tuberculosis control framework and guidelines of local, national tuberculosis programs [26-29]. There is no conclusive evidence that there is a population level effect from household contact investigation [21,30]; thus, national tuberculosis programs may not be motivated to implement it, especially in the setting of limited resources. Household contact investigations lack standard procedures that have been empirically tested. Although on the surface, case detection in a household seems straightforward it can become complicated in the face of HIV infection and lack of effective diagnostics for children or early disease. Finally, household investigations may be resource intensive, and most national tuberculosis programs lack the funding to implement these investigations. In the face of these uncertainties, the World Health Organization has been cautious about its recommendations to national tuberculosis programs.

Most experts agree that the household of an index case is an optimal location to screen for undiagnosed tuberculosis and latent tuberculosis infection. This case

detection would have direct benefit to the individuals because they would be treated and to the family living in the household. But without addressing these salient reasons for not implementing household contact investigation, it is likely that this control measure will not be used.

The proposed research project is designed to address some of the perceived obstacles relating to household contact investigation. I hypothesize that a standardized algorithm for household evaluation of tuberculosis contacts would simplify the decision making process involved in household contact investigation and help to reduce the uncertainty involved in evaluating and treating contacts. Once developed and validated, this algorithm could be taught through standard professional education of tuberculosis control personnel and introduced using more novel technology-driven approaches using smartphones and applications. It is hoped that with the use of a valid algorithm, the process of contact investigation becomes more efficient and requires fewer resources.

Principal Goal of the Dissertation.

The overarching goal of this dissertation is to standardize and optimize possible household contact investigations to improve and control tuberculosis. One way to achieve this simplicity is to develop a standard algorithm for the diagnosis and management of household contacts of tuberculosis index cases. One form of an algorithm is a clinical risk score which may be a useful tool for programmatic use by National Tuberculosis Programs (NTPs). Standardizing household contact investigations has very rarely been performed but could allow and encourage national tuberculosis programs to use active case finding more effectively. This dissertation will fill that gap by giving people a clear direction, methodology, and incentive to perform active case finding through household contact tracing in the field in low-income, high-burden settings.

Specific Aims.

To address the primary goal of this dissertation, I propose three Specific Aims:

Specific Aim 1:

To determine whether the use of household contact investigation as a case-finding approach compared to searching for cases in the general community without known household contact is beneficial.

To address this aim, I will perform a systematic review and meta-analysis on published studies of household contact investigations that include appropriate, corresponding control groups without known contact to an infectious tuberculosis case. By comparing and contrasting the epidemiology of tuberculosis among household contacts of tuberculosis with the epidemiology of controls, I hope to be able to frame the value of household contact investigations at the individual.

Specific Aim 2:

To develop a simple, clinical risk point score for coprevalent tuberculosis disease among household contacts of tuberculosis index patients for use by tuberculosis control programs.

To address this aim, I will use a split-sample approach to develop a risk score in a derivation set and then test its performance in an internal validation set. We will then use an external study population from the same setting and recruited with the same study design to further validate the risk score. This score will then be compared with other risk scores that have been derived previously in the literature.

Specific Aim 3:

To develop a simple, clinical risk point score to detect incident tuberculosis disease amongst household contacts of tuberculosis index cases.

To address this aim, I will use a similar approach as for Specific Aim 2. In a split-sample of household contacts, I will derive a risk score in a derivation set then validate it in a validation set. In addition to this internal validation, I will externally validate the score by applying the risk score to a longitudinal study from Peru [31] and determine the test characteristics.

Methodological Designs of Dissertation Aims.

The study designs of the investigations included in this dissertation are all distinct however they all have the objective of measuring and quantifying tuberculosis transmission dynamics. Since tuberculosis transmission is difficult to measure epidemiologically we endeavored to use multiple methodologies and datasets in order to validate our results as much as possible.

The first aim is to conduct a systematic review and meta-analysis on studies detecting latent tuberculosis infection and tuberculosis disease in household contacts of tuberculosis index cases and control groups without known contact. This search will use multiple databases and additional researchers will be included in the search and abstraction process to provide reliability to the project.

The second aim involves the creation of a prediction risk score by using a derivation cohort from a large cross-sectional, household tuberculosis contact study investigating coprevalent tuberculosis disease. We will then test the validity of this score using internal validation through internal validation using k-fold validating techniques and through external validation using a separate, similarly designed household case-contact cohort. The derivation and validation studies were performed by distinct field workers, principal research investigators, and settings.

The third aim involves the creation of a separate risk score for incident tuberculosis disease from a prospective cohort study of household contacts of tuberculosis patients from Kampala, Uganda. This dataset includes incident cases after two years of follow-up. Multiple risk scores will be performed, depending on the data available in order to augment tuberculosis control programs. A risk score including only

variables that an index case would know when presenting to a health clinic will be a priority. Secondarily, a risk score including all variables, whether the index case would know them or not, will be derived as well. We will attempt to validate our results through several methods. We will self-validate our sample by dividing our study population into two groups and then comparing our risk score results. Next, we will attempt to validate our risk score through the use of another dataset from another location, both inside and outside sub-Saharan Africa. If possible, an individual patient data meta-analysis will be performed from all collaborating studies.

CHAPTER 2: LITERATURE REVIEW

Tuberculosis disease in humans is predominantly caused by the bacteria *Mycobacterium tuberculosis*. There are considered three clinical stages of the disease: 1) individuals without latent tuberculosis infection or tuberculosis disease, 2) individuals with latent tuberculosis infection without tuberculosis disease, and 3) individuals with tuberculosis disease. The disease is transmitted through exposure to airborne aerosols by direct contact with persons with infectious forms of the disease. Tuberculosis transmission occurs through coughing or speaking after which a healthy person acquires latent tuberculosis infection [32].

Latent *Mycobacterium tuberculosis* infection.

One third of the global population is estimated to carry this latent tuberculosis infection, representing a large reservoir of individuals susceptible to developing to disease stage of the disease at some point in their lifetime. This latent form of the disease is acquired through inhalation of aerosols containing *M. tuberculosis* organisms after which T lymphocytes are induced and propagate in an attempt to contain bacterial replication [33,34]. These lymphocytes are circulating in the bloodstream and are pervasive throughout the body within weeks to months after primary infection [34]. This latent stage of tuberculosis is asymptomatic, non-infectious, and includes no clinical manifestations of the disease [35]. Importantly, the incubation period of latent tuberculosis infection can be months, years, or a lifetime [36,37] and therefore many individuals carry the latent form of the disease for many years. Due to this, latent infection rates increase by age in both

the general population and high-exposure groups due to accumulated risk of exposure that occurs over the lifetime [38-40]. Currently, the available tests for latent tuberculosis infection, the tuberculin skin test and several interferon gamma assays, are unable to distinguish between recently acquired latent tuberculosis infection and infection transmitted in the remote past. Due to this, diagnosis of this form of the disease is considered to have limited implications by some experts [41,42].

Prevalence of latent tuberculosis infection varies considerably depending on the setting and risk factors for tuberculosis transmission [43]. Prevalence in high-income, low-burden countries, such as the United States or European countries, is relatively low due to low transmission rates and influenced heavily by immigrant populations coming from high-burden countries [44,45]. These rates can be anywhere from 2 – 20% infected. In the United States, latent tuberculosis infection was estimated to be 4.3% in 1999 – 2000 and 4.7% currently [46-48]. Latent infection rates in high-burden countries however can be substantial. In a tuberculin survey performed in Uganda in 1994, before the HIV epidemic, the rate of infection was estimated to be 14% (95% confidence interval, 12.9% – 15.4%) in children 10 years of age [49]. From this, Migliori and colleagues reported an annual risk of tuberculosis infection to be approximately 1.2% [49]. These rates are likely to be substantially higher currently due to the devastating effect of the subsequent HIV epidemic on the spread of tuberculosis disease throughout Uganda and the rest of sub-Saharan Africa. For example, in a tuberculin survey performed in 2008 – 2009 close to 40% of young adults between the ages of 15 – 24 with latent tuberculosis infection [50]. In addition, 53% of adults between the ages of 25 – 34 showed a tuberculin skin reaction ≥10 millimeters [50]. Latent tuberculosis infection rates in other

sub-Saharan African countries have shown similar results. In South Africa, rates among 5 – 10 year old children was 28% but increased to 88% among 30 – 35 year old individuals in the general population [39].

Diagnosis of latent *M. tuberculosis* infection.

Latent tuberculosis infection is currently diagnosed from two distinct diagnostic tests: the tuberculin skin test and interferon-gamma release assays [51]. Several forms of interferon-gamma release assays exist however two forms are currently licensed and available: the T-spot®.TB test (T-Spot) and Quantiferon-TB Gold test [52]. Both the tuberculin skin test and the various forms of interferon assays measure cell-mediated immune response to antigens specific to tuberculosis bacteria [53]. Despite this, these tests measure this immunological response in distinct ways.

The tuberculin skin test prompts a delayed-type hypersensitivity reaction that measures in-vivo inflammatory immunological response through stimulation of T lymphocytes [34,51]. The reaction to the skin test usually begin within 5 – 6 hours after application of the test, reach a peak from 48 – 72 hours after application, and diminish soon after [34,54]. Reactions from the tuberculin skin test can be detected only 2 – 10 weeks after initial infection however individual tuberculin reaction may diminish over time [55]. Interferon-gamma assays measure T-cell immunological responses through ex-vivo interferon production. Interferon production is prompted by *M. tuberculosis*-specific antigens, such as ESAT-6 and CFP-10 for Quantiferon-TB Gold and purified protein derivative (PPD) and control antigens for the Quantiferon-TB test [51-53].

Both of these tests are imperfect and when positive cannot indicate whether the individual has tuberculosis disease because they measure the host immune response to

tuberculosis antigens and not the quantity of mycobacteria in the host system itself [56]. Further limitations of each test exist. In some studies, the tuberculin skin test has been shown to have low sensitivity in individuals living with HIV and malnutrition [41,42]. Due to this anergy, a positive tuberculin skin test is considered positive at ≥5 millimeter induration rather than the standard ≥10 millimeters for the general population [54]. Low specificity to detect uninfected persons has also been shown in individuals vaccinated with Bacillus Calmette-Guérin (BCG) [57,58]. Interferon gamma assays have high specificity to detect uninfected individuals however has high individual person variability [59-61]. In addition, a major limitation of these tests is that false conversions are much more common than with the tuberculin skin test [59,62,63].

Despite limitations of both tests, a positive tuberculin skin test or interferon gamma assay result has been show to predict the development of incident, active tuberculosis disease in several studies [35,64-69]. A recent meta-analysis concluded that a positive interferon gamma assay result has a higher positive predictive value than a positive tuberculin skin test result, especially in “high-risk” settings [66]. Isoniazid preventative therapy has also been shown to reduce the risk of development of active disease in those positively diagnosed with the tuberculin skin test [64,70-72]. There is a lack of evidence to show that preventative therapy reduces the risk of developing tuberculosis disease among individuals with a positive interferon result however a few studies have been implemented [68].

Treatment of latent *M. tuberculosis* infection.

Treatment of latent tuberculosis infection is currently recommended for some groups at high-risk for progression from latent infection to active tuberculosis disease.

These recommendations have been inconsistent and controversial throughout the past twenty years. Currently the Centers for Disease Control and Prevention recommend that some high-risk groups are eligible for latent tuberculosis infection preventative therapy [54]. These groups include injection drug users, recent immigrants from high tuberculosis burden countries, children under four years of age, residents and employees of high-risk settings such as hospitals, prisons, or homeless shelters, persons living with HIV, recent contacts of tuberculosis cases, and other immunosuppressed individuals [54].

There are various treatment regimens of different lengths and with distinct levels of adverse effects [33,54,73,74]. These regimens include isoniazid for six months, isoniazid for nine months, rifampin for 3 – 4 months, isoniazid and rifampin for 3 – 4 months, and rifampin and isoniazid weekly for three months [33]. Comparison of these regimens is difficult because many of the clinical trials that have been implemented have not compared them directly and instead have compared them to placebo or another regimen [75]. A recently conducted network meta-analysis found that regimens with rifampin for three months or longer was as efficacious as those with isoniazid alone and had much higher adherence [75].

Adherence to treatment regimens for preventative therapy has generally been poor, especially in programmatic settings [28,76,77]. For results from studies that show programmatic results of contacts that initiate or complete preventative therapy can be seen in Table 5. Unsurprisingly, new regimens that are shorter (rifampin and isoniazid for 3 – 4 months, rifampin for 3 – 4 months, or rifampin and isoniazid weekly for three

months) have shown higher adherence than longer six to nine month regimens including isoniazid [78,79].

Preventative therapy for contacts of multi-drug resistant tuberculosis cases is a heavily debated topic amongst experts with differing viewpoints [80]. The most effective therapy and management for these susceptible contacts is currently unclear and national and international global health organizations differ in their recommendations for these contacts [54,74,81]. Currently, the World Health Organization recommends follow-up of contacts of multi-drug resistant tuberculosis cases for two years but does not include any form of preventative therapy [74,82].

Fluoroquinolone preventative therapy for contacts of multi-drug resistant tuberculosis patients has been proposed but is contentious [74,80]. For example, guidelines in the United States [54] and Europe [81] include fluoroquinolones as an option for preventative therapy however the World Health Organization does not [74]. This indecision may be due to the lack of quality studies that have investigated efficacy and effectiveness of fluoroquinolones to prevent progression to tuberculosis disease. No randomized clinical trials in multi-drug resistant tuberculosis patients have been performed to date. Two observational studies have shown promising results [83,84].

Active tuberculosis disease.

Risk of progression to active tuberculosis disease is estimated to be approximately 5% in the 12 – 18 months after initial tuberculosis infection and then 5% for the remaining lifetime, assuming other risk factors such as immunosuppression, diabetes, or other comorbidities are not present [85-87]. Risk of progression to active

tuberculosis increases in the first year upon being infected with HIV and this risk increases over time [88,89].

Clinical manifestations of active pulmonary tuberculosis disease include chronic cough, weight loss, night sweats, and fever. [90-92]. Infrequently, hemoptysis is also clinically presented in patients [90,92]. *M. tuberculosis* causes extensive caseous necrosis and, due to this, individuals with disease have a high prevalence of lung cavities [92].

Tuberculosis patients living with HIV have a distinct clinical presentation compared to those without HIV [93,94]. Coinfected patients have a decreased likelihood of cavitary lesions or pleural effusion and an increased likelihood in smear negative sputum and atypical disease including extrapulmonary tuberculosis disease [93,94]. Individuals coinfected with HIV may also have a reduced period of infectiousness, including duration of cough, likely because they are detected sooner by the health care system [95]. Furthermore, as CD4+ count declines in HIV infected patients, atypical clinical presentations of tuberculosis disease are more likely [94,96-100]. These may include reduced likelihood of cavitation, pulmonary infiltrates, or adenopathy and an increased likelihood for a lower sputum smear grade [94,96-100].

Treatment of active, drug-sensitive tuberculosis disease.

Current standard treatment of drug-sensitive tuberculosis disease is a minimum of six months of the four first line drugs of isoniazid, rifampin, pyrazinamide, and ethambutol [101]. The first two of the six months is called the intensive phase in which all four drugs are concurrently used. The next four months is considered the next four months of treatment which includes isoniazid and rifampin [102]. Supplementation of pyridoxine is sometimes recommended to prevent adverse effects from isoniazid, such

as neuropathy [101]. This regimen has a high treatment success rate. In trial conditions, positive treatment outcomes have been seen in up to 95% of patients while in programmatic settings treatment has been shown at similarly high rates [102].

Tuberculosis patients co-infected with HIV have an increased risk for relapse, treatment failure, and mortality compared to living without HIV. Due to this treatment of individuals coinfected with both diseases differs. A recent systematic review and meta-analysis pooled data from 33 studies and concluded that regimens with rifamycins for more than eight months and daily dosing during the intensive phase of treatment improved tuberculosis treatment outcomes [103,104].

Global Tuberculosis Control.

There are five approaches to TB control. 1) detect cases and give treatment therapy, 2) BCG, 3) Use of isoniazid preventive therapy in LTBI infection, 4) environmental controls in health care settings, 5) treatment of HIV infection. Control is practiced in this way throughout the world. For this dissertation we will focus on case detection. Household contact investigations is a type of active case finding.

Directly Observed Therapy, Short-Course.

In 1991, the World Health Assembly recognized tuberculosis as an international health problem and set two main goals for global control of the disease. These goals were “to detect 70% of existing smear positive tuberculosis cases and to cure 85% of those found by the year 2000”. Directly Observed Therapy, Short-Course, commonly referred to as DOTS, was first presented by the World Health Organization (WHO) in 1994 as guidelines for national tuberculosis programs to achieve these set up on goals.

Upon first implementation, DOTS was based on five main principles and components: governmental commitment for tuberculosis control, detection of new tuberculosis cases through passive case finding, treatment of new sputum smear positive cases through standardized short-course chemotherapy and directly observed therapy, a consistent supply of tuberculosis medication to the national tuberculosis program, and the creation and upkeep of a system of detection to monitor individual tuberculosis patient information. In 2002, the WHO provided an expanded description of DOTS.

There have been some reports of substantial decline in tuberculosis outcomes at a population level due to DOTS in countries such as Peru,[105] China,[106-108] and Bangladesh.[109] These results have been disputed however as economic advances over time, design issues, or inappropriate comparisons were causes for declines in these countries.[110-112] Furthermore, various countries have shown poor results from DOTS and an inability to effectively manage and implement the program.[113] The largely inadequate health system infrastructure results in poor execution of DOTS in real world settings. For example, a recent study in urban India found that even amongst the most highly-qualified clinical practitioners many patients were not directed to tuberculosis clinics for standardized treatment.[114]

Despite high-level recommendations, DOTS seems similarly effective compared to other treatment control programs. Several studies across distinct settings have shown little difference in effectiveness when comparing DOTS to self-administered therapy.[115-117]

Active Case Finding.

Active case finding is defined by the World Health Organization as “the systematic identification of people with suspected active tuberculosis in a predetermined target group by the application of tests, examinations, or other procedures that can be applied rapidly.” This process usually implies screening for tuberculosis outside of locations that provide health services, since this is usually performed from passive case finding and would not detect as many new, undetected cases.

Tuberculosis Household Contact Investigation.

The details on the methodology and specific nuances of performing a household contact investigation have been reviewed in several review manuscripts.[20,118-121] Newly diagnosed adult (usually either ≥15 or ≥18 years old) tuberculosis patients are identified from local health care clinics. Index cases are defined as the first tuberculosis case identified in a household and has one or more household contacts. Tuberculosis patients should be taken consecutively and can be either sputum smear positive or negative. Some guidelines suggest investigations concentrate on sputum smear positive cases only.[20]

Table 1. Index case, contact, and environmental characteristics that have been reported to increase the risk of latent Mycobacterium tuberculosis infection and tuberculosis disease from different studies.

Risk for latent *Mycobacterium tuberculosis* infection		
Index Case	Contact Susceptibility	Environmental
Smear status	History of tuberculosis	Family size
Cavitary Lung Disease	Family history of tuberculosis	Community disease prevalence
Female	Socioeconomic status	Ventilation (windows per room)
Multi-drug resistant disease	Male	Mining population
HIV serostatus	Age	Secondhand smoke exposure
Alcohol use	BCG vaccination status	Housing type
Smoking status	Country of residence	
Socioeconomic status	Smoking status	
Cough duration	Country of origin	
Treatment delay	Nutrition status	
CD4 count	Duration of tuberculosis exposure	

History of incarceration

Relationship to the index case

Occupation

Foreign-born (high-income countries only)

Alcohol use

Risk for Tuberculosis disease

Smear status	History of tuberculosis	Family size
Cavitary Lung Disease	Family history of tuberculosis	Community disease prevalence
Multi-drug resistant disease	Socioeconomic status	Ventilation (windows per room)
Alcohol use	HIV serostatus	Mining population
Country of residence	Age	Secondhand smoke exposure
Smoking status	BCG vaccination status	Housing type
Socioeconomic status	Country of residence	
Cough duration	Smoking status	
Nutrition status	Country of origin	

Genotype strain	Nutrition status/low BMI
Education level	Duration of tuberculosis exposure
Treatment delay	History of incarceration
	Relationship to the index case
	Occupation
	Foreign-born (high-income countries only)
	Alcohol use
	Diabetes status
	Latent tuberculosis infection status
	Silicosis
	Hepatitis B
	Hepatitis C
	Cirrhosis
	Chronic Obstructive Pulmonary Disease

Households with index cases are then visited by trained field workers as soon as possible to tuberculosis diagnosis. During this baseline visit, index cases are evaluated through a physical examination and medical history. Information is collected on a diverse range of demographic characteristics due to the fact that causes of tuberculosis infection and disease are multifactorial. Some of these characteristics may include age, sex, room where they sleep, cigarette smoking status, HIV serostatus, chest radiograph, and duration of cough. Extent of disease can be assessed through radiographic imaging results or sputum or culture smear samples. X-rays are graded independently by an experienced clinician using the National Tuberculosis Association classification system with sub-groupings for cavitary and non-cavitary disease.[122] Sputum samples are collected for laboratory testing of mycobacterial culture and microscopic assessment.

Household contacts of an index case is defined distinctly in different studies.[20] A household may be differ substantially based on the setting and culture in which the investigations is being implemented. Some examples of definitions of households given in contact investigations can be seen below.

Table 2. Definitions of a household from tuberculosis case-contact investigations in distinct settings

First author	Definition of Household
Gustafson[123]	"Houses in the study area are 1-storey, unattached, rectangular buildings, usually with 6-8 rooms and inhabited by 2-4 families. The house is usually owned by 1 of these families. The majority of houses do not have an internal ceiling; this leaves a gap between the internal walls and the roof allowing air to circulate freely among all the rooms."

Gilpin[124]	"defined as people living in the same group of huts .of a patient's kraal or in the same home"
Kenyon[125]	"This included children who reportedly lived at the same address or had a close personal relationship with the index case."
Lienhardt[126]	"The extended family living together in the same area and eating from the same pot"
Nakaoka[127]	"Eligible children were defined as any relative in the household <15 years of age who ate food prepared in the same cooking facilities as the index patient."
Radhakrishna[128]	"A household was defined as a group of persons living together and sharing food from the same kitchen."
Roelsgaard[129]	"A household constitutes a group of people who live and eat together."
Rutherford[130]	These children were required to have been living with the case >=3 months prior to diagnosis.
Whalen[5]	"A household was defined as a group of people living within one residence who share meals together and identified a head of family who made decisions for the household."

After visiting the household, field workers administer a socio-demographic questionnaire and a physical examination to each consenting household contact. Information collected can include age, sex, smoking status, alcohol usage, relationship to the index case, past active tuberculosis, HIV serostatus, diabetes status, and

household characteristics such as if the household has one or multiple families, the number of windows and individuals per household.

Additionally, a tuberculin skin test is performed by placing 0.1 milliliters of 5 tuberculin units of purified protein derivative (Tubersol, Connaught Laboratories, Limited; Toronto, Canada) on the volar surface of the left forearm of each participant using the Mantoux method. After application of each tuberculin skin test, a field worker will visit the household within 48 – 72 hours to record the diameter of the induration. A tuberculin skin test is considered positive if the skin induration reaction was ≥10 millimeters in diameter.[131,132] Evidence of a Bacillus Calmette-Guérin (BCG) vaccination is also assessed through inspecting BCG scars and supplemented with medical records when possible.

Household contacts can also be evaluated for co-prevalent and incident disease. Co-prevalent cases are defined as the identification of tuberculosis disease occurring at the baseline visit. Cases diagnosed within a short period after the baseline visit can also be defined as co-prevalent cases however this time length is not uniformly agreed upon.[133,134] A three month window for this definition is commonly used[5,6,135] however some believe only cases diagnosed at the baseline visit be used as the definition of coprevalent cases.[134,136] Tuberculosis cases diagnosed six months after the baseline visit has also been used.[137] After the initial baseline evaluation, household contacts free of active tuberculosis can be followed for a time frame and evaluated for incident disease. In order to have enough new cases to achieve enough power for statistical analysis contacts are usually followed for >1 year. Incident disease is defined as diagnosis of tuberculosis disease at any subsequent follow-up household visits.

Because members of households are in close proximity to each other, usually spend large amounts of time with each other, and share various environmental risk factors, tuberculosis is spread relatively easily. Household contacts have substantially higher rates of latent tuberculosis infection and disease than their community counterparts without household exposure. For example, a study in Kampala, Uganda found a 47% risk difference in latent infection when comparing household contacts of tuberculosis to community controls.[5] In a large study in South Africa, where the burden of tuberculosis and HIV is amongst the highest in the world, investigators found a wide disparity in tuberculosis disease among household contacts and community controls: amongst members of households with tuberculosis there were 230/2227 (10.3%) while there were only 4/785 (0.5%) tuberculosis cases in the community control group.[138]

Previous Systematic Reviews on Household Contact Investigations.

Four systematic reviews have been performed on contact investigations, the results of which can be seen in Table 6.[23,40,139,140] The outcomes of three of the four systematic reviews were latent tuberculosis infection and tuberculosis disease.[40,139,141] The fourth, most recent, systematic review concentrated solely on tuberculosis disease amongst contacts.[140] Morrison and colleagues searched for and collated data on the prevalence of latent tuberculosis infection and tuberculosis disease in studies of household contacts of tuberculosis index cases.[40] They calculated a pooled yield of 51.4% of latent tuberculosis infection and 2.3% for microbiologically-confirmed tuberculosis disease.[40] Among children, the pooled prevalence of latent tuberculosis infection was also high: 30.4% and 47.9% among

children <5 and between 5 – 14 years of age.[40] Fox and colleagues searched for studies investigating the prevalence and incidence of any type of contact, including close and casual, of a tuberculosis case.[23] After pooling data, they found a 45.4% prevalence of latent tuberculosis infection among household contacts from 73 studies and 51.5% prevalence among studies with any type of contact.[23] The prevalence of active tuberculosis among household contacts from 68 studies in low-income settings was 3.1%.[23] Shah and colleagues searched for published and unpublished studies that measured the prevalence of latent tuberculosis infection and the prevalence and incidence of tuberculosis disease of household contacts of multi-drug resistant tuberculosis index cases.[139] Lastly, Blok and colleagues pooled data from 19 TB REACH funded household contact studies to calculate the prevalence of tuberculosis disease.[140] These systematic reviews have been used to inform current World Health Organization guidelines on household contact investigations of tuberculosis cases.[142]

None of these reviews included control groups that take into account background rates of latent tuberculosis infection and tuberculosis disease in the general population. To supplement our knowledge of the use of contact investigations from current, published systematic reviews, we conducted a systematic review of case-control studies that evaluated either latent tuberculosis infection or tuberculosis disease in both a household contact and control groups. We included any control groups (i.e., community controls, hospital controls, or from the general population). We conducted searches in MEDLINE, Biosis, Web of Science, and Embase using the search terms shown in Table 3:

Table 3. Search terms for systematic review on studies with household contact of tuberculosis cases and control groups

Search terms	Category	Statement
("mycobacterium tuberculosis"	Mesh	OR
"tuberculosis"	Mesh	OR
TB	tiab	OR
“tuberculosis”)	tiab	OR
		AND
("contact tracing"	Mesh	OR
"household*"	All Fields	OR
“family contact*”	WORD	OR
"household contact*"	All Fields	OR
"childhood contact*"	TI	OR
Disease Transmission, Infectious	Mesh	OR
"Household transmission"	WORD	OR
“community controls”)	All Fields	

We found 5608 unique journal articles of which 39 studies were eligible. In all 33 studies evaluated latent tuberculosis infection while 11 studies evaluated tuberculosis disease in both groups. You can see the results from our systematic review below. A household contact was defined as any individual in the same household as a newly identified tuberculosis case. A community control was defined

as an individual from the same neighborhood as the household contact but without a tuberculosis index case in that household. A general population control was defined as a random sampling of individuals from the same population as the group of household contacts. This control group may have individuals with a tuberculosis case in their household although the assumption is that this is a minority of the control group. A hospital control is a selection of individuals without household contact but recruited from a hospital from the same setting.

Table 4 shows differences in latent tuberculosis infection among household contact and control groups. Three different types of controls were used in the 33 studies; 28 studies had community controls, three studies had a general population control, while two studies had a hospital control. Out of 33 studies, the risk difference in latent tuberculosis infection between household contact and control groups varied substantially between -11.5% (control group had more infection) to 54.5%. Thirty studies found that household contact groups had a higher rate of latent tuberculosis infection than while three studies found that control groups had higher rates of infection. This disparity demonstrates that household contacts are at substantially higher likelihood of latent tuberculosis infection and, deducing from this, that they are higher risk of tuberculosis transmission.

Table 5 shows differences in tuberculosis disease amongst household contacts and corresponding control groups. Like in the previous table, there were three different types of control groups; four studies had general population controls, two studies had community controls, while four studies had hospital controls. Five studies were performed in Africa (three in South Africa), two in Asia, two in Asia, two in the

Americas, and one in Australia. In all studies, the risk difference between household contacts and community controls was positive, meaning the household contacts always had more tuberculosis disease. This ranged from a 0.7% to a 23.5% difference. The number needed to screen to detect one additional case is shown for each study on the right hand side of the table. As the risk difference increases the number needed to screen becomes smaller. The number needed to screen was smallest in the hospital controls where it was 4.3, 4.5, and 6.6 in three hospital control studies while it was 58.8 in the fourth study with this type of control. The prevalence of tuberculosis ranged from 0.9 – 23.5% in the household contacts and from 0 – 3.1% in the control groups. Like the previous table, Table 5 shows, fairly definitively, that household contacts are a group at substantially high risk of tuberculosis disease compared to the rest of the population. This makes contacts of tuberculosis cases a potentially ideal risk group to target for tuberculosis prevention through targeted, specific intervention.

Despite these alarmingly high case detection rates, household contact investigations have key weaknesses as a method for tuberculosis control. These limitations involve the implementation and standardization of household contact investigations as a tuberculosis control procedure.

Table 4. Risk difference in latent tuberculosis infection when comparing household contact and community control groups

First Author	Year	Region	Type of Control	Infected Contacts	Total	Yield Contacts	Infected Controls	Total	Yield Controls	RD	NNS
Chan [135]	2008	Taiwan	Community Control	227	802	28.3	66	166	39.8	-11.5	-8.7
Hansted [143]	2009	Lithuania	Community Control	27	45	60.0	34	52	65.4	-5.4	-18.5
Mutsvangwa [144]	2010	Zimbabwe	Community Control	161	222	72.5	132	176	75.0	-2.5	-40
Kenyon [125]	2002	Botswana	Community Control	13	107	12.1	43	697	6.2	6.0	16.7
Narasimhan [145]	2012	India	Community Control	99	177	55.9	100	201	49.8	6.2	16.1
Mandalakas [146]	2012	South Africa	Community Control	158	343	46.1	98	286	34.3	11.8	8.5
Narain [147]	1966	India	Community Control	191	790	24.2	1102	9186	12.0	12.2	8.2
Lutong [148]	2000	China	Community Control	191	646	29.6	55	355	15.5	14.1	7.1
Gilpin [124]	1987	South Africa	Community Control	24	80	30.0	12	94	12.8	17.2	5.8
Connell [149]	2008	Australia	Hospital Control	16	34	47.1	16	54	29.6	17.4	5.8
Abu-Taleb [150]	2011	Egypt	Community Control	8	27	29.6	3	26	11.5	18.1	5.5
Shakak [151]	2013	Sudan	Community Control	27	98	27.6	15	163	9.2	18.3	5.5
Blahd [152]	1946	US	Community Control	32	143	22.4	133	3589	3.7	18.7	5.3
Gustafson [123]	2008	Guinea	Community Control	437	1059	41.3	201	921	21.8	19.4	5.2
Shaw [153]	1952	UK	Community Control	344	823	41.8	157	709	22.1	19.7	5.1
Kang [154]	2005	South Korea	Community Control	34	48	70.8	50	99	50.5	20.3	4.9

Nakaoka [127]	2008	Nigeria	Community Control	52	158	32.9	6	48	12.5	20.4	4.9
Madico [155]	1995	Peru	Community Control	97	175	55.4	129	382	33.8	21.7	4.6
Del Corral [156]	2009	Colombia	General Population	331	502	65.9	327	766	42.7	23.2	4.3
Lienhardt [126]	2002	Gambia	Community Control	1165	2664	36.1	430	2124	20.2	23.5	4.3
Méndez-Echevarría [157]	2011	Spain	Hospital Control	30	83	36.1	37	318	11.6	24.5	4.1
Crampin [158]	2011	Malawi	Community Control	152	214	71.0	244	552	44.2	26.8	3.7
Hill [159]	2006	Gambia	Community Control	174	400	43.5	14	98	14.3	29.2	3.4
McPhedra [160]	1935	US	Community Control	970	1342	72.3	255	705	36.2	36.1	2.8
Yassin [161]	2013	Ethiopia	Community Control	168	330	50.9	20	156	12.8	38.1	2.6
Rutherford [162]	2012	Indonesia	Community Control	144	299	48.2	7	72	9.7	38.4	2.6
Aspin [163]	1953	UK	General Population	219	332	66.0	757	2921	25.9	40.0	2.5
WHO [164]	1961	Kenya	General Population	130	247	52.6	238	2207	10.8	41.8	2.4
Schlesinger [165]	1930	UK	Community Control	42	68	61.8	80	438	18.3	43.5	2.3
Almeida [166]	2001	Brazil	Community Control	67	141	47.5	18	506	3.6	44.0	2.3
Whalen [5]	2011	Uganda	Community Control	1369	1918	71.4	282	1179	23.9	47.5	2.1
Vekemans [167]	2001	Gambia	Community Control	24	28	85.7	11	29	37.9	47.8	2.1
Hertzberg [168]	1957	Norway	Community Control	1248	2118	58.9	5	112	4.5	54.5	1.8

Table 5. Risk difference in tuberculosis disease when comparing household contact and community control groups

First Author	Year	Region	Type of Control	Diseased Contacts	Total	Yield Contacts	Diseased Controls	Total	Yield Controls	RD	NNS
Shapiro [138]	2012	South Africa	Community Control	230	2843	8.1	4	785	0.5	7.6	13.2
Gilpin [124]	1987	South Africa	Community Control	4	132	3.0	2	148	1.4	1.7	58.8
Kumar [169]	1984	India	General Population	25	312	8.0	47	1498	3.1	4.9	20.4
WHO [164]	1961	Kenya	General Population	7	247	2.8	11	2207	0.5	2.3	43.5
Becerra [170]	2005	Peru	General Population	10	1094	0.9	5	2253	0.2	0.7	142.9
Claessens [28]	2002	Malawi	Hospital Control	56	2766	2.0	11	3203	0.3	1.7	58.8
Bekker [171]	2012	South Africa	Hospital Control	7	46	15.2	0	15	0.0	15.2	6.6
Grzybowski [172]	1975	Canada	General Population	197	5960	3.3	3901	2973400	0.1	3.2	31.3
Connell [149]	2008	Australia	Hospital Control	8	34	23.5	0	54	0.0	23.5	4.3
Méndez-Echevarría [157]	2011	Spain	Hospital Control	19	83	22.9	2	318	0.6	22.3	4.5
Narasimhan [145]	2012	India	Community Control	2	191	1.0	0	211	0.0	1.0	100.0

Table 6. Systematic reviews compiling studies that investigated the yield of tuberculosis among contacts of tuberculosis index cases

First Author	Year	No. studies	Study population	Income level	% yield any active TB (95% CI)	% yield confirmed active TB (95% CI)	% yield latent TB (95% CI)
Morrison [40]	2008	27, 23, 19	HH contacts	Low and middle	4.5 (4.3 - 4.8)	2.3 (2.1 - 2.5)	51.4 (50.6 - 52.2)
Fox (Cohort 1) [23]	2013	71, 76	All contacts	Low and middle	3.1 (2.2 - 4.4)	NA	51.5 (47.1 - 55.8)
Fox (Cohort 2) [23]	2013	87, 92	All contacts	High	1.4 (1.1 - 1.8)	NA	28.1 (24.2 - 32.4)
Fox (Cohort 3) [23]	2013	68, 73	HH contacts	Low and middle	3.1 (2.1 - 4.5)	NA	45.4 (40.7 - 50.2)
Fox (Cohort 4) [23]	2013	29, 33	HH contacts	High	3.0 (2.0 - 4.4)	NA	30.0 (21.3 - 40.5)
Shah [139]	2014	25, 14	HH contacts of MDR cases	All	7.8 (5.6 - 10.0)	NA	47.2 (33.0 - 61.4)
Blok [140]	2015	19	HH contacts	Low and middle	1.8 (1.2 - 2.7)	1.5 (1.0 - 2.2)	NA

Difficulties in the Programmatic Implementation of Household Contact Investigations.

Although household contact investigations have a high yield for both latent tuberculosis infection and tuberculosis disease and, due to this, have been widely recommended by researchers and other global tuberculosis experts. Despite this, contact investigations are resource intensive and poorly implemented from a programmatic perspective.

Assessments of contact investigations performed in a programmatic manner are scarce but hint of struggle with the implementation of the intervention. Currently, the vast majority of NTPs, especially in low-income, high-burden settings, do not perform household contact investigations as part of tuberculosis control but instead are designed to identify patients that present themselves to the health care system and then treat these individuals.[25] When contact investigations are performed in a programmatic manner by NTPs they are usually done at a sub-par level where most contacts are not screened or given preventative therapy.[173-175] There may be many reasons why NTPs do not perform household contact investigations or fail to perform them adequately. Some reasons may include that these investigations are resource intensive, that simplistic methods to standardize which contacts should be screened and/or given preventative therapy have not been developed, apparent need for advanced, expensive laboratory facilities to provide acceptable clinical evaluation, and fears about re-infection and poor adherence in causing drug resistance.[25,28,173-175]

We conducted a search for studies that evaluate data that screen the number or proportion of household contacts found in a programmatic manner. We also searched

for studies that evaluated the number and proportion of household contacts who were eligible and were administered isoniazid preventive therapy.

A non-systematic review in MEDLINE (Pubmed) was conducted in preparation of this project using the search terms in Table 7:

Table 7. Search terms for non-systematic review on studies with programmatic data on screening household contacts and implementation isoniazid preventive therapy

Search terms	Category	Statement
("pulmonary tuberculosis"	Mesh	OR
"mycobacterium tuberculosis"	Mesh	OR
tuberculosis	All fields	OR
TB)	All fields	
		AND
(contact tracing	Mesh	OR
infectious disease contact tracing	Mesh	OR
house*	All fields	OR
contact*)	All fields	

We found 6465 unique journal articles. After a complete search of these articles we found twenty two patient cohorts (19 studies; 3 studies stratified cohorts by child and adult contacts) that investigated the proportion or yield of contacts of index cases that were eventually screened by the contact investigation. These studies are shown in Table 8. Most of the studies come from low or middle-income countries while two come

from the United States.[29,176] Nine out of fourteen studies found that contact investigations evaluated less than 50% of total contacts.[26-28,76,77,130,177-179] Further, seven studies found that contact investigations implemented as part of tuberculosis control evaluated less than 25% of total contacts.[26-28,130,177-179] Studies conducted in middle- and high-income countries (India and the United States) had high yield compared to low-income countries when performing contact investigations. The two studies from the United States showed a yield of 95.9% and 54.8% while two out of three studies from India showed a yield >65%.[29,176,180,181] These studies illuminate that implementation of contact investigation is complex and methods to standardize and simplify the process are necessary for this intervention to succeed in the field. In addition, monetary and logistical resources may play an important role in the implementation of contact investigations from a programmatic perspective.

In table 9, programmatic data is shown from studies that recorded the number of screened or eligible contacts that initiated isoniazid preventive therapy. In addition, in a few studies the amount of screen contacts that completed therapy was also reported. These studies again show that there are large disparities between studies concerning the proportion of eligible contacts that initiate therapy. This ranged from 3.9% to close to 70%. There was high heterogeneity between studies including those from only the United States and those from middle and low-income countries such as South Africa, Ethiopia, and India.

Tables 8 and 9 demonstrate the difficulties in the implementation of household contact investigation as a programmatic and supplementary tool in tuberculosis control. A large effort must be made to standardize and simplify the work of local tuberculosis

centers in high tuberculosis burden settings that are largely overwhelmed with insufficient resources. The goal of this dissertation is to attempt to assuage these difficulties and assist local and national tuberculosis programs in implementing household contact investigations as a supplementary tool to directly observed therapy.

Table. Studies reporting programmatic data on the proportion of contacts screened and the number of tuberculosis cases amongst screened contacts

First Author	Publication year	Setting	No. index cases	No. total contacts	No. household contacts screened (% yield)[a]	No. screened household contacts with tuberculosis (% yield)[b]
Claessens [28]	2002	Malawi	267	365	33 (9.0)	6 (18.2)
Assefa [76]	2015	Ethiopia	203	230	78 (33.9)	2 (6.1)
Rekha [27]	2009	India	253	220	31 (14.1)	0 (0)
Gebregergs [177]	2015	Ethiopia	418	1492	278 (18.6)	18 (6.5)
Van Wyk [178]	2010	South Africa	NA	30	7 (23.3)	0 (0)
Van Wyk [26]	2011	South Africa	NA	205	25 (12.2)	NA
Pothukuchi [180]	2011	India	248	172	116 (67.0)	0 (0)
Kliner (≥5 yo cohort) [182]	2013	Swaziland	NA	547	131 (23.9)	2 (1.5)
Kliner (<5 yo cohort) [182]	2013	Swaziland	NA	111	26 (23.4)	2 (7.7)
Osman [77]	2013	South Africa	NA	525	244 (46.5)	NA
Rutherford (cohort 1) [130]	2013	Indonesia	410	437	73 (16.7)	NA
Tornee [183]	2005	Thailand	325	NA	169 (52.0)	NA

Shivaramakrishna [181]	2014	India	188	271	218 (80.4)	9 (4.1)
Nyirenda [179]	2007	Malawi	1438	1891	146 (7.7)	32 (21.9)
Thanh (≥5 yo cohort) [184]	2014	Vietnam	1091	3825	458 (12.0)	26 (5.7)
Thanh (<5 yo cohort) [184]	2014	Vietnam	NA	293	16 (5.5)	1 (6.3)
Gazetta [185]	2006	Brazil	112	263	166 (63.1)	3 (1.8)
Hartwig (<15 yo cohort) [186]	2007	Brazil	NA	104	63 (60.5)	NA
Hartwig (>15 yo cohort) [186]	2007	Brazil	NA	4348	389 (8.9)	NA
Oliviera [187]	2015	Brazil	21	43	15 (34.9)	NA
Webb [176]	2003	USA	2492	33334	31963 (95.9)	212 (0.7)
Reichler [29]	2003	USA	360	3824	2095 (54.8)	24 (1.1)
MMWR (Smear positive) [188]	2016	USA	41646	692672	569526 (82.2)	4307 (0.8)
MMWR (Smear negative) [188]	2016	USA	23549	188422	152877 (81.1)	915 (0.6)

Abbreviations: IPT, isoniazid preventative therapy; No., number.

[a] This is the number and proportion of contacts screened from the total number of contacts.

[b] This is the number and proportion of contacts that were diagnosed with tuberculosis of the number of screened contacts.

Table 9. Studies reporting programmatic data on the proportion of screened household contacts eligible for IPT that initiated and completed treatment

First Author	Publication year	Setting	No. contacts screened eligible for IPT	No. contacts initiated IPT (% yield)[a]	No. contacts completed IPT (% yield)[b]
Claessens [28]	2002	Malawi	33	23 (69.7)	NA
Assefa [76]	2015	Ethiopia	78	3 (3.9)	NA
Rekha [27]	2009	India	31	15 (48.4)	NA
Gebregergs [177]	2015	Ethiopia	278	NA	NA
Kliner [182]	2013	Swaziland	24	12 (50)	NA
Van Wyk [178]	2010	South Africa	7	7 (100)	NA
Van Wyk [26]	2011	South Africa	25	2 (8.0)	NA
Pothukuchi[180]	2011	India	116	97 (83.6)	NA
Osman [77]	2013	South Africa	244	141 (57.8)	19 (13.4)
Rutherford (cohort 1) [130]	2013	Indonesia	73	6 (8.2)	NA
Oliviera [187]	2015	Brazil	9	1 (11.1)	0 (0)

Van Soelen [189]	2013	South Africa	24	4 (16.7)	NA
Rutherford (cohort 2) [130]	2014	Indonesia	112	82 (73.2)	21 (25.6)
Shivaramakrishna [181]	2014	India	218	70 (32.1)	16 (22.8)
Marks (TST+ cohort) [190]	2000	USA	1725	1277 (74.0)	707 (56.0)
Marks (<5 age cohort) [190]	2000	USA	557	252 (45.2)	NA
Marks (HIV+, TST-) [190]	2000	USA	84	19 (22.6)	8 (42.1)
Sprinson [191]	2003	USA	4609	3048 (66.1)	1958 (64.2)
Jereb [192]	2003	USA	12901	9018 (69.9)	5746 (63.7)
MMWR (Smear+) [188]	2016	USA	121837	86975 (71.4)	56514 (46.4)
MMWR (Smear-) [188]	2016	USA	26424	17846 (67.5)	11745 (44.4)

Abbreviations: IPT, isoniazid preventive therapy. USA, United States of America.

[a] These are the number and proportion of screened contacts that initiated IPT

[b] These are the number and proportion of contact that initiated IPT that also completed IPT

Disease Risk Score.

History and Development of Clinical Risk Scores.

Prediction risk scores are a combination of clinical, epidemiologic, environmental, and social risk factors that are combined to predict the presence of current disease or the risk of future disease [193]. Out of all potential risk factors, the most influential factors for the main outcome are each given a potential point score. The more influential the risk factor for the outcome the more points that factor will receive. Each participant will then be given a total, summated point score that equates to their potential risk of disease. These point scores are useful for health programs in that they are easily used and implemented in the field. They are also more interpretable than multivariate regression models which most studies are used and most field workers cannot always comprehend.

A disease prediction risk score is only as good as its ability to validate in other study populations.[194,195] In order to achieve this, internal and external validation are possible.[195,196] Internal validation may include bootstrapping, cross-validation, or split-sampling techniques.[197,198] Validating the score internally can provide useful insight into the validity of your score in another identical population. Despite this, they cannot speak to how well a prediction score performs in an external population.[194-196] This measure of validation speaks to the reproducibility of the prediction score.

External validation allows for implications regarding how suitable a prediction risk score in external populations from the origin study. Validation cohorts are with a separate population from the original study usually with the same study design as the derivation cohort.[199,200] At times, validation cohorts use a different study design than the

derivation cohort, however substantial bias can occur in these cases usually leading to overestimation of the score's performance.[199]

Three studies, Wasson and colleagues (1985), Laupacis and colleagues (1997), and Reilly and colleagues (2006), developed lists of methodological standards used to evaluate clinical prediction scores and evaluated studies from their respective time periods.[200-202] Wasson and colleagues (1985) details seven guidelines for studies using a predictive risk score that include 1) explicit definition of the outcome, 2) explicit definition of findings used to predict the outcome, 3) patient age and sex is stated in the manuscript, 4) the study site is described sufficiently, 5) the mathematical modelling technique is described in detail, 6) a misclassification rate is tested, and lastly 7) effects of clinical use is also prospectively tested.[200] We will perform our disease prediction scores with guidance from these standards by experts and adjust our methodology when needed to conform to these standardized guidelines.

Disease Risk Scores for Tuberculosis.

Disease risk scores have invariably been used in the study of tuberculosis despite the fact that susceptibility and risk of infection and progression to tuberculosis disease differ considerably depending on distinct individual and environmental characteristics. Most of studies using risk scores to study tuberculosis have been to investigate methods to standardize isolation of tuberculosis patients in hospital settings.

Disease risk scores and symptom based clinical indexes can provide practical and timely tools for tuberculosis health workers, laboratory technicians, and clinicians to use in-the-field. Many of the existing risk scores concentrating on tuberculosis have been created to improve the diagnosis of tuberculosis disease.[203-205] Other studies have

tried to perfect scores to identify which patients should be isolated in a hospitalized or emergency department setting.[206-209] One study tested and validated a risk score for the development of tuberculosis in child contacts.[135] This study included all contacts (household and community level contacts) and restricted their study population to children ≤12 years of age. Evaluating the effect of any type of contact may be important for high-income, low-burden countries such as Taiwan or the United States that have the resources and tuberculosis control infrastructure to track contacts in such a high volume.[29,190] However, tracking all contacts of tuberculosis would be difficult for low-income, high-burden countries. Household contact investigation is seen as an effective, supplementary control method to current tuberculosis control.[21,210,211]

To our knowledge, there has only been one study creating a point score quantifying *M. tuberculosis* exposure and evaluating latent tuberculosis infection.[212] This risk score included only children with and without tuberculosis exposure between the ages of three months and fifteen years of age and therefore is restricted to pediatric populations. In total, 536 children were included in Mandalakas and colleagues study; 350 household contacts of tuberculosis cases and 186 community controls not exposed in the household. The characteristics of the risk score created by Mandalakas and colleagues can be seen in Table 10.

Table 10. Predictive risk score questions used in Mandalakas and colleagues, 2012 [212]
Group 1. Sleep Proximity and Maternal Tuberculosis
Is the index case the child's mother?
Is the index case the child's primary caregiver?
Does the index case sleep in the same bed as the child?

Does the index case sleep in the same room as the child?
Group 2. Infectivity of the Tuberculosis Index Case Is the index case coughing? Does the index case have reported pulmonary tuberculosis? Does the tuberculosis index case have smear-positive sputum?
Group 3. Frequency of the Child's Exposure to the Tuberculosis Index Case Does the index case live in the same household as the child? Does the index case see the child every day?
Group 4. Number of Adults with Tuberculosis in the Household Is there more than one adult tuberculosis case in the child's household?

* Each question counts for one point (0 or 1) on the risk score for latent tuberculosis infection.

Latent tuberculosis infection was measured with three tests (tuberculin skin test, T-spot. TB, and Quantiferon assay) and individuals were considered infected if two of the three tests were positive. Mandalakas and colleagues did not include a validation cohort, either through self-validation or with an external cohort.

Quantification of Tuberculosis Exposure.

Tuberculosis is transmitted almost exclusively by airborne contact through the release of mycobacteria tuberculosis bacilli by a diseased individual into the atmospheric environment of a susceptible, healthy person.[213-215] *M. tuberculosis* transmission is assumed to occur primarily through coughing in a shared space however talking, breathing, singing, and others may also cause spread of the

disease.[16,32,216-221] Measuring tuberculosis transmission is difficult because defining adequate exposure for a new transmission event is difficult and can vary based on a myriad of factors. The setting specific characteristics necessary for tuberculosis transmission to occur is not completely understood however and may depend upon host (contact), vector (tuberculosis bacilli), the source case (individual with disease), the duration and intensity of exposure, or environmental (setting of exposure, ventilation, etc.) characteristics.[6,16,17,32,118,126,216] Further complicating tuberculosis transmission dynamics are that characteristics in these routes may positively or negatively interact with one another to impact extent of disease spread.[6,118,126] These factors are numerous, complex, and may work independently or synergistically complicating how to measure exposure when studying tuberculosis transmission dynamics. Designing a study that can measure transmission adequately has varied over time and involved different study designs.

Current knowledge of tuberculosis transmission comes primarily from classic studies performed from the 1950s – 1960s by Riley and colleagues demonstrating that droplet nuclei from infectious tuberculosis patients led to tuberculosis transmission among guinea pigs.[213-215] In these studies, hundreds of healthy guinea pigs were isolated and exposed to exhaust airborne droplet nuclei from a tuberculosis ward. Riley and colleagues were also able to show that tuberculosis patient infectiousness was highly distinct[213,214] and that transmission was markedly reduced once treatment began.[213-215] These studies were later recreated in Peru[222-224] and then elsewhere[225] with similar results. Methods used in these investigations are compelling because the guinea pigs included in the study were completely isolated and temporal effects are

controlled for. A similar study in humans is unfeasible due to ethical reasons. In addition, exposures outside the study environment (whether it be a household, workplace, hospital, etc.) may be unmeasured and therefore where the transmission event occurred is not certain.[223]

Other methodological approaches to accurately measure tuberculosis transmission have been attempted in humans by creating environments of exposure to tuberculosis cases while also reducing the impact of external exposures. Several studies on long airline flights with an individual with tuberculosis have been implemented.[226-228] An airplane is a relatively isolated, cramped environment of intense exposure. Driver and colleagues demonstrated that airplane contacts of the tuberculosis case had increased risk of infection with increasing hours of exposure.[228] Kenyon and colleagues displayed similar results on a flight with a case of multi-drug resistant tuberculosis.[227] Tuberculosis transmission dynamics has been investigated in other closed, isolated settings such as submarines.[229]

Household contact investigations have also been conducted numerous times to investigate tuberculosis dynamics.[23,40] These types of investigations allow for

CHAPTER 3: METHODOLOGY

This section is split into two separate sections that discusses the methodology for the three aims of the dissertation. Aim 1 will be discussed separately from Aims 2 and 3 due to the distinct study design of the systematic review that will be conducted. Since Aims 2 and 3 and very similar in their methodological and analytical process they will be discussed jointly in one section.

Methodology for Specific Aim 1.

In aim 1 of this dissertation, I plan to implement a systematic review and meta-analysis on studies detecting latent tuberculosis infection and tuberculosis disease in household contacts of tuberculosis index cases and corresponding control groups without known contact. As seen above, a systematic search in MEDLINE has already been performed (Table 5 and 6). This search will be expanded to use multiple databases and additional researchers will be included in the search and abstraction process to provide reliability to the project.

Search Strategy.

I will first search the literature for systematic reviews investigating *M. tuberculosis* infection or disease in household contact and control groups. Four systematic reviews on contact evaluations exist, however none included control groups.[23,40,139,140] We will then aim to compile all studies investigating two groups: individuals in household contact with a tuberculosis case and those in some form of control group. We will not restrict inclusion to studies with a specific type of control. Contacts and controls of all ages will be included.

We will search journal articles of any study design in Medline, Web of Science, Biosis, and Embase electronic databases. The search approach will be conducted with the help of a librarian database consultant and was updated on October 2014. Key words in these database searches will include tuberculosis, *Mycobacterium tuberculosis*, tuberculin, contact*, transmission, childhood contact, and household contact. We will not restrict articles by publication date and will include articles in English and Spanish. The references of multiple reviews, both systematic and descriptive, will also be searched and evaluated for eligibility.[23,40,139,216,217,230] I will hand search the table of contents of the following journals: *The International Union of Tuberculosis and Lung Disease*, *Tubercle*, and the *American Review of Respiratory Disease,* as well as online abstract books from The Union Conference on Lung Disease (2004 – 2013). Dissertations and conference abstracts will be included for collation if eligible. Corresponding authors of journal articles will be contacted for additional data if a study met eligibility criteria but did not stratify by age.

After the search and exclusion of duplicate articles, I will independently screen articles by title, abstract, and text for full review and inclusion in the study. A data extraction form will be developed and piloted. Using this form, I will independently extract all data from eligible studies and then compare results. From each article, I will collect information on the year of publication and implementation, the definition used for latent infection, study design, and recruitment methods. Characteristics extracted from index cases will include method of diagnosis, total number of cases found in household, and smear grade. From contacts and controls, I will collate information on age, number with latent tuberculosis, number with tuberculosis disease, and matching characteristics

between groups (neighborhood, age, sex, etc.). I will also collect national tuberculosis prevalence data from World Health Organization (WHO) databases for each study conducted after 1990.[231] Studies will be classified into income levels through use of World Bank definitions (high, middle, and low income countries) as of 2013.[232] Additional data on methods and results included in each study will also be extracted when available to compare differences in study design in each study.

Definition of key terms.

Tuberculosis cases in the household will be considered source cases and eligible if diagnosis was confirmed either bacteriologically (sputum smear or culture positive) or radiographically. Descriptions of the household is defined differently between studies and therefore we will use each study's definition of household (see Table 1 for definition used for household within a selection of household contact studies). Studies using the tuberculin skin test or any type of interferon gamma assay to diagnose latent tuberculosis infection will be included.

Statistical Analysis.

I will estimate the odds ratio for infection and disease in the household compared to the control group for each study and then combine these odds ratios using a random effects model. A random effects model with DerSimonian and Laird weights, equalizing the weight of the studies to the pooled estimate, will be used because of the high level of heterogeneity found in the odds ratio estimates among studies.[233] After this, the number needed to screen (NNS) to detect one additional case (either latent tuberculosis infection or active tuberculosis disease) will be calculated for each study and then pooled together. This statistic is calculated through the formula: NNS

$= \frac{1}{Absolute\ Risk\ Reduction}$. The I^2 statistic will be used to assess heterogeneity between studies.[234] I will stratify the analysis by pre-specified characteristics of the chosen studies and then use random-effects univariable and multivariable meta-regression to calculate ratio of odds ratios and investigate causes of heterogeneity. Variables will be chosen for inclusion in the multivariate model by use of the coefficient of determination, or adjusted R^2 statistic, which represents the proportion of between-study variance explained by the model. The adjusted R^2 will be estimated by use of the restricted maximum likelihood and the model that explained the most between-study variance was chosen. Stata statistical software will be used to perform all analyses; the metan command will be used to create forest plots and the metareg command will be used to perform meta-regression.

Various sensitivity analyses will be conducted to assess potential bias including comparing crude and adjusted odds ratios when provided, stratification by study design, and comparing studies from various time periods.

Methodology for Specific Aims 2 and 3.

Study Setting.

Kampala, Uganda

The study populations for the main two datasets used in this dissertation will be located in Kampala, Uganda. Uganda is one of 22 countries with the highest burden of tuberculosis globally. The incidence rate of all forms of disease is 300 cases per 100,000 and 155 cases per 100,000 for smear-positive tuberculosis. These rates have increased since 1993 despite a fully implemented DOTS program in the country [3]. Nearly one quarter of the country's cases occur in the greater metropolitan area of

Kampala which includes the divisions of Rubaga and Kawempe (contiguous divisions in the western part of the city), where rates of tuberculosis have been measured to be 800 to 1000 cases per 100,000.[3,235]

Study design and populations.

Two primary studies, the Kawempe Community Health study (1995 – 2008) and the Community Health Social Network study (COHOSONET; 2012 – present), will be used to perform aims 2 and 3. One or two other studies will be selected to validate aim 3 on detection of tuberculosis disease. These studies were conducted in Peru[31,72,236] or South Africa.[237] Van Schalkwyk and colleagues and Zelner and colleagues were conducted in 2014[72,237] while Grandjean and colleagues[31] was conducted in 2015.

Kawempe Community Health Study.

The Kawempe Community Health study is a prospective investigation studying risk factors for latent tuberculosis infection and tuberculosis disease in household contacts of adult index cases. This study began in 1995 and was completed in 2008. Numerous studies from this investigation have been reported.[5,6,131,238-240]

The recruitment and study population will be discussed below and all characteristics collected from tuberculosis index cases, household contacts, and about the household environment are shown in table 11.

Table 11. Variables collected from index cases, household contacts, and the household environment in the Kawempe Community Health survey

Individual	Characteristic
Tuberculosis index case	Age
	Sex
	Height
	Weight
	Sputum smear status
	HIV status
	Duration of cough
	Chest radiograph
	Cigarette smoking status
	Room where they sleep
	Alcohol usage
	Tuberculin skin test induration (millimeters)
	No. contacts associated with each index case
	Marital status
	Religion
	Tribe
	Weight loss
	Anorexia status
	Presence of blood in cough

	Education level
Household contacts	Age
	Sex
	Height
	Weight
	Sputum smear status
	HIV serostatus
	Duration of cough
	Chest radiograph
	Cigarette smoking status
	Room where they sleep
	Alcohol usage
	Relationship to the index case
	Known contact with tuberculosis case outside household
	BCG vaccination status
	Past active tuberculosis
	Closeness to the index case (same bed, same room, etc.)
	Tuberculin skin test induration (millimeters)
	Marital status
	Religion
	Tribe

	Weight loss
	Anorexia status
	Cough duration
	No. of hours per day with index case
	Education level
Environmental	Number of individuals in household
	Smoker in the household
	Number of windows in the household
	Number of rooms in the household
	Number of families in the household
	Charcoal in the household
	Number of individuals per room in household
	Number of doors per room

First, newly diagnosed tuberculosis patients ≥18 years old were identified from the National Tuberculosis and Leprosy Program at Old Mulago Hospital in Kampala, Uganda. Index cases were defined as the first tuberculosis case identified in a household, in their first disease episode, laboratory diagnosed with either sputum culture or smear positive tuberculosis, and had one or more household contacts.

Households with index cases were visited by trained field workers within two weeks of tuberculosis diagnosis. During this baseline visit, index cases were evaluated

through a physical examination and medical history. Information was collected on age, sex, room where they sleep, cigarette smoking status, HIV serostatus, chest radiograph, and duration of cough. Extent of disease through radiographic imaging results was graded independently for cavitary and noncavitary disease by an experienced clinician using the National Tuberculosis Association classification system with standard sub-groupings (normal, minimal, moderately advanced, far advanced).[122] Sputum samples were also collected for laboratory testing of mycobacterial culture and microscopic assessment.

Household contacts of an index case were defined as any individual within the same household for at least seven consecutive days within three months of diagnosis. Field workers administered a socio-demographic questionnaire and a physical examination to each consenting household contact, collecting age, sex, height, weight, smoking status, alcohol usage, relationship to the index case, contact with an individual with tuberculosis outside the household, past active tuberculosis, HIV serostatus, and household characteristics such as if the household has one or multiple families, the number of windows and individuals per household. Additionally, a tuberculin skin test was performed by placing 0.1 milliliters of 5 tuberculin units of purified protein derivative (Tubersol, Connaught Laboratories, Limited; Toronto, Canada) on the volar surface of the left forearm of each participant using the Mantoux method. After application of each tuberculin skin test, a field worker revisited the household within 48 – 72 hours to record the diameter of the induration. Evidence of a BCG vaccination was assessed through inspecting BCG scars and supplemented with medical records when possible.

HIV testing was performed on both index cases and household contacts older than five years old with an enzyme-linked immunosorbent assay (Cambridge BiosScience, Worcester, Massachusetts). Children under five years old were HIV tested if they were diagnosed with tuberculosis or their mother tested positive for HIV. If the mother tested negative for HIV then the child was also presumed to be negative. HIV seropositive individuals and children less than six years of age without active tuberculosis were offered a six month course of isoniazid treatment.

Contacts with a tuberculin skin test induration <5 millimeters at the baseline household visit were followed up three months later to test for skin test conversion. Conversion was defined a second tuberculin skin test induration ≥10 millimeters in diameter and an increase of ≥6 millimeters from the first skin test.

Household contacts were also evaluated for co-prevalent and incident disease. Co-prevalent cases were defined as the identification of tuberculosis disease occurring at or within three months of the baseline visit. After the initial baseline evaluation, household contacts free of active tuberculosis were followed for two years at six month intervals and evaluated for incident disease. These contacts could have either a positive or negative tuberculin skin test. Incident disease was defined as diagnosis of tuberculosis disease at any of these follow-up household visits.

Table 12. Definitions of participants in the Kawempe Community Health study in Kampala, Uganda.

Individual	Definition
Tuberculosis index case	≥18 years of age; first tuberculosis case identified in the household; has at least one household contact; first episode of

	tuberculosis; laboratory diagnosed with either sputum smear or culture positive test result
Household tuberculosis case-contact	Household contacts of an index case were defined as any individual within the same household for at least seven consecutive days within three months of diagnosis.
Co-prevalent tuberculosis case	Identification of tuberculosis disease occurring at or within three months of the baseline visit.
Incident tuberculosis case	Incident disease was defined as diagnosis of tuberculosis disease at any of these follow-up household visits.
Latent tuberculosis infection	A tuberculin skin test ≥5 or ≥10 millimeters
Tuberculin skin test conversion	A second tuberculin skin test induration ≥10 millimeters in diameter and an increase of ≥6 millimeters from the first skin test.
Community Controls	Households with no tuberculosis case in the past one year, at least one member in the household was within five years of age to the index case, and the household had more than one household member

Community controls were also included in the Kawempe Community Health study to provide a measure of background latent tuberculosis infection. Recruitment and selection of community controls is both important and difficult.[20,120] Since tuberculosis outcomes is influenced by so many different environmental, individual, and genetic characteristics choosing appropriate, similar controls is problematic and may create selection bias.[120]

In this study, controls were matched to index households through socioeconomic status and age of the index. Control households were identified by selecting a neighboring village to the index household within the same parish; then investigators randomly selected a control household either from a preassembled list of village homes or through consecutively recruiting households along a road. Households were eligible to be controls if no case of tuberculosis was present in the household for at least one year, at least one member in the household was within five years of age as the index case, and the household contained two or more members.

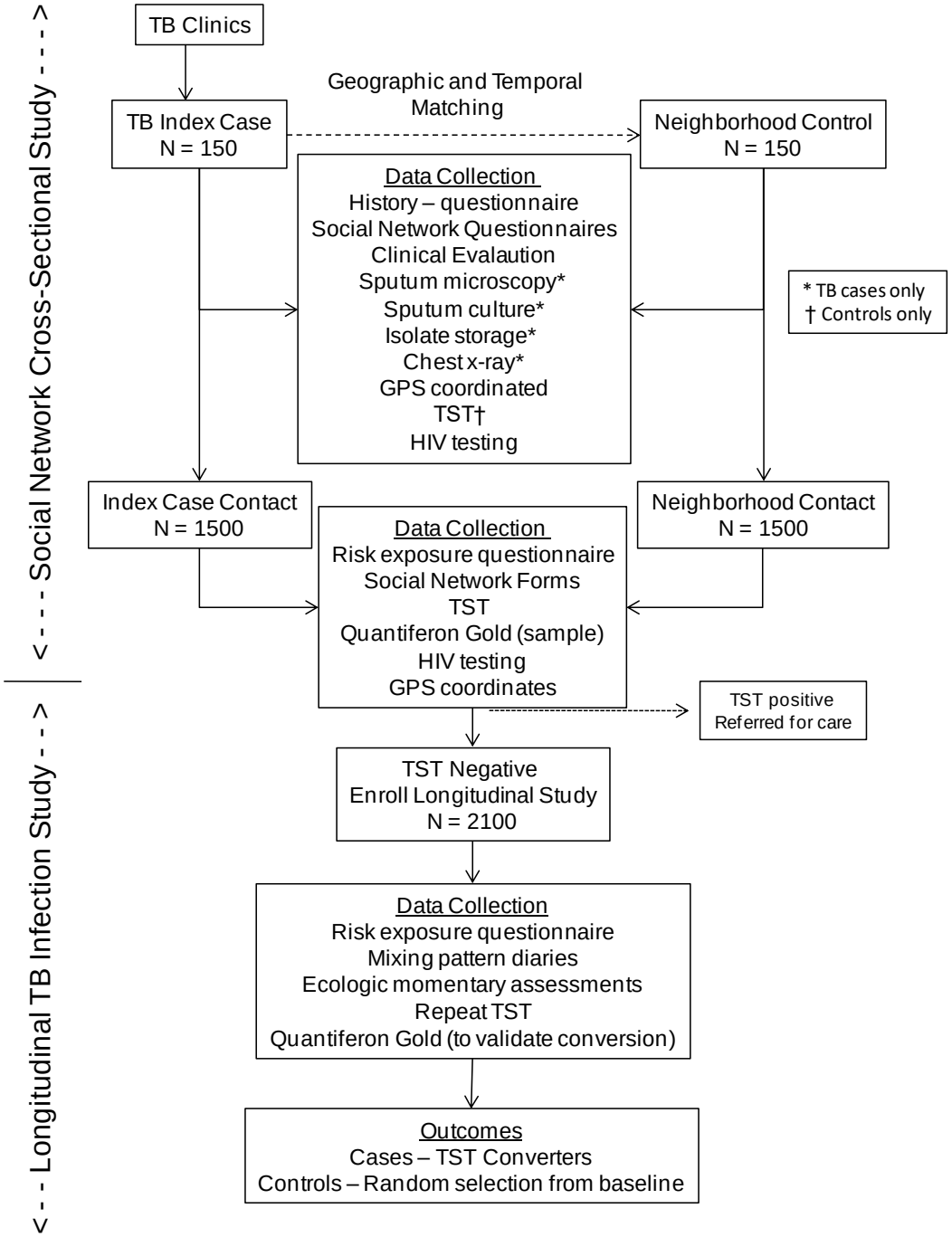
Community Health and Social Networks of Tuberculosis (COHSONET) Study.

COHOSNET is a large social network study set in Kampala, Uganda with collaboration from University of Georgia and Makerere University. The three primary aims of the study are to estimate the probability of infection and disease according to proximity to index tuberculosis case, to determine the likelihood of direct transmission between tuberculosis cases with the same strain of *M. tuberculosis*, and to determine the risk of new infection with *M. tuberculosis* in high risk environments in an urban African setting. To answer these aims a cross-sectional, community based study including tuberculosis contacts and controls followed by a longitudinal, tuberculin skin

test conversion study will be performed. The complete recruitment profile and study designs from the COHSONET study can be seen in figure 1 below. For this dissertation we will be focusing on the cross-sectional, community-based portion of the recruitment profile including baseline evaluation for tuberculosis infection and disease amongst household contacts and community controls.

To attempt to answer these research questions, research teams in Kampala, Uganda, with statistical collaboration from teams in Georgia, recruited 150 adult tuberculosis index cases who reside in the Rubaga division of Kampala and who present to one of the clinics operated by the National Tuberculosis Control Program. A case of tuberculosis was defined as a patient with signs and symptoms consistent with pulmonary tuberculosis who has at least one positive sputum smear for acid-fast bacilli. Smear-positive cases of tuberculosis were specifically recruited because they are most likely to transmit infection to contacts. These index cases will be frequency matched by age, sex, and parish with 120 community control index cases. Both tuberculosis index cases and community controls will be between 15 and 65 years old. Household and social network contacts of index cases and controls are also being enrolled for an expected total between 2500 – 3000 participants. These contacts will be of any age or gender and all will be evaluated at baseline for latent *M. tuberculosis* infection and disease through a cross-sectional, community-based survey.

Figure 1. Recruitment for the Community Health and Social Networks of Tuberculosis study



Similar to the Kawempe Community Health study, community controls were recruited into COHSONET. As index cases are enrolled in the study, a randomly selected community member will be frequency matched with the index case according to age group, sex and parish. We include parish of residence as a matching criterion so that we increase the likelihood of detecting overlapping and interacting social networks among participants. To identify potential control residents, we will approach the Local Council in the parish of the index case and obtain a registry of households within the parish. We will then randomly select a list of potential households to approach for the study. The field workers will then move from one household to the next in order of random selection to identify a control resident who meets the prescribed matching criteria. If a registry of households was not available, consecutive homes were visited starting from the road junction closest to the center of a village or from a storm drain where no junction exists.

Additional Datasets.

We will contact various authors that have published cohort studies on co-prevalent and incident tuberculosis disease among household case-contacts. A systematic literature review will be performed to identify all studies with relevant data. Both prospective and retrospective cohort studies that diagnose tuberculosis (either through laboratory confirmation or radiographical methods) will be included in the search. Investigations with study populations containing underlying conditions (for example, dialysis patients that are also household contacts of a tuberculosis case), those that do not distinguish between household and casual contacts, studies conducted or published before 2000, and household contact investigations including

only index cases with confirmed drug resistance will be excluded. Index cases with drug resistance potentially have distinct transmission dynamics compared to drug susceptible tuberculosis index cases[31,241,242] and for this reason studies that have only these type of index cases will be excluded. Contact information of the corresponding author will be collected from each study.

A non-systematic review in MEDLINE (Pubmed) was conducted in preparation of this project using the terms in Table 13:

Table 13. Search terms for non-systematic review on studies co-prevalent and incident data on household contacts of tuberculosis cases

Search terms	Category	Statement
("pulmonary tuberculosis"	Mesh	OR
"mycobacterium tuberculosis"	Mesh	OR
tuberculosis	All fields	OR
TB)	All fields	
		AND
("cohort studies"	Mesh	OR
"cohort"	Mesh	OR
"prospective study")	Mesh	OR
		AND
(“incidence”	Mesh	OR
“co-prevalent”	All fields	OR
“coprevalent”)	All fields	
		AND

("contact tracing"	Mesh	OR
infectious disease contact tracing	Mesh	OR
"contact$"	All fields	OR
"household*"	All fields	OR
"household contact*")	All fields	

The results are listed in Table 14. Twenty-four studies were found in the final search. There were 16 prospective cohort studies,[5,6,31,72,141,156,158,237,243-250] seven retrospective cohort studies,[64,137,251-255] and one study that did not specify.[256] All studies followed contacts for at least one year and two studies followed household contacts for tuberculosis disease for ten years. The amount of household contacts screened in each investigation ranged from 109 to 17334; the mean number of household contacts was 3682. The amount of index tuberculosis cases was not given in five studies; among those where the number of index cases was extractable it ranged from 20 to 6653. The mean number of index cases was 942. The oldest study (based on the year of publication) was from 2001 by Carvalho and colleagues[250] while the most recent was published in 2015 by Altet and colleagues[256] from Spain. Six of the 24 studies were published very recently in 2014 and 2015. Only six (five cohorts) of the 24 studies were performed in Africa.[5,6,158,237,243,244] Two were performed in Uganda,[5,6] one each in The Gambia,[243] Malawi,[158] Senegal,[244] and South Africa.[237] Five studies were set in South America; two recent prospective studies in Peru, a prospective from 2009 set in Colombia, and two studies from Brazil.[31,72,156,250,251] One study was completed in the

USA[64] while five studies were set in Europe[137,247,248,254,256] and six studies in Asia.[141,245,246,249,252,253]

Two studies[5,6] were from the Kawempe Community Health study, which will be the derivation cohort for the analysis. One dataset is available through the Dryad Digital Repository (http://datadryad.org/).[31] Corresponding authors agreed upon beforehand will be sent a formal invitation to participate and collaborate on the predictive score on tuberculosis incidence amongst household contacts.[64,72,137,141,156,158,237,243-256] Studies included in this process will be used to validate the initial predictive score.

Table 14. List of studies with co-prevalent and incident tuberculosis among household contacts

First Author	Publication Year	Setting	Study Design	N HH contacts	N Cases	Follow-Up Time (yrs)
Guwatudde[a 6]	2003	Uganda	Prospective	1206	302	2
Whalen[a 5]	2011	Uganda	Prospective	1993	503	2
Hill [243]	2008	The Gambia	Prospective	2346	317	2
Lienhardt [244]	2010	Senegal	Prospective	2679	206	1
Zelner [72]	2014	Peru	Prospective	14041	3446	1
Grandjean [31]	2015	Peru	Prospective	2362	487	3
Del Corral [156]	2009	Colombia	Prospective	2060	366	2 – 3
Hussain [245]	2007	Pakistan	Prospective	109	20	2
Crampin [158]	2011	Malawi	Prospective	183	183	2
Fox [141]	2012	Vietnam	Prospective	545	212	1
Singh [246]	2013	India	Prospective	1608	483	2

Van Schalkwyk [237]	2014	South Africa	Prospective	2337	670	1
Bakir [247]	2008	Istanbul	Prospective	908	443	2
Salinas [248]	2007	Spain	Prospective	1719	596	10
Carvalho [250]	2001	Brazil	Prospective	360	86	1
Lee [249]	2008	China	Prospective	3925	NA	5
Guo [252]	2012	China	Retrospective	17334	6653	2
Anger[c] [64]	2012	USA	Retrospective	13393	NA	4
Cailleux-Cezar [251]	2009	Brazil	Retrospective	536	NA	2
Ling [253]	2011	Taiwan	Retrospective	5358	NA	2
Kilicaslan [254]	2009	Istanbul	Retrospective	3310	1570	2.3[b]
Chakhaia [255]	2014	Georgia	Retrospective	869	396	2
Sloot[d] [137]	2014	Amsterdam	Retrospective	NA	NA	10
Altet [256]	2015	Spain	Not provided	1335	103	4

[a] These two studies used the same cohort of household contacts and are the primary dataset used for the development of the risk score.

[b] Mean years of follow-up. Household contacts were not all followed up for the same time periods.

[c] Included contacts both inside and outside of the household

[d] This study used all types of contacts (N=9332). From the manuscript alone, household contacts and casual contacts cannot be stratified. Contact the authors will be necessary for inclusion.

CHAPTER 4: STATISTICAL ANALYSIS

Because both coprevalent and incident tuberculosis disease have a large array of contributing causal factors that invariably interact with one another, we will develop a multivariate model and construct a prediction disease risk score for coprevalent and incident tuberculosis disease. We do this to clarify the highly complex, interrelated relationship between host (household contact), vector (index case), and environmental characteristics and how they impact tuberculosis transmission and progression to disease.

Figure 2. Statistical Formula for Predictive Scores for latent tuberculosis infection and tuberculosis disease.

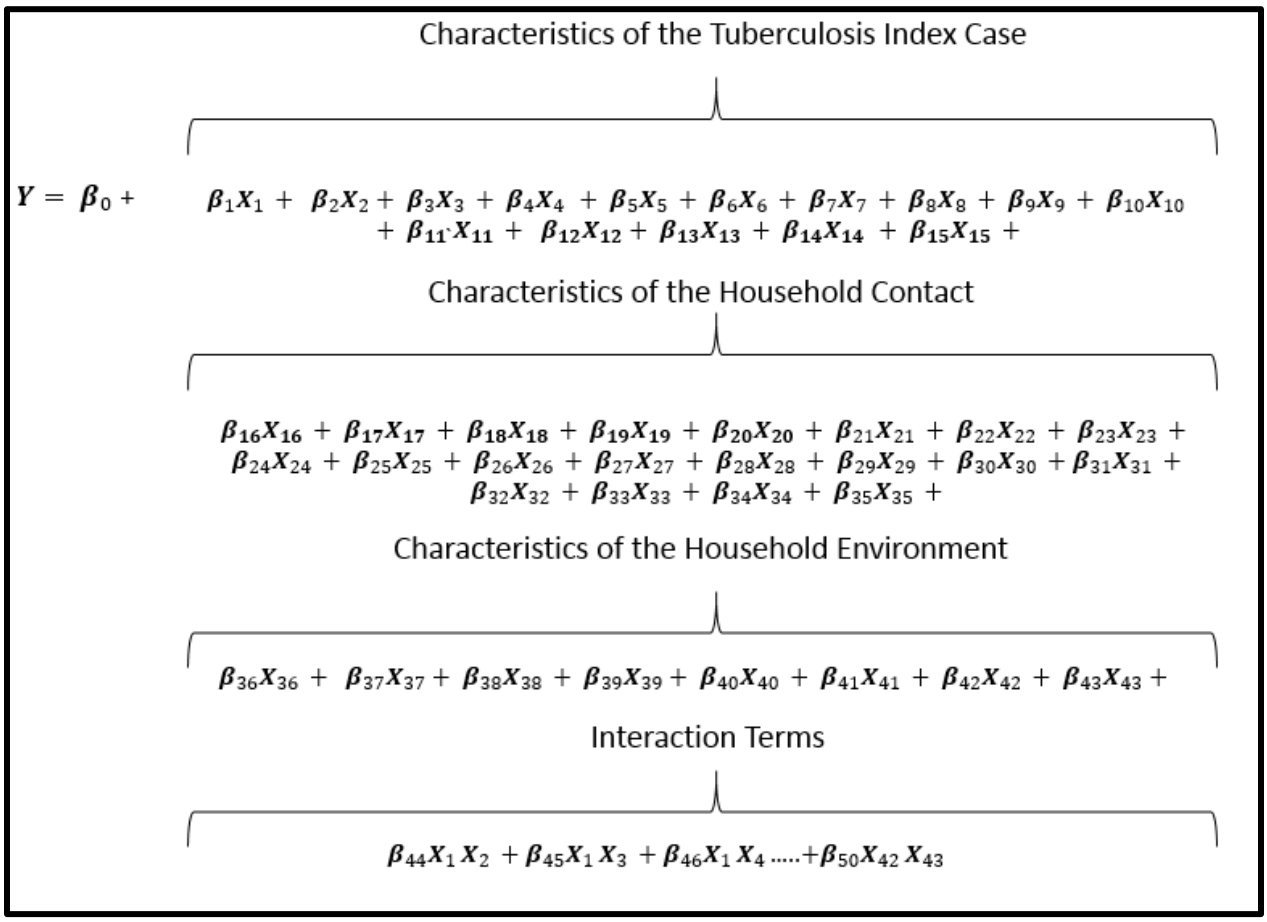


Table 15. Potential variables used in the formula established above in Figure 2

Individual	Characteristic	Term
Tuberculosis index case	Age	X_1
	Sex	X_2
	Height	X_3
	Weight	X_4
	Sputum smear status	X_5
	HIV status	X_6
	Duration of cough	X_7
	Chest radiograph	X_8
	Cigarette smoking status	X_9
	Room where they sleep	X_{10}
	Alcohol usage	X_{11}
	Tuberculin skin test induration	X_{12}
	No. contacts associated with each index case	X_{13}
	Marital status	X_{14}
	Religion	X_{15}
	Tribe	X_{16}
	Weight loss	X_{17}
	Anorexia status	X_{18}
	Presence of blood in cough	X_{19}
	Education level	X_{20}
Household contacts	Age	X_{21}

Sex	X_{22}
Height	X_{23}
Weight	X_{24}
Sputum smear status	X_{25}
HIV serostatus	X_{26}
Duration of cough	X_{27}
Chest radiograph	X_{28}
Cigarette smoking status	X_{29}
Room where they sleep	X_{30}
Alcohol usage	X_{31}
Relationship to the index case	X_{32}
Known contact with tuberculosis outside household	X_{33}
BCG vaccination status	X_{34}
Past active tuberculosis	X_{35}
Closeness to the index case	X_{36}
Tuberculin skin test induration (millimeters)	X_{37}
Marital status	X_{38}
Religion	X_{39}
Tribe	X_{40}
Weight loss	X_{41}
Anorexia status	X_{42}
Cough duration	X_{43}

	No. of hours per day with index case	X_{44}
	Education level	X_{45}
Environmental	Number of individuals in household	X_{46}
	Smoker in the household	X_{47}
	Number of windows in the household	X_{48}
	Number of rooms in the household	X_{49}
	Number of families in the household	X_{50}
	Charcoal in the household	X_{51}
	Number of individuals per room in household	X_{52}
	Number of doors per room	X_{53}

Analysis Plan for Aims 2 and 3.

Data management.

Our analysis plan will begin by first performing an exploratory analysis looking for cleaning and irregular errors in the data, ascertaining the quality of the dataset. This will involve inspecting and analyzing the dataset for invalid character and numerical values. Since all the variables in the Kawempe Community Health study are numerical examining out-of-range values in variables will be important to detect irregularities in the dataset. Checking the range of each variable will also be performed in this step. Given that the Kawempe Community Health study has been used for other studies,[5,6,131,240] this dataset is somewhat clean in the current state.

I will then be check for missing data from all the variables in the dataset. I will check all datasets and compare missing values between datasets. The frequency of missing values for both household contacts, tuberculosis index cases, and environmental characteristics will be inspected for every variable and displayed accordingly. I will do this separately for household contacts, tuberculosis index cases, and environmental characteristics. This will include every variable in the dataset whether it will be included in any forthcoming analysis. We will then assess whether the data is “Missing Completely at Random” (MCAR), “Missing at Random” (MAR), or “Missing Not at Random” (MNAR) by testing any patterns between other covariates and missing data. If a variable is an influential variable and has a large frequency of missing values the implications of the missing data and potential approaches to deal with it will be discussed between members of the committee.

Split-Sample Methods.

The primary cohort, which will be the Kawempe Community Health study for both predictive scores, will be split into two randomly sampled datasets using the statistical analysis software Stata 12.0. The original dataset will be split into 70 – 30% samples of individuals. Because of the large sample size in the Kawempe Community Health study (N=1941) splitting the sample into these groups will still allow for a large sample of participants in both cohorts. The dataset with 70% of the data will represent the derivation cohort and the 30% sample will represent the internal validation cohort. If split exactly at 70/30 ratio the derivation cohort will have approximately 1359 participants while the internal validation cohort will have approximately 582 participants. Statistical methods to randomly split the sample using Stata have been described previously [257].

Definition of Outcome.

Latent tuberculosis infection will be defined as a tuberculin skin induration ≥10 millimeters in diameter. The definition will be ≥5 millimeters in diameter for household contacts that are living with HIV. Sensitivity analysis will be performed on other induration measurements that have been applied in other studies such as ≥5 millimeters in diameter for all household contacts.

Tuberculosis disease will be defined as diagnosed through either a clinical and radiographical diagnosis from an expert physician in respiratory diseases or through sputum smear or culture laboratory test results. Each study defines tuberculosis disease differently (some use only sputum smear positive individuals) and therefore individuals that are assessed by the above definitions only will be used. For example studies that include only sputum smear positive tuberculosis index cases will be omitted since the Kawempe Community Healthy study includes both types of index cases.

Descriptive Analysis.

I will then perform distributions and frequencies of missing values for all variables included in each dataset. If the variable is continuous the mean, median, range, interquartile range, and a host of graphs (box-plot, histogram, etc.) will be created to inspect how the variable values change throughout the cohort.

Correlations between all variables will be calculated and inspected for collinearity and reduce the number of variables considered in the model. Since the Kawempe Community Health dataset contains over 50 variables (Table 15) we will assess which variables react similarly to each other throughout the cohort. Polychoric (or tetrachoric if both variables are dichotomous) correlation coefficients will be calculated for categorical

variables[258] while Spearman's rank correlation coefficients will be used for continuous variables. Subsequently, we will reduce the number of variables in our dataset. Due to the fact that the Kawempe Community Health dataset has so many variables we will exclude some variables that have exceedingly high statistical correlation with another variable. For example, height and weight may have high statistical correlation with body mass index (BMI) because the latter variable is made from the two former variables. Similarly, "Chest Radiograph Findings" is used to create the variable "Cavitary disease" and therefore using only one may be more feasible in a dataset with so many variables. Discussion with other researchers (on and off the dissertation committee) may need to be necessary in order to include all relevant variables into the impending analysis process. To identify the most relevant variables to our analysis we will perform either a factor analysis or a principal component analysis.

I will then calculate proportions of the outcome of interest (Aim 2, latent tuberculosis infection; Aim 3, All tuberculosis disease) overall and by each variable included in the analysis. This step is necessary in order for the investigator, collaborators, and audience to see the actual data as shown rather than just the prediction risk score results and/or regression analysis.

Regression analysis Approach.

We will then calculate and provide univariate regression analysis for each variable. For both outcomes we will construct a modified Poisson generalized estimating equation regression model with robust standard error variance.[259] This regression model takes into account the clustering of household contacts[147] and allows for direct estimation of

relative risk.[259-261] After this step, we will build a multivariate model and subsequently create a clinical prediction score.

Creation of the prediction risk models will be performed with reference to guidelines in the literature.[262] For the outcome of interest, we will perform a multivariate regression model using a backward stepwise regression process using either the Akaike Information Criterion (AIC) or the Bayesian Information Criterion (BIC). After selection of the final variables in the model for the outcome, regression coefficients will be calculated for each covariate. Reference values will be selected for categorical variables and these will be assigned a 0 score. The lowest regression coefficient between all the variables will be given a score of 1 point. Subsequently, regression coefficients will be compared to this coefficient and given a score based on a multiplier of the lowest regression coefficient. For example, if the lowest coefficient was 0.85, equaling one point on the risk score, another coefficient equaling 2.3 will equal 3 points while a further regression coefficient equaling 1.7 will be 2 points on the risk score scale. Further calculation of scores based on the other regression coefficients will be used to tabulate a full risk score.

Risk Score Validation

We will use both internal and external validation of the risk scores from Aim 2 and 3. In both Aims 2 and 3, we will use a split-sample internal validation by splitting the Kawempe Community Healthy study dataset into a 70% – 30% random sample. We will then create a derivation risk score with 70% of the data and apply this score to 30% of the remaining individuals in the dataset. Measures of validity and reliability to predict the

outcome will be measured, such as positive predictive value, sensitivity, specificity, and rate of misclassification of each score will be then calculated on the 30% sample.[200]

If this risk score was accurately validated in 30% sample a new score with 100% of the Kawempe Community Health study data will be created. We will then validate this score with an external dataset. For Aim 2 we will use individuals tested for latent tuberculosis infection from the COHSONET dataset to validate our risk score. Similarly to our split-sample internal validation, we will calculate the accuracy of the Kawempe risk score by calculating the positive predictive value, sensitivity, and specificity in this secondary dataset. We will then select one or two datasets from the list in Table 15 to validate our risk score. Grandjean and colleagues [31] published their dataset online and therefore we will use this cohort from Peru.

Studies that have substantial similarity with the Kawempe Community Health study were assessed for congruent variables. These are shown in Table 16. Out of 29 total possible variables present in the Kawempe Community Health study, Zelner and colleagues[72] has 23 congruent variables, Van Schalkwyk and colleagues[237] has 15, Grandjean and colleagues [31] has 14, Hill and colleagues[243] has 11, Lienhardt and colleagues[244] has 18, and Singh and colleagues[246] has 15. Important to mention is that all of the same variables do not need to present in order for a corresponding dataset to be suitable to use as a validation study. Only variables that are included in the final clinical prediction risk score need to be included. Therefore variables that have high likelihood for progression to active tuberculosis, such as HIV status of the household contact, baseline tuberculin skin status of the household contact, smear status of the index case and others carry more importance than other less influential variables.

Currently, we have access to data from Grandjean and colleagues study[31] since they posted this on a data sharing website. Because Zelner and colleagues[72] has such congruent data we will attempt to contact this research group for possible collaboration. In addition, Van Schalkwyk and colleagues[237] has many congruent variables and this study was conducted in South Africa. We will also contact this group of researchers for possible collaboration in an attempt to externally validate our risk score in another African setting other than Uganda. Other research groups in Table 16 will be approached to assess interest if needed.

Table 16.Variables included in the Kawempe Community Healthy study and other prospective cohort studies assessing incident tuberculosis disease

Variables in the Kawempe Community Health Study	Zelner, 2014	Grandjean, 2015	Van Schalkwyk, 2015	Hill, 2008	Lienhardt, 2012	Singh, 2013
Household contact characteristics						
Age group, years	□	□	□	□	□	□
Sex	□	□	□	□	□	□
Tuberculin skin test result (≥10 millimeters)	□			□	□	□
Tuberculin skin test induration, millimeters	□			□	□	□
BCG vaccination	□			□	□	□
Education level		□				
Cigarette smoker	□		□		□	
Relation to index case	□					□
Past active tuberculosis	□		□		□	□

Nutritional status (BMI and/or z-scores)	□					
Anorexia						□
Alcohol usage	□					
Cough			□			□
HIV status	□	□	□	□		
Sleeping proximity		□		□	□	□
Know tuberculosis case outside household						
Index case characteristics						
Median age, years (IQR)	□	□	□	□	□	□
Age group, years	□	□	□	□	□	□
Sex	□	□	□	□	□	□
Cigarette smoker	□	□	□			
Sputum smear status	□	□	□	□	□	□
Sputum culture status			□		□	□
Chest radiograph findings					□	
Lung cavitation	□				□	

Duration of cough	□	□	□		□	
HIV status	□	□	□		□	
Environmental characteristics						
Charcoal or fire smoke exposure	□					
Median no. windows per room						
No. windows per room						
Median density, persons/home	□	□	□		□	□
Household size (persons/home)	□	□	□		□	□
House type	□	□	□			
Number of the same variables, 31 total possible	23	15	17	11	19	17

Dealing with Missing Values.

When attempting to create predictive risk scores we will strive to have the most complete dataset possible. However, there are key variables in our datasets in which we have missing values. Many of these variables are important and at times crucial to any potential analysis. Some variables in the Kawempe Community health survey with >5% missing values include the HIV status of the household contact (279/1941; 14.4%) and the cigarette smoking status of the contact (419/1941; 21.6%). Other variables with between 2 – 5% missing values include the cavitary status of the index case (53/1941; 2.7%), duration of cough of the index case (39/1941; 2.0%), relationship to the index case (38/1941; 2.0%), and charcoal or fire smoke exposure (40/1941; 2.1%). These numbers show that this dataset is very well managed and the majority of variables have almost complete data. However, some of the variables with missing data are important for investigating tuberculosis incident or co-prevalent tuberculosis disease. For example, the HIV status of the household contact is critical when analyzing tuberculosis incidence since immunosuppression in susceptible individuals have an elevated risk of primary progressive tuberculosis disease and reactivation of an old infection.

We will use multiple imputation modeling methods to deal with missing values in our dataset. The chained equations approach will be our primary method of imputation however the multivariate normal method will be used to provide sensitivity analysis. Lastly, we will compare these approaches to a complete cases analysis approach which uses only individuals with values on all variables included in our final model. Since HIV status of the household contact is likely to be included in our final model this approach will exclude >14% of our sample.

Limitations.

Although prediction risk scores have been used for over 30 years[200] there are limitations to this approach.[232,263] For many clinical and programmatic decisions there are a substantial number of rules created in the literature. Deciding which decision rule to implement for practitioners can be difficult and lead to confusion. In addition, "overfitting" is a concern when the ratio of variables to outcomes is small.[194,232,263] Also, validation of a clinical decision rule is not always guaranteed and many times can show less accuracy in predicting disease.[202,263,264] Lastly, a disease prediction score cannot be judged effective unless it has been tested in programmatic settings, even if it is validated internally and externally.[200,265] This is an uncommonly performed step in the process of justifying the use of a clinical prediction score.[200,265]

CHAPTER 5: TUBERCULOSIS DISEASE AND LATENT TUBERCULOSIS IN HOUSHOLD CONTACTS OF TUBERCULOSIS CASES AND UNEXPOSED CONTROL GROUPS

Aim 1, A systematic review and meta-analysis

INTRODUCTION.

Ambitious targets for global tuberculosis elimination by 2050 have been set by global health organizations. To reach these goals, substantial improvements in case detection must be achieved in low-income settings where tuberculosis disease is most prevalent and 40–50% of cases are undiagnosed. Household contact investigation has been proposed as a supplementary control measure to current control practices to improve case detection, however is rarely performed in high-burden settings.

METHODS.

We systematically searched and included studies if latent tuberculosis infection or active tuberculosis disease was assessed from a group exposed to tuberculosis in the household and an unexposed control group. We extracted data from eligible studies on smear and culture status of index cases, age and bacillus Calmette-Guérin vaccination status of contacts, and study design characteristics.

RESULTS.

Of 5608 unique citations identified and reviewed from our multiple database strategy, 41 studies (12 studies with disease outcome data, 15641 household contacts, 2985271 controls; 34 studies with latent tuberculosis outcome data, 16644 household contacts

and 29564 controls) met our inclusion criteria and were included in the meta-analysis. The increased odds of tuberculosis disease and latent tuberculosis was 9.8 (95% CI, 4.0 – 24.0) and 3.4 (95% CI, 3.5 – 3.6). The yield of tuberculosis disease was >8% in five household contacts groups and <1% in 10 of 12 control groups. The odds of latent tuberculosis was lowest when in Asia (OR, 2.1 [95% CI, 1.8 – 2.4]) and when the index case was sputum smear negative (OR, 2.6 [95% CI, 1.0 – 6.4]) and did not sharply vary when the Quantiferon Gold In-Tube test (OR, 3.1 [95% CI, 1.9 – 5.0]) and T-Spot (OR, 2.6 [95% CI, 1.3 – 4.9]) were used.

CONCLUSIONS.

Household contact investigation had a substantially larger yield when compared to any control groups. As a supplementary tool to passive case finding, household contact investigation is highly efficient compared to community-based interventions. Methods to encourage use of contact tracing in low-income settings should be further investigated.

Key words. *Mycobacterium tuberculosis*; case-detection; transmission; contact tracing.

INTRODUCTION.

In 2006, the World Health Organization set a highly ambitious global target of tuberculosis elimination, defined as one tuberculosis case per million individuals, by 2050. Currently, tuberculosis incidence is reducing at approximately 1 – 2% per year globally. To reach this 2050 target, this rate of decline would need to accelerate to approximately 15 – 20% per year. Supplementary interventions that effectively increase tuberculosis case detection, prevent tuberculosis transmission, and identify individuals at high-risk for primary progressive tuberculosis disease are needed to current tuberculosis control, which is predominantly reliant on health care seeking by symptomatic patients.

Globally, approximately one in every three tuberculosis cases are undetected, undiagnosed, and untreated every year. The proportion of undetected cases reaches close to 50% in high-burden settings such as India or sub-Saharan Africa. Most of these hidden tuberculosis cases consistently transmit *Mycobacterium tuberculosis* infection to susceptible individuals in their social network until they are detected, self-cure, or become deceased. Increasing tuberculosis case-detection to identify and diagnose these difficult to find cases is critical and reducing this diagnostic gap is among the top priorities for global health organizations.

Household contact investigation of tuberculosis cases has been widely proposed as a potential supplementary measure to current tuberculosis control. This intervention acts as both a case detection and prevention control measure. When new tuberculosis cases are detected through household contact investigation these individuals are often detected far earlier than through passively detected cases. In addition, the tuberculosis

transmission cycle occurring in household members is immediately stopped preventing further individuals from developing disease. An important meta-analysis from 2008 collated household contact data from 19 studies measuring latent tuberculosis infection and 27 studies reporting active tuberculosis disease and found a high yield (51.4% yield of latent tuberculosis infection; 4.5% yield for clinically or bacteriologically confirmed tuberculosis disease) of both outcomes. However, studies from this meta-analysis did not include any type of control group and therefore the effectiveness of household contact investigation versus other types of interventions remains unclear.

METHODS.

STUDY DESIGN.

A systematic review and meta-analysis was performed on studies detecting latent tuberculosis infection and tuberculosis disease in household contacts of tuberculosis index cases and a corresponding control group. We aimed to evaluate the yield of active case finding interventions in household and community-based areas and therefore only included case-control studies. Cohort and cross-sectional studies were not eligible even if both household contacts and community controls were present.

SEARCH STRATEGY.

We first searched the literature for systematic reviews investigating *M. tuberculosis* infection or active tuberculosis disease in household contact and control groups. We found five systematic reviews investigating tuberculosis contact evaluations. Martinez and colleagues (2016) included both household contact and control groups but limited their analysis to only children and the study's goal was to estimate overall household and community transmission and not to detect the overall increased yield of contact investigations as a control strategy. The other four systematic reviews did not include control groups.

Subsequently, we compiled all studies investigating two groups: individuals in household contact with a tuberculosis case and those in a control group without known tuberculosis exposure. We did not restrict inclusion to studies with a specific type of control and contacts and controls of all ages were included.

We searched journal articles from any time period in Medline, Web of Science, Biosis, and Embase electronic databases. The search approach was conducted with the help of a librarian database consultant and was updated on October 2014. Key words in

these database searches included tuberculosis, *Mycobacterium tuberculosis*, tuberculin, contact*, transmission, childhood contact, and household contact. The entire search strategy for each electronic database is detailed in the supplementary appendix (Table. Search Strategy). We did not restrict articles by publication date and included articles in any language. The references of multiple reviews, both systematic and descriptive, were also searched and eligible studies not included in the database search strategy were included in the meta-analysis. We also hand searched the table of contents of the following journals: *The International Union of Tuberculosis and Lung Disease*, *Tubercle*, and the *American Review of Respiratory Disease,* as well as online abstract books from The Union Conference on Lung Disease (2004 – 2013). Dissertations and conference abstracts were included for collation if eligible. Corresponding authors of journal articles were contacted for additional data if a study met eligibility criteria but did not stratify certain characteristics.

MANUSCRIPT REVIEW AND DATA EXTRACTION.

After the search and exclusion of duplicate articles, two researchers (MW, FX) independently screened articles by title and abstract. The selected manuscripts were evaluated by a third researcher (LM) and articles selected by only one reviewer were listed and examined. A meeting between the two initial reviewers (MW, FX) and the primary author (LM) was arranged to evaluate discrepancies in manuscript selection and differences were resolved by a consensus of authors. Subsequently, two researchers (LM, MEC) independently read and reviewed the full text of each manuscript to assess each study's eligibility. After both authors completed full-text review, inconsistencies were assembled and discussed by the two reviewers and a

decision was again achieved by consensus. If an agreement could not be achieved, a third reviewer (CCW) reviewed and determined the study's eligibility.

A data extraction form was developed and piloted. Using this form, two authors independently extracted all data from eligible studies and then compared results. From each article, we collected information on the year of publication and implementation, the definition used for latent infection and/or active tuberculosis disease, study design, and recruitment methods. Characteristics extracted from index cases included method of diagnosis, total number of cases found in household, and smear grade. From contacts and controls, we collated information on age, number with latent tuberculosis infection, number with tuberculosis disease, BCG vaccination status, and matching characteristics between groups (neighborhood, age, sex, etc.). We also collected study-level data such as which type of test was used for latent tuberculosis (tuberculin skin test, Quantiferon T-Spot, Quantiferon Gold In-Tube test, ESTAT-6, CFP-10, etc.), the year of study implementation (when available), the country and World Health Organization region (Americas, Europe, Africa, Asia) in which the study was performed, and the type of control group (community, general population, hospital). The sputum smear status of the tuberculosis index case that the contact was exposed to was also collated.

KEY DEFINITIONS.

Tuberculosis cases in the household were considered source cases and eligible if diagnosis was confirmed either bacteriologically (sputum smear or culture positive), radiographically, or clinically. Descriptions of a household were defined differently between studies and therefore we used each study's definition of household. Studies using the tuberculin skin test or any type of interferon gamma assay to diagnose latent

tuberculosis infection were included. If a study used multiple tests to classify latent tuberculosis infection (such as both the tuberculin skin test and a Quantiferon test) only the tuberculin skin test was used when pooling and stratification of studies. Stratification was done for the type of latent tuberculosis test but due to the minimal number of studies using a type of interferon-gamma assay we did not restratify results of this test.

Among eligible studies, three types of controls were used: community controls, general population controls, and hospital controls. A community control was defined as an individual neighborhood-matched to household contacts without current household exposure to a tuberculosis case. A general population control was defined as any individual within the same “general population” as the household contact group. This may have included the same neighborhood, region, or city. These controls were recruited at random and were not selected based on their tuberculosis exposure status – therefore it’s possible a small proportion may have been exposed to tuberculosis in the household. Lastly, a hospital control was any individual not exposed to tuberculosis in the household but recruited in a hospital or clinical setting.

STATISTICAL ANALYSIS.

We derived the odds ratio for latent tuberculosis infection and active tuberculosis disease in the household compared to the corresponding control group for each study. To pool these odds ratios, a random effects model with DerSimonian and Laird weights, equalizing the weight of the studies to the pooled estimate, was used because of the high level of heterogeneity found in the odds ratio estimates among studies. Afterward, the number needed to screen (NNS) was calculated. Two forms of this marker were calculated. The NNS to detect one additional case (for either latent tuberculosis

infection or active tuberculosis disease) was calculated for each study and then pooled together. This statistic is calculated through the formula:

$$\text{NNS} = \frac{1}{Absolute\ Risk\ Reduction}.$$

The NNS to detect one tuberculosis case for each group (contact and control) was also calculated and this was calculated by dividing the percent infected or diseased by 100.

The I^2 statistic was used to assess heterogeneity between studies. We stratified by pre-specified characteristics of chosen studies and then used random-effects univariable meta-regression to calculate ratio of odds ratios and investigate causes of heterogeneity. Stata statistical software (Statacorp, College Station, Texas; Version 14.1) was used for all analyses. Forest plots were created with the metan command and the metareg command was used to perform univariable meta-regression modelling parameters.

Various sensitivity analyses were conducted to assess potential bias. Since there is no gold standard diagnostic test for latent tuberculosis infection we compared LTBI prevalence results from studies that used both the interferon-gamma assay and tuberculin skin test. We also stratified included studies by their study design, by type of diagnostic test, and by the various time periods in which they were implemented.

RESULTS.

SYSTEMATIC SEARCH RESULTS

From our multiple database search, 5608 unique citations were reviewed. All but 397 were excluded based on title and abstract. After full-text review, 41 unique manuscripts with outcome data on either latent tuberculosis infection, tuberculosis disease, or both in household contacts and some type of control group. Thirty-four studies had information on latent tuberculosis infection while 12 had information on tuberculosis disease. Seven studies had outcome data on both latent tuberculosis and tuberculosis in both groups.

All studies evaluating latent tuberculosis infection did so with the tuberculin skin test however some of these studies also used an addition test. Four other tests were used to assess latent tuberculosis: the Quantiferon Gold In-Tube test, Quantiferon T-Spot, ESTAT-6, and CFP-10. Seven studies used the Quantiferon Gold In-Tube test, four studies used T-Spot, and ESTAT-6 and CFP-10 were used in two studies each. Twenty-one studies used only one test to evaluated latent tuberculosis, ten studies used two tests, and 3 studies evaluated latent tuberculosis infection with three different tests. In all, 29 studies had a community control group, three studies had a general population control, and two studies had hospital controls. Most studies were conducted after 2000 however eight studies were conducted in 1960 or before. All four global regions were represented: 16 studies were conducted in Africa, seven studies in Asia, five studies in Europe, and five studies in the Americas.

All 12 studies investigating tuberculosis disease in household contacts and controls used bacteriological laboratory diagnosis except for one which used self-report

and medical records. Four studies used only bacteriological confirmation to diagnose disease while six studies complemented laboratory results with additional diagnostic measures: three studies additionally used chest radiographs while three other studies used clinical symptoms. Six studies were conducted before and after 2000. Six studies were conducted in Africa, all in sub-Saharan Africa. Few studies were performed in other global regions: three studies were performed in Asia, two in the Americas, and one study in Europe. The type of control group was balanced amongst the studies: community, general population, and hospital control groups had four studies each. Eight studies had sputum smear-positive and -negative tuberculosis index cases while two studies included only sputum smear positive index cases. Two studies did not specific the smear status of the index case.

YIELD OF TUBERCULOSIS DISEASE AND NUMBER NEEDED TO SCREEN.

The yield of tuberculosis disease was consistently higher, at times much higher, in the household contact group compared to any specific control group. The yield of disease in contact groups ranged from 23.5% in Connell and colleagues to 0.9% in Becerra and colleagues. Five studies had a yield of tuberculosis disease greater than 8% in household contact groups, three of these over 15%. Household contacts that were recruited in hospital settings had substantially higher rates of tuberculosis disease in three of the four studies (15.2%, 23.5%, and 22.9%; a fourth study had a 2% rate) however this was not also true in control groups recruited in hospitals (0% in two studies; 0.6% and 0.3% in the other two studies). Four control groups had no outcome events in the control group and all studies had less than 1% yield of tuberculosis in the control group except Gilpin and colleagues (1.4%) and Kumar and colleagues (3.1%).

The pooled yield of tuberculosis disease in household contacts and control groups was 5% (95% CI, 3 – 6; I^2=95.3%) and 0% (95% CI, 0 – 1; I^2=83.6%). The increased odds of tuberculosis disease between household contacts and control groups was 9.8 (95% CI, 4.0 – 24.0). The odds tuberculosis disease was higher when hospital controls (OR, 14.1 [95% CI, 3.8 – 52.3]) or community controls (OR, 11.2 (95% CI, 2.3 – 54.8]) were used and when contacts were below 20 years of age.

YIELD OF LATENT TUBERCULOSIS.

The odds of latent tuberculosis were significantly higher in household contacts compared to controls when all studies were pooled using the tuberculin skin test (OR, 3.4, 95% CI, 3.5 – 3.6). This strong association remained consistent after stratification by several risk factors. When interferon gamma assays were used to diagnose latent tuberculosis, odds ratios (Quantiferon Gold In-Tube test, OR, 3.1, 95% CI, 1.9 – 5.0; Quantiferon T-Spot, OR, 2.6, 95% CI, 1.3 – 4.9) were comparable to results seen from the tuberculin skin test although lower. Among studies that used the ESTAT-6 and CFP-10 tests (2 studies each), odds ratios were substantially higher (ESTAT-6, OR, 10.3, 95% CI, 3.3 – 32.0; CFP-10, OR, 10.4, 95% CI, 3.3 – 33.0) then for other tests. Upon stratification by the type of control group community control (OR, 3.3, 95% CI, 3.1 – 3.5) and hospital control (OR, 3.4, 95% CI, 2.1 – 5.5) groups had similar odds ratios. In the three studies using a general population control, the pooled odds of latent tuberculosis increased to 4.5 (95% CI, 3.9 – 5.2) although this was highly heterogeneous (I^2=95.9%). The odds ratio of infection was largest in Europe (OR, 4.4, 95% CI, 3.8 – 5.1) and the Americas (OR, 4.0, 95% CI, 3.5 – 4.5) compared to Asia (OR, 2.1, 95% CI, 1.8 – 3.4) and Africa (OR, 3.7, 95% CI, 3.4 – 3.9). In addition, amongst studies with sputum smear

positive tuberculosis index cases the OR was significantly higher compared to studies with sputum smear negative tuberculosis index cases (OR, 3.3 [95% CI, 2.5 – 4.4] versus 2.6 [95% CI, 1.0 – 6.4]).

DISCUSSION.

To reach 2050 targets for global tuberculosis elimination, tuberculosis case detection in low-income settings must be drastically improved. Although household contact tracing has been widely recommended by tuberculosis experts, implementation has been slow or nonexistent in low-income settings where improvement in case detection is most needed. We present results of a meta-analysis of household contact studies, comparing them with control groups to assess the increased yield of tuberculosis disease and latent tuberculosis in household contacts compared to unexposed populations. From 41 studies of exposed and unexposed groups, we found that the risk of finding undiagnosed, coprevalent tuberculosis disease was almost ten times higher in individuals exposed to a tuberculosis cases in the household. This finding is alarming and illustrates the need to implement household contact tracing programmatically. This elevated odd of tuberculosis disease was present in all studies regardless of the control group. Odds of tuberculosis was increased in studies from Europe and the Americas compared to Africa and Asia however these differences did not reach statistical significance.

This study reinforces past work demonstrating a high yield of tuberculosis disease and latent tuberculosis infection in household contacts of tuberculosis cases. Our study also describes an important and clear increased efficiency to detect undiagnosed diseased cases compared to other interventions such as hospital-based or community-wide screening. Although household contact screening is highly efficient and cost-effective, there are important limits to this intervention. In high-burden settings, a majority, at times as high as 70–90%, of tuberculosis transmission occurs in community

settings where contact tracing interventions specific to the household are unlikely to reach. Due to this, the epidemiological impact of household contact tracing should not be overestimated. However, the effectiveness of such an intervention to detect undiagnosed tuberculosis cases is important for low-income countries that need efficient interventions that take into account cost-effectiveness and available resources.

CHAPTER 5 – TABLES AND FIGURES.

TABLES.

Table. Search Strategy.

Pubmed.

Search used:

("mycobacterium tuberculosis"[Mesh] OR "tuberculosis"[Mesh] OR TB[tiab] OR "tuberculosis"[tiab])

AND

("contact tracing"[Mesh] OR "household*"[All Fields] OR "family contact*"[WORD] OR "household contact*"[All Fields] OR "childhood contact*"[TI] OR "Disease Transmission, Infectious"[Mesh] OR "Household transmission"[WORD] OR "community controls" [All Fields])

Results: 1559 papers found from search

Biosis.

Search used:

[(Topic="Mycobacterium tuberculosis") OR (Topic=tuberculosis) OR (Topic=TB)]

AND

[(Topic="contact tracing") OR (Topic="household contact") OR (Topic="childhood contact") OR (Topic="Household transmission") OR (Topic="community controls") OR (Topic="family contact*") OR (Topic="close contact*") OR (Topic="tuberculosis transmission")]

Results: 748 papers found from search

Web of Science.

Search used:

[(Topic="Mycobacterium tuberculosis") OR (Topic=tuberculosis) OR (Topic=TB)]

AND

[(Topic="contact tracing") OR (Topic="household contact") OR (Topic="childhood contact") OR (Topic="Household transmission") OR (Topic="community controls") OR (Topic="family contact*") OR (Topic="close contact*") OR (Topic="tuberculosis transmission")]

Results: 2280 papers found from search

Embase.

Search used:

[(Topic="Mycobacterium tuberculosis") OR (Topic=tuberculosis) OR (Topic=TB)]

AND

[(Topic="contact tracing") OR (Topic="household contact") OR (Topic="childhood contact") OR (Topic="Household transmission") OR (Topic="community controls") OR (Topic="family contact*") OR (Topic="close contact*") OR (Topic="tuberculosis transmission")]

Results: 640 papers found from search

Table 1. Characteristics of includes studies evaluating either latent tuberculosis infection or tuberculosis disease in household contact and control groups

First Author [Reference]	Year	Region	Age	Type of Control	Diagnostic Method	Index Smear
Latent tuberculosis infection						
Chan, 2008	2005 – 2006	Taiwan	0 – 14	Community Control	TST	Positive only
Abu-Taleb, 2011	2008 – 2009	Egypt	All ages	Community Control	TST, QFT-G	Positive only
Almeida, 2001	1998	Brazil	0 – 14	Community Control	TST	Positive only
Aspin, 1953	1953	UK		General Population	TST	
Blahd, 1946	1946	US		Community Control	TST	
Connell, 2008	2008	Australia	0 – 19	Hospital Control	TST, QFT-G, T-Spot	NA
Crampin, 2011	1999 – 2005	Malawi	NA	Community Control	TST	Positive only
Del Corral, 2009	2005 – 2006	Colombia	All ages	General Population	TST, CFP-10	Positive only
Gilpin, 1987	1984	South Africa	0 – 14	Community Control	Heaf	Positive only
Gustafson, 2008	1999 – 2000	Guinea-Bissau	All ages	Community Control	TST	Positive only
Hansted, 2009	2005 – 2007	Lithuania	10 – 17	Community Control	TST, T-Spot	NA
Hertzberg, 1957	1957	Norway		Community Control	TST	

Hill, 2006	2002 – 2004	The Gambia	All ages	Community Control	TST, T-Spot	Positive only
Jensen, 2013	2007 – 2008	Tanzania	16 – 40	Community Control	QFT-G	Positive only
Kang, 2005	2004 – 2005	South Korea	16 – 70	Community Control	TST, ESAT-6	Positive only
Kenyon, 2002	1997	Botswana	0 – 10	Community Control	TST	All
Lienhardt, 2003	1999 – 2000	Gambia	All ages	Community Control	TST	Positive only
Lutong, 2000	1993 – 1996	China	0 – 55	Community Control	TST	Positive only
Madico, 1995	1990	Peru	0 – 14	Community Control	TST	Positive only
Mandalakas, 2015	2015	South Africa	0 – 14	Community Control	TST, QFT-G, T-Spot	Positive only
McPhedra, 1935	1935	US	0 – 80	Community Control	TST	
Méndez-Echevarría, 2011	2007 – 2009	Spain	0 – 14	Hospital Control	TST	All
Mutsvangwa, 2010	2002 – 2004	Zimbabwe	10 – 82	Community Control	TST, T-Spot	All
Nakaoka, 2008	2006	Nigeria	0 – 14	Community Control	TST, QFT-G	All
Narain, 1966	1960 – 1961	India	0 – 14	Community Control	TST	
Narasimhan, 2012	2012	India	All ages	Community Control	TST, QFT-G	All
WHO, 1961	1955 – 1960	Kenya	All ages	General Population	TST	
Rutherford, 2012	2012	Indonesia	0 – 9	Community Control	TST, QFT-G	Positive only
Schlesinger, 1930	1929	UK		Community Control	TST	
Shakak, 2013	2013	Sudan	≥15	Community Control	TST	Positive only

Shaw, 1952	1952	UK		Community Control	TST	
Vekemans, 2001	2001	Gambia	NA	Community Control	TST, ESAT-6	Positive only
Whalen, 2011	1998 – 2008	Uganda	All ages	Community Control	TST	All
Yassin, 2013	2013	Ethiopia	1 – 14	Community Control	TST, QFT-G, CFP-10	Positive only
Active Tuberculosis Disease						
Shapiro, 2012	2009	South Africa	All ages	Community Control	Bacteriological	All
Becerra, 2005	1996 – 1998	Peru	All ages	General Population	Bacteriological	All
Bekker, 2012	2009	South Africa	<1	Hospital Control	Bacteriological/clin.	All
Claessens, 2002	2001	Malawi	NA	Hospital Control	Self-reported	Positive only
Connell, 2008	2008	Australia	0 – 19	Hospital Control	Bacteriological/clin.	NA
Gilpin, 1987	1984	South Africa	≥15	Community Control	Bacteriological	Positive only
Grzybowski, 1975	1975	Canada	All ages	General Population		All
Kumar, 1984	1982 – 1983	India	All ages	General Population	Bacteriological & x-ray	All
Méndez-Echevarría, 2011	2007 – 2009	Spain	0 – 15	Hospital Control	Bacteriological/clin.	All
Narasimhan, 2012	2012	India	All ages	Community Control	Bacteriological & x-ray	All

WHO, 1961	1955 – 1960	Kenya	All ages	General Population	Bacteriological & x-ray	All
Whalen, 2011	1998 – 2008	Uganda	All ages	Community Control	Bacteriological	Al

Table 2. Risk difference in tuberculosis disease in household contact and control groups

First Author	Year	Region	Type of Control	% Yield Contacts	NNS contacts	% Yield Controls	NNS controls
Shapiro	2012	South Africa	Community Control	8.1	12.3	0.5	200.0
Gilpin	1987	South Africa	Community Control	3.0	33.3	1.4	71.4
Kumar	1984	India	General Population	8.0	12.5	3.1	32.3
WHO	1961	Kenya	General Population	2.8	35.7	0.5	200.0
Becerra	2005	Peru	General Population	0.9	111.1	0.2	500.0
Claessens	2002	Malawi	Hospital Control	2.0	50.0	0.3	333.3
Bekker	2012	South Africa	Hospital Control	15.2	6.6	0.0	NA
Grzybowski	1975	Canada	General Population	3.3	30.3	0.1	1000.0
Connell	2008	Australia	Hospital Control	23.5	4.3	0.0	NA
Méndez-Echevarría	2011	Spain	Hospital Control	22.9	4.4	0.6	166.7
Narasimhan	2012	India	Community Control	1.0	100.0	0.0	NA
Whalen	2011	Uganda	Community Control	4.6	25	0.0	NA

Table 3. Subgroup analysis of studies assessing latent tuberculosis in household tuberculosis contact and control groups

Characteristic	No. studies	Pooled odds ratio (95% CI)	I^2
Crude	34	3.4 (3.5 - 3.6)	93.6
Type of test			
Tuberculin skin test	34	3.4 (3.5 - 3.6)	93.6
Quantiferon Gold In-Tube Test	7	3.1 (1.9 - 5.0)	83.7
Quantiferon T-Spot	4	2.6 (1.3 - 4.9)	86.4
ESTAT-6	2	10.3 (3.3 – 32.0)	49.0
CFP-10	2	10.4 (3.3 – 33.0)	90.0
Type of control group			
Community	29	3.3 (3.1 - 3.5)	93.7
General population	3	4.5 (3.9 - 5.2)	95.9
Hospital	2	3.4 (2.1 - 5.2)	43.1
Region			
Asia	7	2.1 (1.8 - 2.4)	92.7
Africa	16	3.7 (3.4 - 3.9)	93.4

Europe	5	4.4 (3.8 - 5.1)	91.7
Americas	5	4.0 (3.5 - 4.5)	94.2
Sputum smear status of tuberculosis case			
Positive	18	3.3 (2.5 - 4.4)	90.4
Negative	6	2.6 (1.0 - 6.4)	96.3

Table 4. Subgroup analysis of studies assessing tuberculosis in household tuberculosis contact and control groups

Characteristic	No. studies	Pooled odds ratio (95% CI)	I^2
Crude	12	9.8 (4.0 – 24.0)	92.5
Type of control group			
Community	4	11.2 (2.3 – 54.8)	62.9
General population	4	6.5 (1.1 – 38.2)	97.7
Hospital	4	14.1 (3.8 – 52.3)	58.4
Region			
Asia	3	5.0 (1.1 – 22.1)	41.5
Africa	6	8.1 (3.5 – 18.6)	59.9
Europe	1	46.9 (10.7 – 206.4)	NA
Americas	2	11.1 (1.5 – 84.0)	92.9
Year of study implementation			
1990 and before	4	5.8 (0.9 – 36.6)	97.7
post-1990	8	12.4 (5.5 – 28.0)	56.6

FIGURES.

Figure 1. Flow Chart of Selected Studies

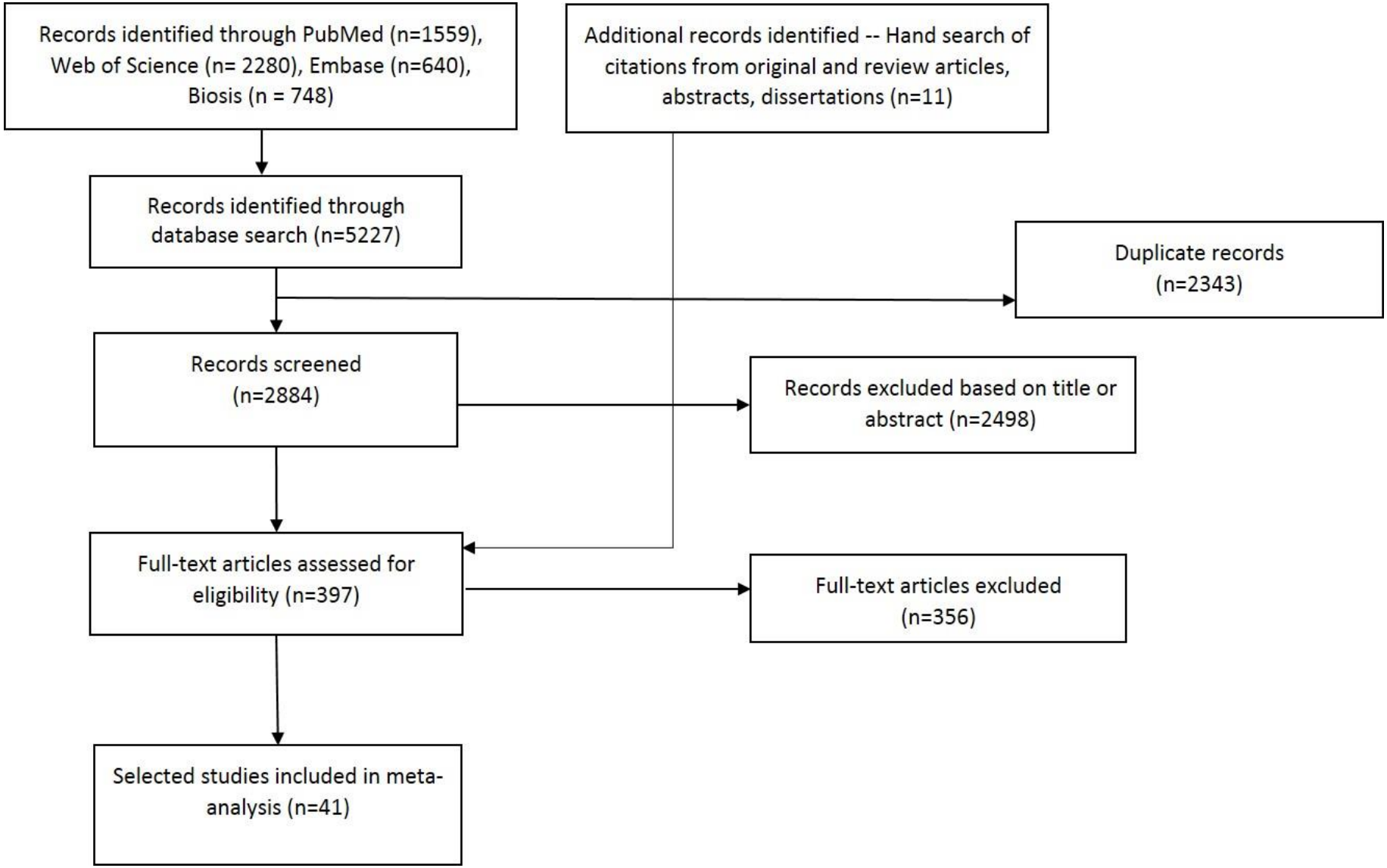


Figure. Odds of tuberculosis disease in twelve studies with household contacts of tuberculosis cases and unexposed control groups

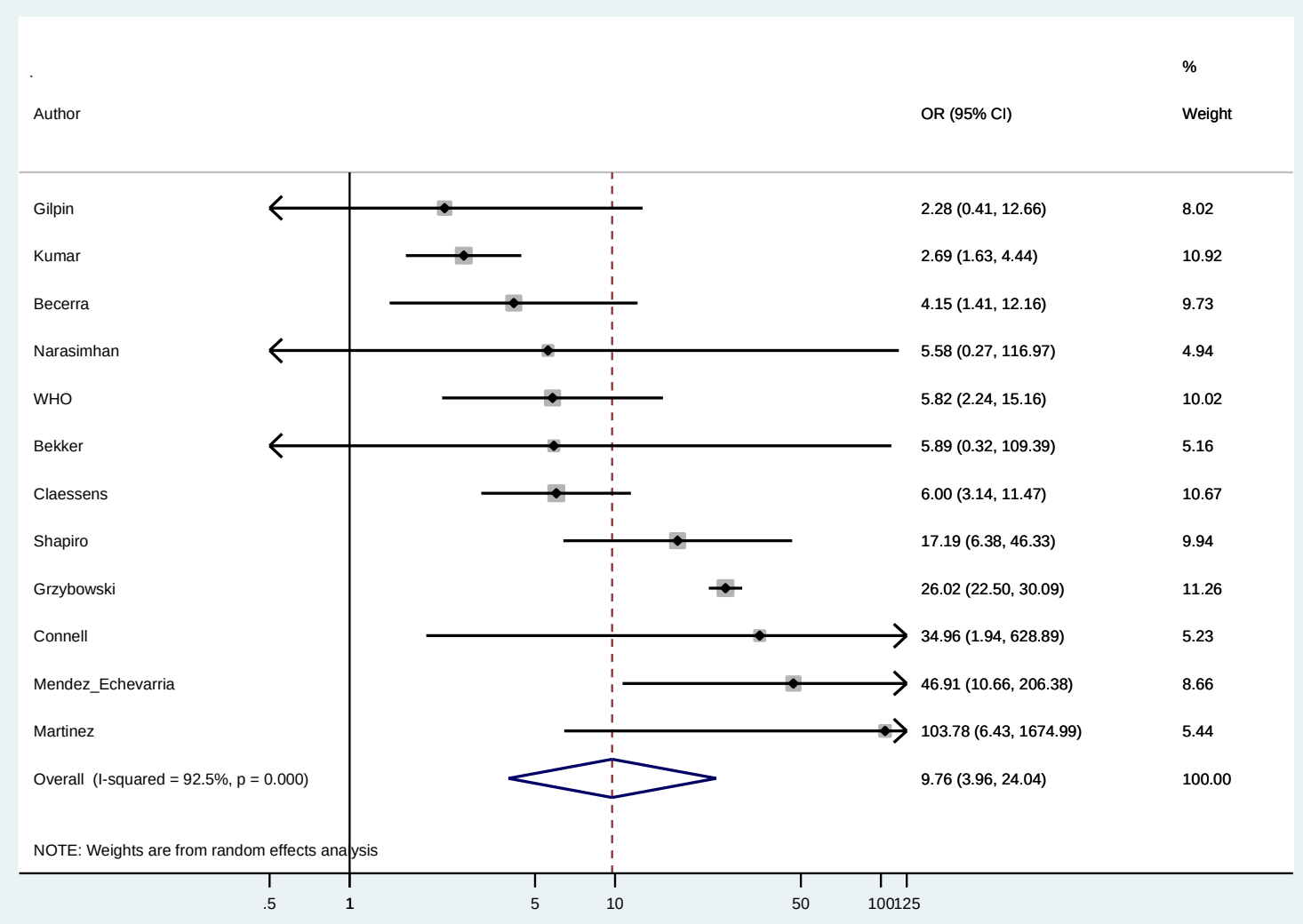


Figure 2. Yield of tuberculosis disease in household contacts of tuberculosis cases from selected studies.

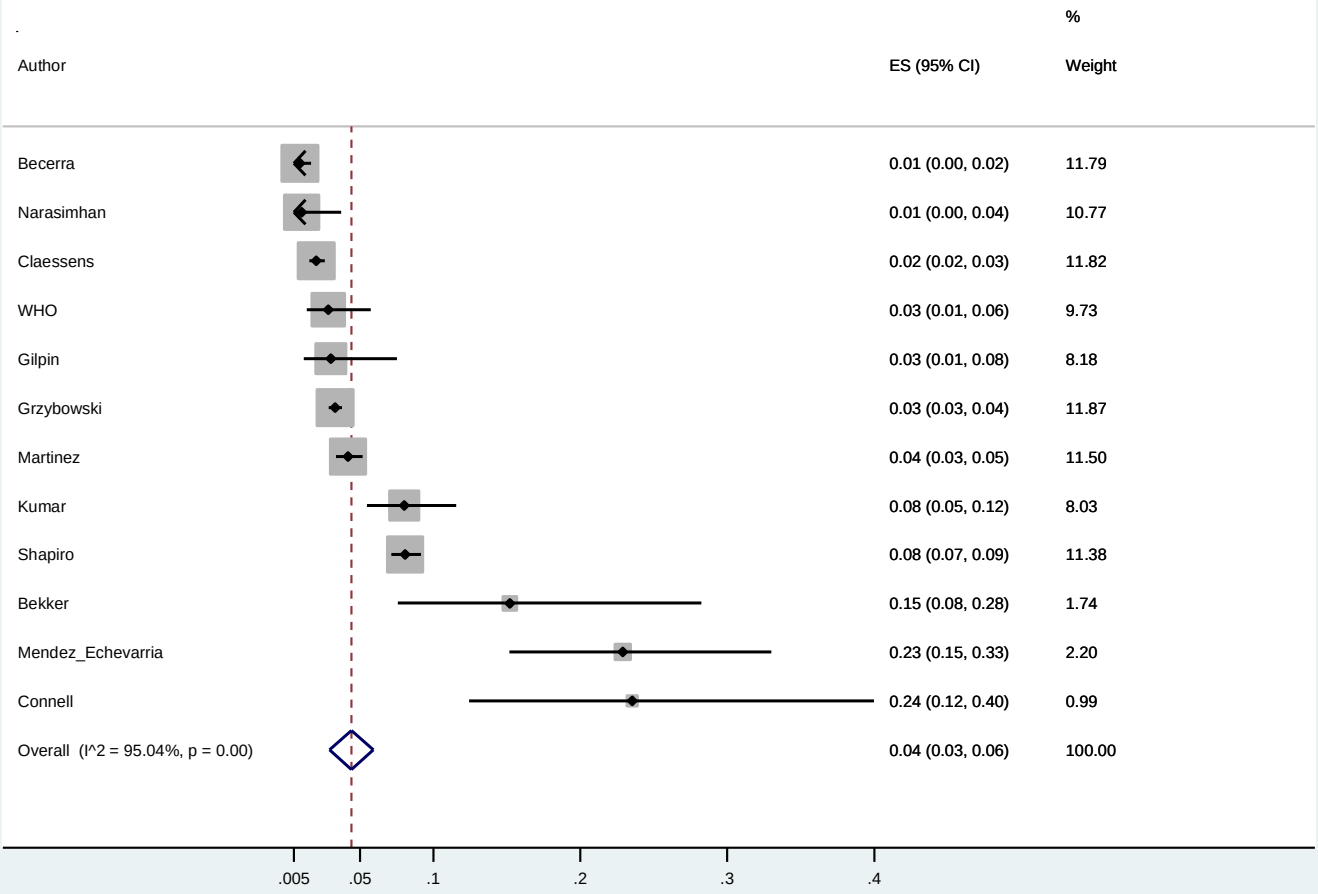


Figure 3. Yield of tuberculosis disease in community controls of tuberculosis cases from selected studies.

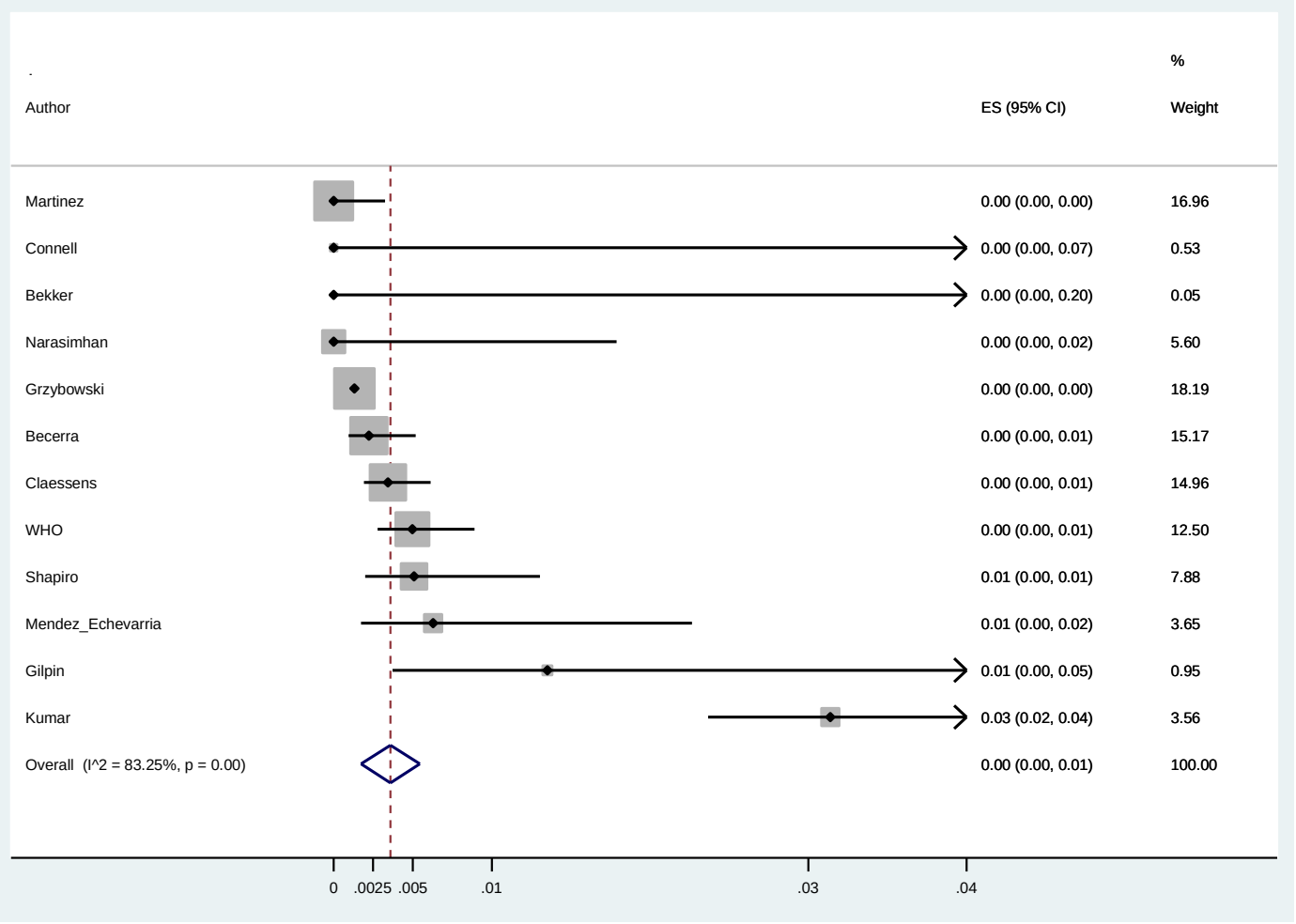


Figure. Odds of tuberculosis disease in twelve studies from household contacts and unexposed controls after stratification by global region

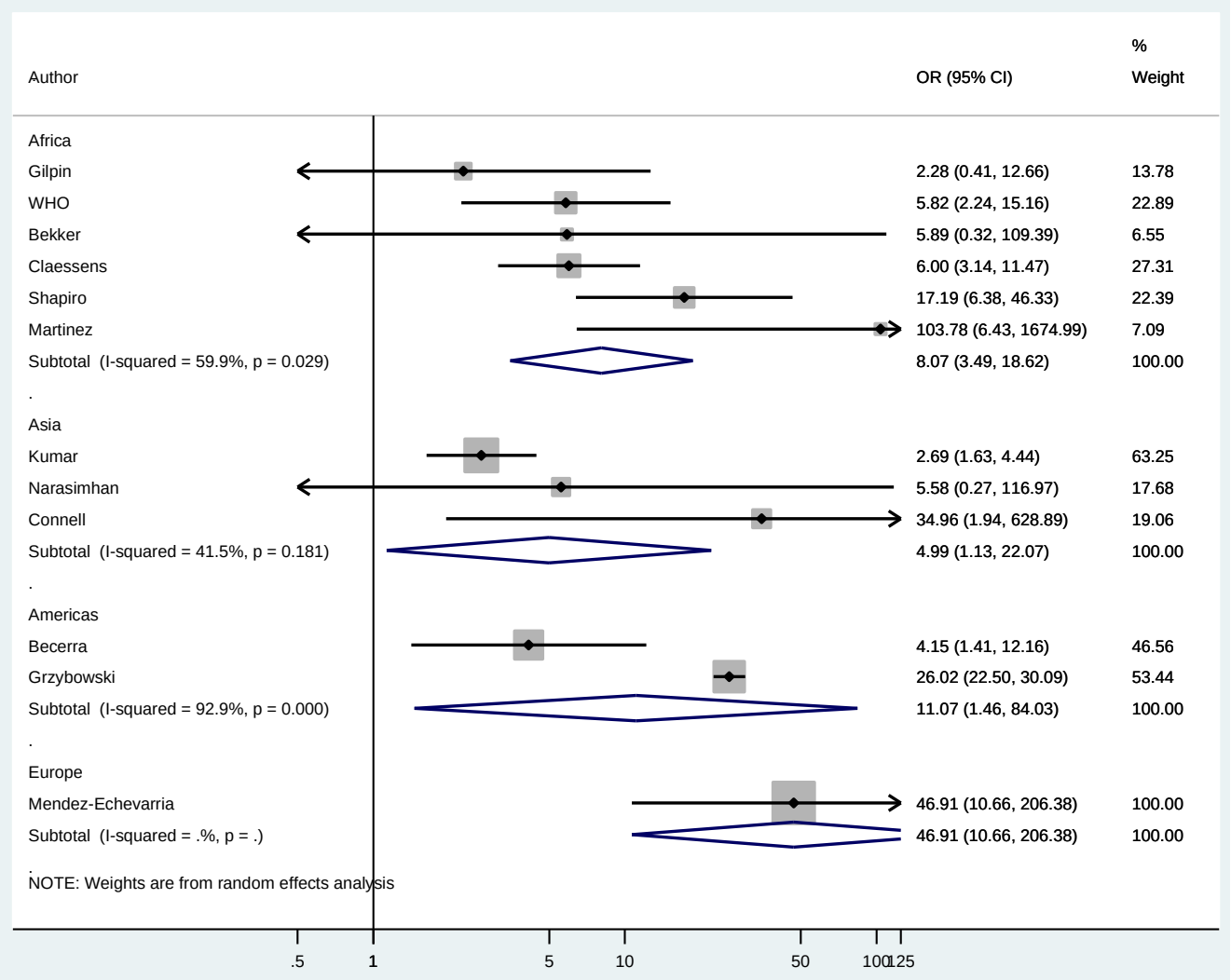


Figure 6. Odds of latent tuberculosis infection after stratification by type of diagnostic measure used to define latent tuberculosis

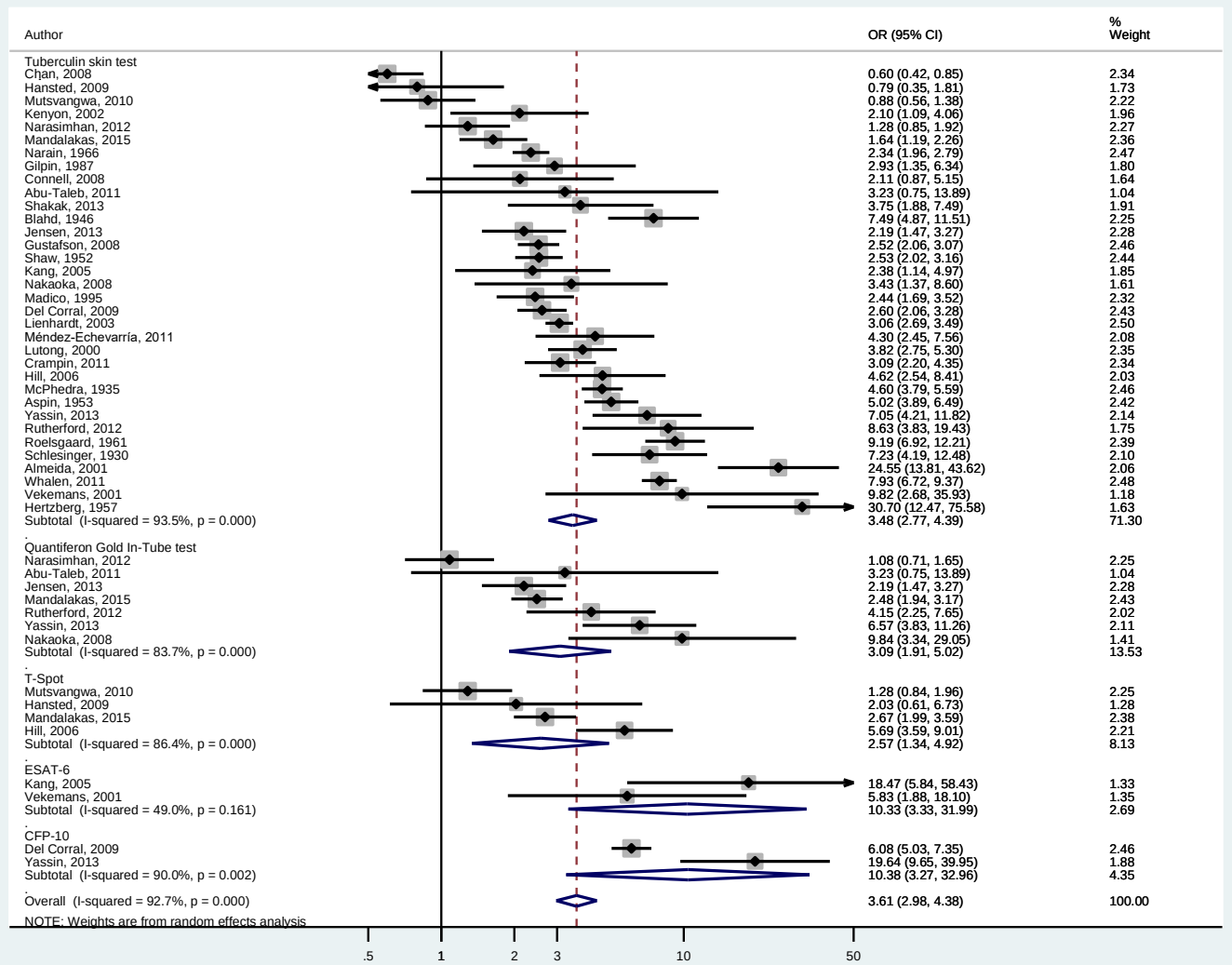


Figure 7. Odds of latent tuberculosis infection after stratification by sputum smear status of the tuberculosis index case

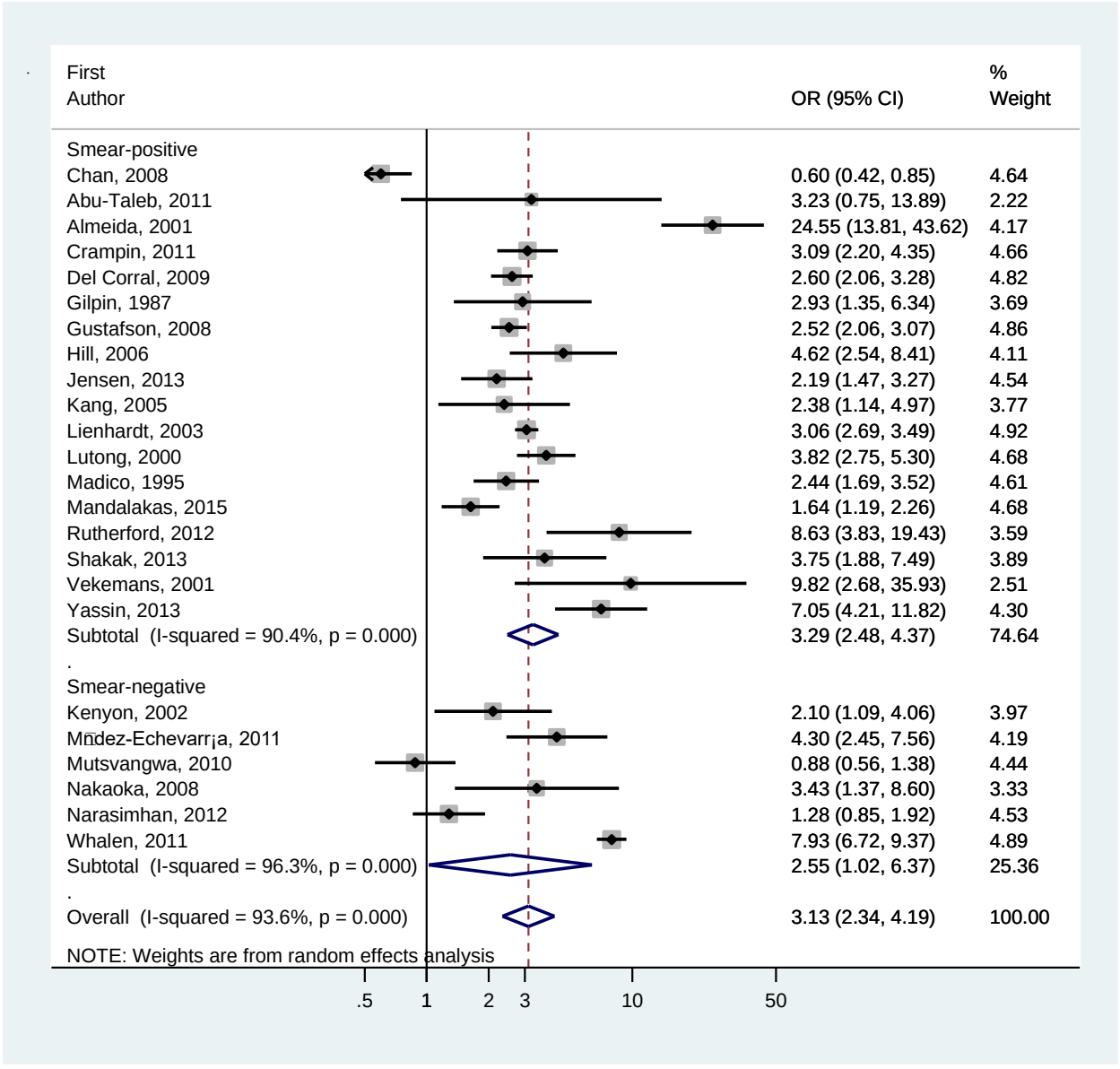


Figure 8. Odds of latent tuberculosis infection after stratification by type of control group

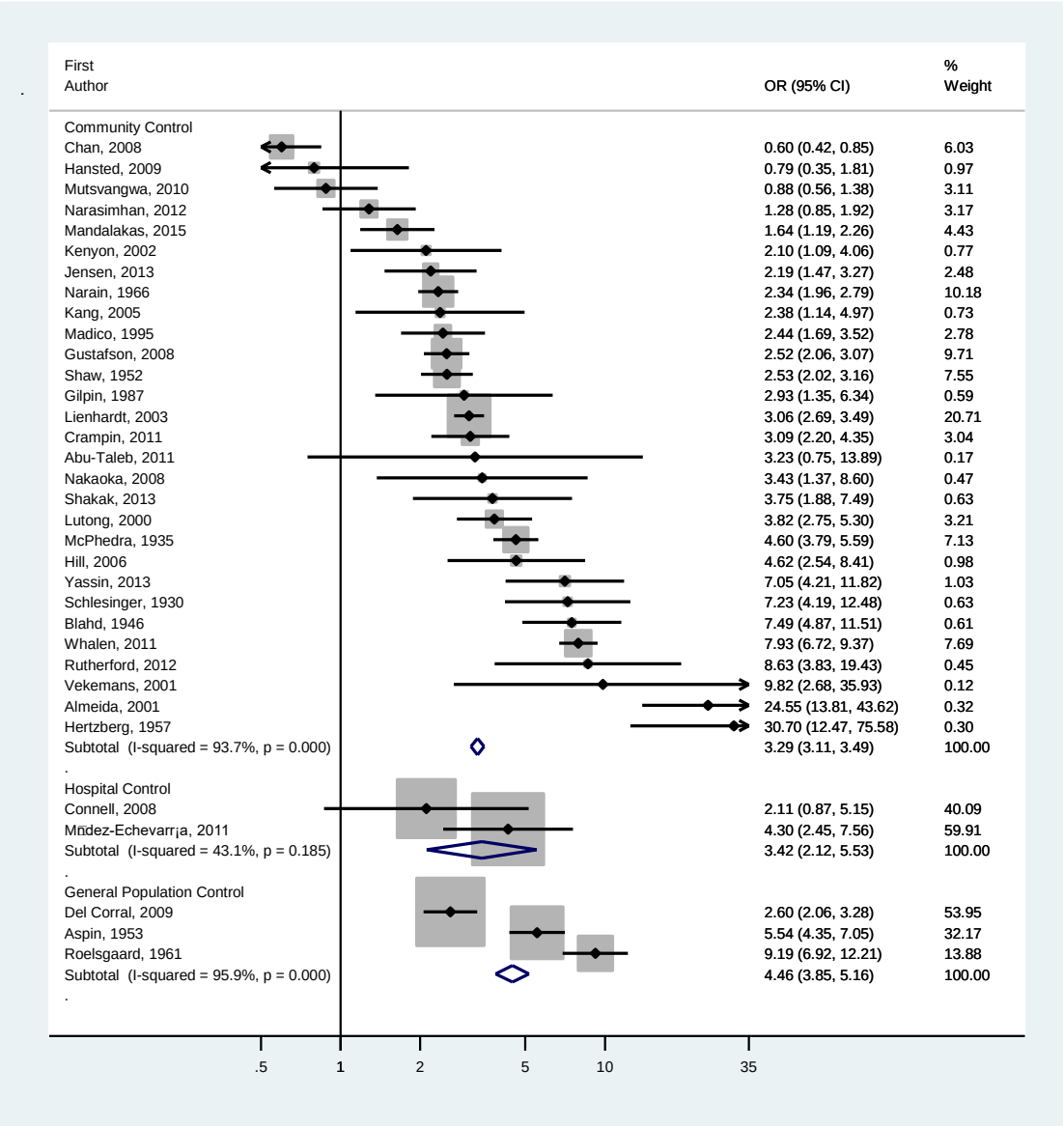
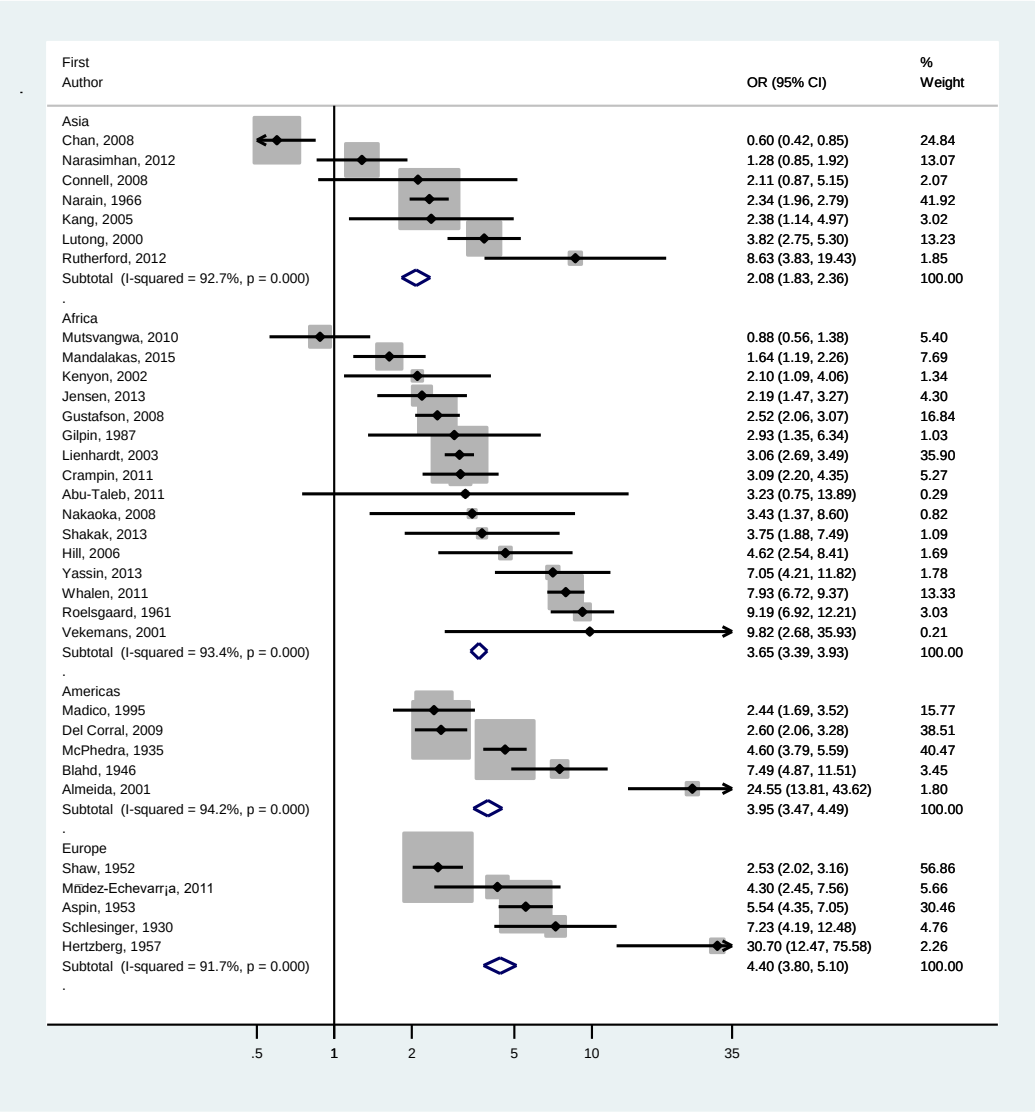


Figure 9. Odds of latent tuberculosis infection after stratification by global region.



CHAPTER 6: SYSTEMATIC SCREENING OF HOUSEHOLD CONTACTS OF TUBERCULOSIS CASES IN SUB-SAHARAN AFRICA

Aim 2, Derivation and validation of a predictive risk score.

SHORT RUNNING HEAD. Risk score for tuberculosis in household contacts

INTRODUCTION.

Household contact tracing of tuberculosis cases has been proposed as a complementary strategy to current tuberculosis control but has been implemented poorly or not at all in high-burden settings due to its resource intensiveness and high number needed–to–screen. We developed a predictive risk score to detect contacts at most risk for undetected, co-prevalent tuberculosis disease.

METHODS.

Adults with newly diagnosed tuberculosis disease were identified and their household contacts were enrolled in Kampala, Uganda. Field workers administered an extensive questionnaire to all contacts after which clinical information (sputum smear samples, chest radiograph findings, and HIV status) was tested and collected. A predictive score was assessed for ability to correctly identify household contacts with co-prevalent tuberculosis disease. We calculated risk scores for each patient and an area under the receiver operating characteristic (AUC) curves of the model for different scores. The model was validated internally through 10-fold cross–validation.

RESULTS.

In all, 1940 household contacts were evaluated for co-prevalent tuberculosis disease and 94 (4.9%) were diagnosed. Five independent risk factors (past active tuberculosis, age, and contact HIV status; cavitary status of the index case; family size of the household) were identified and each was assigned a number of points based on their regression coefficient. The AUC of the score was 0.80 (95% CI, 0.75 – 0.84). The risk of coprevalent disease increased with increasing score (P_{trend}<0.0001). Coprevalent disease risk in contacts with a score of 0–2 and 3–8 was 1.4% and 14.1%, respectively. Screening only contacts with a score from 3–8 would detect almost 80% of cases screened despite only screening 27% of contacts.

DISCUSSION.

A simple-to-use risk score was developed to predict co-prevalent tuberculosis disease in household contacts in a high-burden setting and was validated internally. Using this risk score, systematic household contact tracing may be a highly efficient supplementary control intervention to current tuberculosis control measures in high-burden settings.

INTRODUCTION.

Currently, global tuberculosis incidence is lowering at approximately 1–2% per year.[14] Although this reduction represents millions of saved lives improvement was expected to be much higher.[12,14] If these current trends continue, 2030 goals for global tuberculosis elimination are unlikely to be met. In high-burden, low-income settings, tuberculosis case detection is poor.[15,266,267] Globally, approximately 35% of tuberculosis cases remain undetected.[15,267] In sub-Saharan Africa, close to 50% of tuberculosis cases are concealed by health services.[267] As long as these cases remain undetected *Mycobacterium tuberculosis* transmission persists.[268,269]

Active case finding, through screening household contacts of tuberculosis index cases, has been proposed as a method to supplement current tuberculosis control.[23,40,67,211,270,271] Despite policy recommendations from epidemiologists and global health organizations, contact tracing been implemented poorly or not at all in low-income, high-burden settings.[25,130] Household contact tracing has a high disease yield[23,40,270] however uses substantial resources and has a high number needed to screen to detect a tuberculosis case, deterring use among National Tuberculosis Programs.

We conducted a large household contact investigation in urban Kampala, Uganda. Our main objective was to develop a predictive risk score for coprevalent tuberculosis disease amongst household contacts derived from a combination of independent predictors available to health workers when a tuberculosis index case presents to health services. The validity of this risk score was tested internally using 10-fold cross-validation.

METHODS.

STUDY POPULATION AND SETTING.

The study design has been described previously.[5,6,270] Briefly, we identified newly diagnosed tuberculosis patients ≥18 years old from the National Tuberculosis and Leprosy Program at Old Mulago Hospital in Kampala, Uganda from 1995 through 2006. Index cases were microbiologically confirmed through a positive culture test and defined as the first eligible case of pulmonary tuberculosis in a household with one or more contacts.

Upon enrollment, index cases were evaluated through a physical examination and medical history. Information was collected on age, sex, room where they sleep, cigarette smoking status, chest radiograph, and duration of cough. Extent of disease through radiographic imaging results was graded independently by an experienced clinician using the National Tuberculosis Association classification system with sub-groupings for cavitary and non-cavitary disease. Sputum samples were also collected for laboratory testing of mycobacterial culture and microscopic assessment.

Households with index cases were visited by trained field workers within two weeks of the tuberculosis index case's diagnosis. Household contacts were defined as any individual spending at least seven consecutive days in the same household as the index case in the three months preceding diagnosis. Household members were invited to participate and complete a baseline socio-demographic questionnaire and physical examination collecting data on age, sex, height, weight, cigarette smoking status, alcohol usage (yes or no), relationship to the index case (spouse, parent, child, sibling, or other), education level, past active tuberculosis, and household characteristics

(crowding, housing structure, ventilation, or smoke exposure). Bacillus Calmette-Guérin (BCG) vaccination was assessed through inspecting BCG scars and confirmed with medical records when possible.

Index cases and household contacts over the age of 5 years were offered HIV testing with an enzyme-linked immunosorbent assay (Cambridge BiosScience, Worcester, Massachusetts). Parents gave informed consent for child contacts. Children under five years of age were offered HIV testing if the mother was living with HIV. If the mother was negative then the child was also presumed to be negative. Contacts with HIV or less than six years old without active tuberculosis disease were offered a six-month course of isoniazid preventative therapy.

Coprevalent tuberculosis disease was defined as the identification of tuberculosis disease at the baseline visit or within three months of the initial evaluation. The identification of tuberculosis disease amongst contacts was conducted using a multi-pronged approach. At baseline, posteroanterior chest radiographs were taken on all participants and were examined independently by two experienced pulmonary physicians. Household contacts were evaluated for active tuberculosis disease through a medical examination, specimen microscopy, and mycobacterial culture if they were under six years of age or HIV seropositive. Subjects with any tuberculosis symptoms, which included cough, fever, night sweats, dyspnea, weight loss, lymphadenopathy, loss of appetite, were evaluated using similar methods. Contacts classified without tuberculosis at baseline were followed and assessed for active tuberculosis at six month intervals for two years. All baseline information on contacts that developed tuberculosis within one year were re-evaluated and those with subtle, abnormal chest radiographs

and nonspecific symptoms were re-classified by a physician as co-prevalent rather than incident disease even if after the three-month window.

STATISTICAL ANALYTICAL PLAN.

The prevalence of active tuberculosis disease from household contact tracing were estimated using standard contingency tables and stratified by index case, household contact, and household environmental risk factors. In order for the risk score to be used programmatically in an efficient manner we only selected variables that the tuberculosis index case would know in an interview after being first diagnosed at the clinic. In a “real-world” setting, an effective score without these variables would allow health workers and clinicians to evaluate the risk of contacts without visiting all households and therefore would save substantial resources to the programmatic use of household contact tracing. Due to this, we excluded tuberculin skin test results, body mass index, and BCG vaccination as potential variables to be included in our score. To describe our study population, we keep these variables in our demographic and univariate tables.

To reduce the pool of candidate risk factors for co-prevalent tuberculosis disease, we performed univariate item analysis on all contacts. We evaluated correlations among variables using polychoric correlation coefficients which measure correlation between ordered levels where the latent trait can be considered continuous and normally distributed. We added variables one at a time that were related to coprevalent tuberculosis disease ($P < 0.20$). A series of modified poisson regression models were fit using a generalized estimating equation to take into account the

clustering of household contacts.[272-274] Two-sided p-values and 95% confidence intervals were used to assess statistical significance in all models.

ETHICAL CONSIDERATIONS.

Institutional review boards at the Uganda National Council for Science and Technology, the Uganda National AIDS Research Subcommittee, Case Western University, and Makerere University approved this study. Informed consent was obtained for all index cases and household contacts. Parents or guardians of child contacts provided written consent in addition to verbal assent from the children.

RESULTS.

DEMOGRAPHIC CHARACTERISTICS.

In all, 1940 household contacts of 499 tuberculosis index cases were enrolled in the derivation cohort. The median age of the index cases was 30 years of age (interquartile range [IQR], 25 – 37), 24% were smokers, and 53% were male. After laboratory and clinical testing, 75% were tested sputum smear positive, 48% were HIV seropositive, and 55% had lung cavitary disease. The median duration of cough was 90 days.

The median age of contacts was 12 years of age (IQR, 5 – 21). Approximately 70% were tuberculin skin test positive and BCG vaccinated. In all, 5% were smokers while only 1% previously had tuberculosis. Of the 1662 contacts (85.7% of the study population) that tested for HIV, 10.4% tested positive. After clinical evaluation, chest radiographs, and microbiological tests, 94 contacts (4.9%) were diagnosed with co-prevalent tuberculosis disease. The number needed to screen to detect one coprevalent tuberculosis case was 20.

RISK FACTORS FOR COPREVALENT TUBERCULOSIS DISEASE.

After stratification, several contact, index case, and environmental characteristics were risk factors for elevated levels of coprevalent tuberculosis disease. Risk factors of the household contact included age (10.8% prevalence in children 0 – 4 years old, 5.9% in those 35 – 44 years old), sex (6% prevalence versus 4% in males and females), education level (10.5% prevalence in those with no education), past active tuberculosis (18.2% prevalence), HIV serostatus of the contact (12.6% prevalence), and closeness to the index case (P_{trend}<0.0001 from sharing bed, sharing room, and not sharing a

room). Index case characteristics that led to elevated risk of coprevalent disease in contacts included lung cavitation in the index case (6.1% prevalence). Environmental characteristics with high rates of coprevalent tuberculosis included multifamily households (6.7% prevalence) and a family size between 1 and 5 (6.7% prevalence).

In univariate regression analysis, age of the contact, sex, education level, relation to the index case, past active tuberculosis, HIV serostatus, and closeness to the index case were all statistically significant predictors of contact disease. Only index lung cavitation and age were statistically significant predictors of coprevalent disease while housing type, charcoal smoker exposure, and family size all showed statistically different rates of coprevalent tuberculosis disease.

RISK SCORE CREATION USING COMPLETE CASE ANALYSIS.

We created a risk score assigning contact, index case, and environmental risk factors with a number of points proportional to its regression coefficient. Using a complete case analysis, five variables included and their corresponding point totals were: HIV serostatus (1 point), age (2 points if <5 years of age), and past active tuberculosis from the household contact (2 points); the presence of lung cavitation in the index case (1 point); and family size of the household (1 point if household has between 1 and 5 household members). The score ranged from 0 – 8 and contacts were divided into eight subgroups based on their point total. The risk of coprevalent tuberculosis disease increased with increasing score (P_{trend}<0.0001). Coprevalent disease risk in contacts with a score of 0–2 and 3–8 was 1.4% and 14.1%, respectively. Coprevalent disease risk in contacts with a score of 0–3 and 4–8 was 3.1% and 19.7%, respectively. Screening only contacts with a score from 3–8 would detect almost 80% of cases

screened despite only screening 27% of contacts while screening only those 4–8 would detect 42.6% of cases despite only screening 10.5% of contacts. The AUC of the score was 0.80 (95% CI, 0.75 – 0.84) and 0.82 (95% CI, 0.75 – 0.85) after 10–fold cross-validation.

RISK SCORE CREATION USING MULTIPLE IMPUTATION.

Using multiple imputation of missing variables, five variables included and their corresponding point totals were: HIV serostatus (2 point), age (3 points if <5 years of age, 1 point if 15 – 24 years of age), and past active tuberculosis from the household contact (2 points); the presence of lung cavitation in the index case (1 point); and family size of the household (1 point if household has between 1 and 5 household members). The score ranged from 0 – 9 and contacts were divided into nine subgroups based on their point total. The risk of coprevalent tuberculosis disease increased with increasing score (P_{trend}<0.0001). Coprevalent disease risk in contacts with a score of 0–3 and 4–9 was 1.8% and 18.3%, respectively. Coprevalent disease risk in contacts with a score of 0–4 and 5–9 was 3.4% and 27.1%, respectively. Screening only contacts with a score from 4–9 would detect 74% of cases screened despite only screening 19% of contacts while screening only those 5–9 would detect 38.0% of cases despite only screening 6.6% of contacts. The AUC of the score was 0.81 (95% CI, 0.77 – 0.85).

DISCUSSION.

Household contact tracing has been recommended as a potential supplementary measure to current tuberculosis control[23,40,267,271] however due to resource intensiveness has not been implemented in low-income settings where health resources are scarce.[25,130] We derived a clinical risk score using a large, diverse cohort of household contacts of pulmonary tuberculosis cases in a setting with a high burden of both HIV and tuberculosis. The discrimination of the risk score model was strong (AUC, 0.80). Our derived risk score incorporated only five clinical variables from household contact, index case, and household environmental risk factors. Evaluation using internal validation demonstrated good test characteristic retention (AUC, 0.82) after 10–fold cross-validation.

Although household contact tracing has been extensively investigated[5,20,23,40,270,275] much of this work has been research-based and methods to optimize the detection of tuberculosis in household contacts programmatically has rarely been explored. Importantly, we included only characteristics that would be available to the index case upon diagnosis at the clinic allowing health workers to interview index cases and visit only a select few high-risk households. Use of this risk score may be contingent on the available resources of the tuberculosis control program. For example, if contacts with a score of 3 – 8 are selected for a household visit 79% of all tuberculosis cases would be detected with 27% of contacts visited. However, if a tuberculosis control program has fewer resources they may only visit households with a score of 4 – 8, detecting 43% of all cases but visiting only 10.5% of households. Therefore, this score

may be used differently by distinct tuberculosis control programs that have variable resources.

Several steps are needed before this predictive risk score can be used programmatically. External validation using independent household contact cohorts in Africa and other high-burden settings.[195,276,277] External validation of our derived score is critical but for several reasons may be difficult. First, this score is unlikely useful in low-burden, high-income settings where tuberculosis risk factors amongst contacts are highly distinct from high-burden settings. For example, foreign-born individuals are highly susceptible to tuberculosis in these settings while HIV infection is uncommon and largely uninfluential. Second, household contact methodology varies between studies.[40,278,279] Ascertainment of tuberculosis amongst household contacts was extensive in our study. All household contacts were given chest radiograph and clinical examinations and most were tested with sputum culture and smear testing. Differential ascertainment of tuberculosis disease from other household contact studies[20,275,280,281] may substantially limit the ability of other studies to adequately externally validate this score. In addition, the definition of exposure in these studies may also be different and this depend on the specific culture and setting.[20]

We report a new prediction model that quantifies the risk of coprevalent, undiagnosed tuberculosis disease in household contacts using programmatic data available to health workers when the index case presents to health services. External validation of this score is needed but, if validated, this score may provide an important programmatic tool for National Tuberculosis Programs in low-income, high-burden

settings where tuberculosis case detection is especially poor and resources for implementation of further tuberculosis health programming is extremely limited.

CHAPTER 7: PROGRESSIVE PRIMARY DISEASE IN HOUSEHOLD CONTACTS OF TUBERCULOSIS CASES: RISK FACTORS AND EVALUATION OF POLICY

Aim 3, Section 1: Attempt at derivation of predictive risk score for incident tuberculosis disease

INTRODUCTION

Prevention of tuberculosis transmission through preventative therapy has been widely acknowledged as essential in high-burden settings to supplement current control measures. Despite this, preventative therapy has been largely ignored by National Tuberculosis Programmes in low-income settings due to resource intensiveness and a high number-needed-to-treat to prevent one case. Methods to optimize the programmatic implementation of preventative therapy are needed. We attempted to derive a predictive risk score for incident tuberculosis disease amongst household contacts that are not currently included in global recommendations – specifically, HIV-negative and those older than 5 years of age.

METHODS.

Adults with newly diagnosed tuberculosis disease were identified and their household contacts were enrolled in Kampala, Uganda. Field workers administered an extensive questionnaire to all contacts after which clinical information (sputum smear samples,

chest radiograph findings, and HIV status) was tested and collected. Because current policy on isoniazid preventative therapy includes contacts that are HIV-positive and <5

years of age these contacts were given preventative therapy as part of study protocol. To attempt to expand current policy recommendations, we excluded contacts covered by current World Health Organization policy in addition to those with tuberculosis disease at baseline. We calculated the frequency of incident tuberculosis disease for all contacts and then for each risk factor of the household contact, tuberculosis index case, and household environmental characteristic. We attempted to derive a predictive score and assessed the ability of the score to correctly identify household contacts with incident tuberculosis disease.

Table 1. Demographic characteristics of 1764 household contacts of tuberculosis cases, Kampala, Uganda

Variable	Frequency	Percent
Household contact characteristics		
N	1764	100
Median age, years (IQR)	16 (10 – 24)	
Age group, years		
5 – 14	744	42.2
15 – 24	583	33.1
25 – 34	220	12.5
35 – 44	116	6.6
≥45	101	5.7
Sex		
Male	731	41.4
Female	1033	58.6
Education level		
None	138	7.8
Primary	943	53.5
Secondary or higher	683	38.7
Tuberculin skin test		
Positive	1239	70.2
Negative	518	29.4
Missing	7	0.4

BCG vaccinated		
Yes	1193	67.6
No	437	24.8
Unknown	134	7.6
Cigarette smoker		
Yes	81	4.6
No	1683	95.4
Relation to index case		
Spouse	259	14.7
Parent	87	4.9
Child	540	30.6
Sibling	277	15.7
Other	596	33.8
Missing	5	0.3
Past active tuberculosis		
Yes	28	1.6
No	1735	98.4
Missing	1	0.1
Nutritional status		
Underweight	195	11.1
Normal	1156	65.5
Overweight	411	23.3
Missing	2	0.1

Alcohol usage		
Yes	261	14.8
No	1502	85.2
Missing	1	0.1
Closeness to index case		
Share bed	292	16.6
Share room, not bed	717	40.7
Different room	743	42.1
Missing	12	0.7
Current cough		
Yes	154	8.7
No	1610	91.3
Know another tuberculosis case		
Yes	171	9.7
No	1447	82.0
Unknown	146	8.3
Index case characteristics		
Age group, years		
18 – 29	908	51.6
30 – 39	510	29.0
40 – 49	241	13.7
≥50	101	5.7
Sex		

Male	880	51.2
Female	840	48.8
Cigarette smoker		
Yes	305	17.3
No	1418	80.4
Missing	41	2.3
Lung cavitation		
Cavitary disease	706	41.0
Noncavitary disease	444	25.8
Missing	573	33.3
Median cough duration, days (IQR)	90 (45 – 150)	
Duration of cough		
<30 days	110	6.2
≥30 and <60 days	346	19.6
≥60 and <90 days	323	18.3
≥90 days	815	46.2
Missing	170	9.6
HIV serostatus		
Positive	700	40.6
Negative	1022	59.3
Household characteristics		
Housing type		
Multi-family household	834	47.3

Single family household	915	51.9
Missing	15	0.9
Charcoal or fire smoke exposure		
Inside household	417	23.6
Outside household	1250	70.9
None	55	3.1
Missing	42	2.4
Ventilation, Mean no. windows/room (SD) (continuous)	0.6 (0.5)	
Ventilation (No. windows/room)		
>1	176	10.0
≤1	1576	89.3
Missing	12	0.7
Median density, persons/home (IQR)	6 (4 – 8)	
Household size (persons/home)		
1 – 5	767	43.5
6 – 10	793	45.0
>10	204	11.6

Definition of abbreviations: BCG = bacillus Calmette-Guerin; BMI = body mass index; IQR = interquartile range.

* Percentages may not total 100% because within-column percentages were rounded to the nearest integer.

† We used Pearson chi-square tests to derive P values for all categorical variables. For continuous variables, we used Wilcoxon rank sum tests for comparison of two-sample medians. ‡ Nutritional status was assessed for each contact through BMI measurements for adults greater than or equal to 18 years of age and through weight-for-age z scores for child contacts. Individuals were classified as underweight if their z score was less than 22 or a BMI less than 18.5, normal weight if z scores were between 22 and 2 or their BMI was greater than or equal to 18.5 and less than 25, and overweight if z scores were greater than 2 or BMI was greater than or equal to 25.
x Evaluated through BCG scar, verified by medical records when available.
jj Includes other relatives, such as grandparents, grandchildren, aunts, uncles, and cousins. Also includes nonrelatives living in the household.

Table 2. Frequency and proportion of incident tuberculosis disease among household contacts in Kampala, Uganda (N=1764)

Variable	Contacts with incident disease (%)	No. Household Contacts	p-value
N	29 (1.6)	1764	–
Household contact characteristics			
Age group, years			0.52
5 – 14	12 (1.6)	744	
15 – 24	7 (1.2)	583	
25 – 34	6 (2.7)	220	
35 – 44	3 (2.6)	116	
≥45	1 (1.0)	101	
Sex			0.45
Female	15 (1.5)	1033	
Male	14 (1.9)	731	
Education level			0.79

None	2 (1.5)	138	
Primary	14 (1.5)	943	
Secondary or higher	13 (1.9)	683	
Tuberculin skin test positive			0.92
Negative	8 (1.5)	518	
Positive	21 (1.7)	1239	
BCG vaccinated			0.77
No	8 (1.8)	437	
Yes	18 (1.5)	1193	
Unknown	2 (2.2)	134	
Cigarette smoker			0.136
No	26 (1.5)	1683	
Yes	3 (3.7)	81	
Relation to index case			0.006
Other	4 (0.7)	596	
Sibling	7 (2.5)	277	

Child	9 (1.7)	540	
Parent	2 (2.3)	87	
Spouse	6 (2.3)	259	
Past active tuberculosis			<0.01
No	26 (1.5)	1735	
Yes	3 (10.7)	28	
Nutrition status			0.11
Overweight	2 (0.5)	411	
Normal	21 (1.8)	1156	
Underweight	6 (3.1)	195	
Weight loss			<0.01
No	21 (1.3)	1668	
Yes	8 (8.3)	96	
Chronic cough			<0.01
No	17 (1.1)	1610	
Yes	12 (7.8)	154	

Alcohol usage			0.37
No	23 (1.5)	1502	
Yes	6 (2.3)	261	
Closeness to index case			0.60
Different room	13 (1.8)	743	
Share room, not bed	9 (1.3)	717	
Share bed	6 (2.1)	292	
Index case characteristics			
Age group, years			0.62
18 – 29	18 (2.0)	908	
30 – 39	5 (1.0)	510	
40 – 49	4 (1.7)	241	
≥50	2 (2.0)	101	
Sex			0.151
Male	11 (1.3)	880	
Female	18 (2.1)	840	

Cigarette smoker			0.95
No	24 (1.7)	1418	
Yes	5 (1.6)	305	
Sputum smear status			
Negative			
Positive			
Lung cavitation			0.34
Noncavitary disease	5 (1.1)	444	
Cavitary disease	13 (1.8)	706	
Duration of cough			0.046
<30 days	0 (0)	110	
≥30 and <60 days	12 (3.5)	346	
≥60 and <90 days	5 (1.6)	323	
≥90 days	12 (1.5)	815	
HIV serostatus			0.29
Positive	9 (1.3)	700	

Negative	20 (2.0)	1022	
Household characteristics			
Family size (No. in household)			0.74
>10	4 (2.0)	204	
6 – 10	11 (1.4)	793	
1 – 5	14 (1.8)	767	

Table. Univariate model for incident tuberculosis disease among household contacts, Kampala, Uganda (N=1764)

Variable	Crude Relative Risk (95% CI)
N	–
Household contact characteristics	
Age group, years	
5 – 14	1 (Referent)
15 – 24	0.74 (0.30 – 1.86)
25 – 34	1.69 (0.64 – 4.46)
35 – 44	1.60 (0.46 – 5.63)
≥45	0.61 (0.08 – 4.69)
Sex	
Female	1 (Referent)
Male	1.32 (0.64 – 2.71)
Education level	
None	1 (Referent)
Primary	1.02 (0.24 – 4.42)
Secondary or higher	1.31 (0.30 – 5.67)
Tuberculin skin test positive	
Negative	1 (Referent)
Positive	1.10 (0.49 – 2.44)
BCG vaccinated	

No	1 (Referent)
Yes	0.82 (0.36 – 1.87)
Unknown	1.22 (0.33 – 4.54)
Cigarette smoker	
No	1 (Referent)
Yes	2.40 (0.74 – 7.76)
Relation to index case	
Other	1 (Referent)
Sibling	3.77 (1.12 – 12.65)
Child	2.48 (0.77 – 7.99)
Parent	3.43 (0.63 – 18.59)
Spouse	3.45 (0.98 – 12.12)
Past active tuberculosis	
No	1 (Referent)
Yes	7.15 (2.25 – 22.67)
Nutrition status	
Overweight	1 (Referent)
Normal	3.73 (0.87 – 15.96)
Underweight	6.32 (1.28 – 31.17)
Weight loss	
No	1 (Referent)
Yes	6.62 (2.96 – 14.79)
Chronic cough	

No	1 (Referent)
Yes	7.38 (3.52 – 15.47)
Alcohol usage	
No	1 (Referent)
Yes	1.50 (0.63 – 3.59)
Closeness to index case	
Different room	1 (Referent)
Share room, not bed	0.71 (0.31 – 1.67)
Share bed	1.17 (0.45 – 3.05)
Index case characteristics	
Age group, years	
18 – 29	1 (Referent)
30 – 39	0.49 (0.19 – 1.30)
40 – 49	0.84 (0.28 – 2.48)
≥50	1.00 (0.25 – 4.05)
Sex	
Male	1 (Referent)
Female	1.71 (0.83 – 3.56)
Cigarette smoker	
No	1 (Referent)
Yes	0.97 (0.38 – 2.47)
Lung cavitationll	
Noncavitary disease	1 (Referent)

Cavitary disease	1.64 (0.60 – 4.43)
Duration of cough	
<30 days	NA
≥30 and <60 days	1 (Referent)
≥60 and <90 days	0.45 (0.16 – 1.21)
≥90 days	0.42 (0.20 – 0.91)
HIV serostatus	
Negative	1 (Referent)
Positive	0.66 (0.30 – 1.42)
Household characteristics	
Housing type	
Single family household	1 (Referent)
Multifamily household	1.00 (0.60 – 1.65)
Charcoal or smoke exposure	
None	1 (Referent)
Outside household	2.22 (0.30 – 16.66)
Inside household	2.39 (0.30 – 18.71)
Ventilation, windows/room (continuous)	
Ventilation (No. windows/room)††	
>1	1 (Referent)
≤1	3.13 (0.45 – 21.53)
Family size, persons/home (continuous)	
Family size (No. in household)	

>10	1 (Referent)
6 – 10	0.76 (0.35 – 1.65)
1 – 5	1.07 (0.38 – 3.06)

Aim 3, Section 2: Risk of incident tuberculosis disease among household contacts of tuberculosis cases – a prospective cohort study from Kampala, Uganda

INTRODUCTION.

Investigating incident tuberculosis disease is difficult because large cohorts, lengthy follow-up, and extensive evaluation of individuals are needed to have sufficient statistical power and reliable ascertainment of cases. Due to these difficulties, few studies have been performed, especially in low-income or high HIV-burden settings. Furthermore, most of these studies have had a retrospective design. Policy development and implementation for tuberculosis preventative therapy has been slow due to a lack of evidenced-based research on risk factors for tuberculosis disease development. We present the largest prospective cohort study of household contacts in Africa to assess overall risk and potential risk factors for primary progressive tuberculosis disease.

METHODS.

Adults with newly diagnosed pulmonary tuberculosis disease were identified and their household contacts were enrolled in Kampala, Uganda. Field workers administered an extensive questionnaire and extensive clinical examination (tuberculin skin tests, sputum smear samples, chest radiograph findings, and HIV status) to all contacts at the first household visit. After the baseline evaluation, all household contacts free of active TB were followed for up to 2 years and evaluated for incident tuberculosis disease.

RESULTS.

In all, 3048 household contacts were recruited into the study. After excluding 193 contacts with coprevalent disease, 2855 participants were included in the follow-up analysis. At baseline, 2048 (67.2%) had a tuberculin skin test ≥10 millimeters, 265 (8.7%) were HIV seropositive, and 418 (13.7%) had chronic cough. After contact follow-up, 61 (2.1%) individuals were diagnosed with incident tuberculosis disease. After controlling for potential confounders, risk factors for incident tuberculosis included past active tuberculosis disease of the contact (Adjusted Relative Risk [ARR], 3.0 [95% confidence interval [CI], 1.1 – 7.8]), HIV serostatus of the contact (Adjusted Relative Risk [ARR], 5.9 [95% confidence interval [CI], 3.5 – 9.8]), and lung cavitation of the index case (ARR, 1.9 [95% CI, 1.1 – 3.3]). Contacts with a tuberculin skin test ≥10 millimeters were not at increased risk of incident tuberculosis disease (RR, 1.5 [95% CI, 0.8 – 2.6]).

DISCUSSION.

In a large prospective cohort study in sub-Saharan Africa, over 2% of contacts progressed to tuberculosis disease after two years of follow-up. Contacts infected with *Mycobacterium tuberculosis* were not at increased risk of disease and other risk factors for choosing who receives preventive therapy should be used.

INTRODUCTION.

Currently, global tuberculosis incidence is lowering at approximately 1–2% per year. Although this reduction represents millions of saved lives improvement was expected to be much higher. If these current trends continue, 2030 goals for global tuberculosis elimination are unlikely to be met.

Investigating incident tuberculosis disease is difficult because large cohorts, lengthy follow-up, and extensive evaluation of individuals are needed to have sufficient statistical power and reliable ascertainment of cases. Due to these difficulties, few studies have been performed, especially in low-income or high HIV-burden settings. Furthermore, most of these studies have had a retrospective design. Policy development and implementation for tuberculosis preventative therapy, especially in low-income settings, has been slow due to a lack of evidenced-based research investigating risk factors for tuberculosis disease development.

We present the largest prospective cohort study of household contacts in Africa to assess overall risk and potential risk factors for primary progressive tuberculosis disease. We aimed to inform policymakers

METHODS.

STUDY POPULATION AND SETTING.

The study design has been described previously. Briefly, we identified newly diagnosed tuberculosis patients ≥18 years old from the National Tuberculosis and Leprosy Program at Old Mulago Hospital in Kampala, Uganda from 1995 through 2006. Index cases were microbiologically confirmed through a positive culture test and defined as the first eligible case of pulmonary tuberculosis in a household with one or more contacts.

Upon enrollment, index cases were evaluated through a physical examination and medical history. Information was collected on age, sex, room where they sleep, cigarette smoking status, chest radiograph, and duration of cough. Extent of disease through radiographic imaging results was graded independently by an experienced clinician using the National Tuberculosis Association classification system with sub-groupings for cavitary and non-cavitary disease (21). Sputum samples were also collected for laboratory testing of mycobacterial culture and microscopic assessment.

Households with index cases were visited by trained field workers within two weeks of the tuberculosis index case's diagnosis. Household contacts were defined as any individual spending at least seven consecutive days in the same household as the index case in the three months preceding diagnosis. Household members were invited to participate and complete a baseline socio-demographic questionnaire and physical examination collecting data on age, sex, height, weight, cigarette smoking status, alcohol usage (yes or no), relationship to the index case (spouse, parent, child, sibling, or other), education level, past active tuberculosis, and household characteristics

(crowding, housing structure, ventilation, or smoke exposure). Bacillus Calmette-Guérin (BCG) vaccination was assessed through inspecting BCG scars and confirmed with medical records when possible.

Index cases and household contacts over the age of 5 years were offered HIV testing with an enzyme-linked immunosorbent assay (Cambridge BiosScience, Worcester, Massachusetts). Parents gave informed consent for child contacts. Children under five years of age were offered HIV testing if the mother was living with HIV. If the mother was negative then the child was also presumed to be negative. Contacts with HIV or less than six years old without active tuberculosis disease were offered a six-month course of isoniazid preventative therapy.

Coprevalent tuberculosis disease was defined as the identification of tuberculosis disease at the baseline visit or within three months of the initial evaluation. The identification of tuberculosis disease amongst contacts was conducted using a multi-pronged approach. At baseline, posteroanterior chest radiographs were taken on all participants and were examined independently by two experienced pulmonary physicians. Household contacts were evaluated for active tuberculosis disease through a medical examination, specimen microscopy, and mycobacterial culture if they were under six years of age or HIV seropositive. Subjects with any tuberculosis symptoms, which included cough, fever, night sweats, dyspnea, weight loss, lymphadenopathy, loss of appetite, were evaluated using similar methods. Contacts classified without tuberculosis at baseline were followed and assessed for active tuberculosis at six month intervals for two years. All baseline information on contacts that developed tuberculosis within one year were re-evaluated and those with subtle, abnormal chest radiographs

and nonspecific symptoms were re-classified by a physician as co-prevalent rather than incident disease even if after the three-month window.

STATISTICAL ANALYTICAL PLAN.

The prevalence of active tuberculosis disease from household contact tracing were estimated using standard contingency tables and stratified by index case, household contact, and household environmental risk factors. In order for the risk score to be used programmatically in an efficient manner we only selected variables that the tuberculosis index case would know in an interview after being first diagnosed at the clinic. In a “real-world” setting, an effective score without these variables would allow health workers and clinicians to evaluate the risk of contacts without visiting all households and therefore would save substantial resources to the programmatic use of household contact tracing. Due to this, we excluded tuberculin skin test results, body mass index, and BCG vaccination as potential variables to be included in our score. To describe our study population, we keep these variables in our demographic table.

We evaluated correlations among variables using polychoric correlation coefficients which measure correlation between ordered levels where the latent trait can be considered continuous and normally distributed.

To reduce the pool of candidate risk factors for co-prevalent tuberculosis disease, we performed univariate item analysis on 1800 contacts (93.1%) with complete data on all variables. We added variables one at a time that were related to latent TB infection ($P < 0.20$). A series of logistic regression models were fit using a generalized estimating equation to take into account the clustering of household contacts (24). Two-

sided p-values and 95% confidence intervals were used to assess statistical significance in all models.

ETHICAL CONSIDERATIONS.

Institutional review boards at the Uganda National Council for Science and Technology, the Uganda National AIDS Research Subcommittee, Case Western University, and Makerere University approved this study. Informed consent was obtained for all index cases and household contacts. Parents or guardians of child contacts provided written consent in addition to verbal assent from the children.

RESULTS.

In all, 3048 household contacts of 1175 tuberculosis index cases were enrolled. 193 contacts were excluded after being diagnosed with tuberculosis disease at baseline. The median age of the index cases was 28 years of age (interquartile range [IQR], 23 – 35), 19% were smokers, and 53% were male. After clinical and laboratory testing, 35% were HIV seropositive and 46% had lung cavitary disease. The median duration of cough was 90 days (IQR, 45 – 150). 67% of households were multifamily units while 76% had intrahousehold charcoal exposure. A clear majority of households had poor ventilation (93% with ≤1 window per room) and between 1 and 5 family members in the household (71%).

The median age of the contacts was 13 years of age (IQR, 6 – 23). Approximately 70% were tuberculin skin test positive and BCG vaccinated. In all, 5% were smokers while only 1% previously had tuberculosis. Of the 1662 contacts (85.7% of the study population) that tested for HIV, 10.4% tested positive. After clinical evaluation, chest radiographs, and microbiological tests, 193 contacts (6.3%) were diagnosed with co-prevalent tuberculosis disease. After exclusion of these contacts 2855 household contacts were eligible for inclusion in the analysis of incident tuberculosis disease. 61 (2.1%) of these contacts progressed to incident tuberculosis disease after two years of follow-up.

In general, only characteristics of the household contacts influenced the rate of incident tuberculosis disease. Household contact risk factors for incident tuberculosis included age (age 25 – 34 years old [4.2%] and 35 – 44 years old [6.4%]), smoking status (5.2% versus 2.0%), relation to the index case (spouse, 5.1%), past active

tuberculosis (12.2% versus 2.0%), alcohol use (4.2% versus 1.8%), HIV serostatus (10.1%), and closeness to the index case (3.7% incidence if sharing a bed). Index case characteristics that led to increased rate of incident tuberculosis in contacts included female index (2.7% versus 1.7% amongst males) and lung cavitation status (2.7% versus 1.6%). No household environmental characteristics indicated increased risk of incident tuberculosis.

In univariate analysis, increased rates of incident tuberculosis were seen in contact smokers (Relative Risk [RR], 2.6 [95% CI, 1.3 – 5.5]), contacts with past active tuberculosis (RR, 6.1 [95% CI, 2.6 – 14.4]), contact use of alcohol (RR, 2.3 [95% CI, 1.3 – 4.0]), HIV seropositivity (RR, 5.9 [95% CI, 3.7 – 9.5]), age (RR, 3.3 [95% CI, 1.6 – 7.0] and RR, 5.0 [95% CI, 2.3 – 11.0] for age groups 25 – 34 years old and 35 – 44 years old, respectively). No index case characteristics had statistically significantly predicted incident tuberculosis however female index cases (RR, 1.6 [95% CI, 1.0 – 2.6], *P*=0.07 versus males) and lung cavitation of the index case (RR, 1.7 [95% CI, 1.0 – 2.9], *P*=0.05) were suggestive of an association. No household environmental characteristics predicted incident tuberculosis disease amongst household contacts in this analysis.

In a multivariate regression analysis controlling for HIV seropositivity, nutritional status, and past active tuberculosis of the contact, and lung cavitation of the index case, multiple variables predicted incident tuberculosis. Contacts with past active tuberculosis were almost three times (RR, 3.0 [95% CI, 1.1 – 7.8], *P* = 0.03) more likely to have incident tuberculosis while contacts that test positive for HIV were almost six times as likely to have incident tuberculosis (RR, 5.9 [95% CI, 3.5 – 9.8]], *P*<0.0001). Contacts exposed to index cases with lung cavitary disease had almost twice the risk of incident

tuberculosis (RR, 1.9 [95% CI, 1.1 – 3.3], P=0.017). Compared to contacts with normal weight, overweight (RR, 1.5 [95% CI, 0.8 – 3.0]) or underweight (RR, 0.6 [95% CI, 0.3 – 1.4]) contacts did not have statistically different rates of tuberculosis however the trend was suggestive (P_{trend}=0.06).

In a separate multivariate interaction model, age modified the relationship between nutritional status and incident tuberculosis disease ($P_{interaction}$<0.0001). In children (age <20 years old), there was no relationship between nutritional status and incident tuberculosis (overweight versus normal weight, RR, 0.9 [95% CI, 0.3 – 3.0]; underweight versus normal weight, RR, 0.8 [95% CI, 0.3 – 2.2]). In adults (age ≥20 years old), overweight contacts had almost three times the risk of incident tuberculosis compared to normal weight contacts (RR, 2.8 [95% CI, 1.2 – 6.7]). Underweight contacts had half the risk of incident tuberculosis (RR, 0.5 [95% CI, 0.2 – 1.5]) however this did not reach statistical significance.

DISCUSSION.

Over the past three decades, global tuberculosis control has revolved around identifying cases through patient self-referral and management. However, in recent years, there has been almost universal acknowledgement that an emphasis on tuberculosis prevention is necessary to curb the epidemic. However, recommendations on preventive therapy of at-risk contacts has been hampered by a lack of epidemiologic evidenced-based research on risk factors for incident tuberculosis disease. In a sub-Saharan African setting with a high-burden of both tuberculosis and HIV, we found a high risk (2.1%) of primary progressive disease in household contacts over two years of follow-up equating to an incidence of more than 2000 tuberculosis cases per 100,000 persons. This rate of incident disease was higher than several estimates from other studies in both high- and low-income settings and was present even though all HIV-infected and young child contacts were given isoniazid preventive therapy.

Although we found several traditional risk factors for incident tuberculosis disease, a positive tuberculin skin test, representing a latent form of *Mycobacterium tuberculosis*, was not predictive. The tuberculin skin test has low specificity in individuals that are BCG-vaccinated which constitutes >70% of our study population. In addition, the tuberculin skin test lacks sensitivity in persons infected with HIV.

Several cohort studies have been performed in recent years investigating progression to tuberculosis disease amongst contacts of tuberculosis cases. However, few have had statistical power to identify risk factors for incident tuberculosis. For example, Sloot and colleagues followed 9332 contacts for 10 years in a retrospective cohort study in Amsterdam and found only 36 incident tuberculosis cases. Another

retrospective cohort study in Taiwan followed 11,816 child contacts for three years and found only 35 eventually progressed to active tuberculosis. There are several reasons for the low number of events in these studies. Long-term follow-up, a high sampled study population, and a high rate of tuberculosis disease are needed. In addition, our study provides a prospective rather than retrospective study design. This has several advantages however most important is that all contacts were evaluated for tuberculosis disease and therefore bias through case ascertainment was likely minimal in our study. Retrospective cohort studies rely on passive reporting by diseased individuals and this leads to substantial underestimation of new tuberculosis disease, especially in Africa. Recent estimates suggest that >40% of tuberculosis cases in Africa are undiagnosed and untreated by health services.

There are several limitations to this analysis that are important to mention. First, we do not have genotyping data and therefore whether new tuberculosis cases are due to the investigated household exposure or to another exposure cannot be known. This bias is more important in high-burden settings where community transmission is ubiquitous and contacts are repeatedly exposed. Second, contacts were not tested with Gene Xpert which has substantial advantages in sensitivity and specificity. Despite this, sputum smear and culture laboratory testing was performed in addition to clinical examinations, tuberculin skin testing, and chest radiographs to confirm diagnosis.

In conclusion, we found an extremely high rate of incident tuberculosis disease in household contacts of tuberculosis cases. In settings with a high prevalence of tuberculosis and HIV, tuberculin skin testing may not be the most useful tool for identifying individuals at most risk for primary progressive disease. Contacts that have

HIV infection or past tuberculosis disease should be prioritized. Chest radiography of index cases may be a useful method for identifying highly infectious cases and should be further explored.

CHAPTER 8 – TABLES AND FIGURES.

TABLES.

Table 1. Demographic characteristics of 1175 tuberculosis index cases, Kampala, Uganda

Variable	No. of Index Cases	Percent
N	1175	100.0
Index case characteristics		
Median age, year (IQR)	28 (23 - 35)	
Age group, years		
18 – 29	662	56.3
30 – 39	333	28.3
40 – 49	134	11.4
≥50	46	3.9
Sex		
Male	618	52.6
Female	556	47.4
Cigarette smoker		
Yes	223	19.0
No	952	81.0

Sputum smear status		
Positive		
Negative		
Missing		
HIV serostatus (only HIV tested included)		
Seropositive	410	34.9
Seronegative	763	64.9
Missing	2	0.2
HIV status (untested are supplemented with self-report)		
Positive	410	34.9
Negative	765	65.1
Lung cavitation§		
Cavitary disease	542	46.1
Noncavitary disease	323	27.5
Missing	311	26.5
Duration of cough, days (continuous)	90 (45 - 150)	

Duration of cough		
<30 d	60	5.1
≥30 and <60 d	191	16.3
≥60 and <90 d	189	16.1
≥90 d	483	41.1
Missing	252	21.5
Household characteristics		
Housing type		
Multifamily household	787	67.0
Single family household	380	32.3
Missing	8	0.7
Charcoal or fire smoke exposure		
Inside household	888	75.6
Outside household	195	16.6
None	45	3.8
Missing	47	4.0

Ventilation, Mean no. windows per room (SD) (continuous)	0.66 (0.52)	
Ventilation (No. windows per room)		
>1	75	6.4
≤1	1091	92.9
Missing	9	0.8
Family size, Median No. in household (IQR)	4 (3 - 6)	
Family size (No. in household)		
1 – 5	836	71.3
6 – 10	304	25.9
>10	32	2.7

Table 2. Demographic characteristics of 3048 household contacts of tuberculosis cases, Kampala, Uganda

Variable	Frequency	Percent
Household contact characteristics		
N	3048	100
Median age, years (IQR)	13 (6 – 23)	
Age group, years		
0 – 4	625	20.5
5 – 14	1048	34.4
15 – 24	709	23.3
25 – 34	344	11.3
35 – 44	182	6.0
≥45	140	4.6
Sex		
Male	1342	44.0
Female	1706	56.0
Education level		
None	780	25.6
Primary	1327	43.5
Secondary or higher	941	30.9
Tuberculin skin test		
Positive	2048	67.2
Negative	975	32.0

Missing	25	0.8
BCG vaccinated		
Yes	2147	70.4
No	711	23.3
Unknown	189	6.2
Missing	1	0.0
Cigarette smoker		
Yes	143	4.7
No	2904	95.3
Missing	1	0.0
Relation to index case		
Spouse	414	13.6
Parent	130	4.3
Child	1204	39.5
Sibling	352	11.6
Other	942	30.9
Missing	6	0.2
Past active tuberculosis		
Yes	52	1.7
No	2992	98.2
Missing	4	0.1
Nutritional status		
Underweight	344	11.3

Normal	2064	67.7
Overweight	635	20.8
Missing	5	0.2
Alcohol usage		
Yes	394	12.9
No	2653	87.0
Missing	1	0.0
HIV serostatus (only HIV tested included)		
Positive	265	8.7
Negative	2352	77.2
Missing	431	14.1
HIV status (untested supplemented with self-report)		
Positive	748	13.1
Negative	4119	72.3
Missing	829	14.6
Closeness to index case		
Share bed	610	20.0
Share room, not bed	1263	41.4
Different room	1139	37.4
Missing	19	1.2
Current cough		
Yes	418	13.7
No	2624	86.1

Missing	6	0.2
Know another tuberculosis case		
Yes	293	80.9
No	2465	9.6
Unknown	290	9.5
Index case characteristics		
Age group, years		
18 – 29	1492	50.1
30 – 39	935	31.4
40 – 49	391	13.1
≥50	162	5.4
Sex		
Male	1488	50.8
Female	1439	49.2
Cigarette smoker		
Yes	552	18.1
No	2378	78.0
Missing	118	3.9
Sputum smear status		
Positive		
Negative		
Missing		
Lung cavitation		

Cavitary disease	1724	58.8
Noncavitary disease	1186	40.5
Missing	20	0.7
Median cough duration, days (IQR)	90 (45 – 140)	
Duration of cough		
<30 days	193	6.3
≥30 and <60 days	586	19.2
≥60 and <90 days	599	19.7
≥90 days	1375	45.1
Missing	295	9.7
HIV serostatus		
Positive	1263	41.4
Negative	1666	54.7
Household characteristics		
Housing type		
Multi-family household	1552	50.9
Single family household	1473	48.3
Missing	23	0.8
Charcoal or fire smoke exposure		
Inside household	2201	72.2
Outside household	670	22.0
None	106	3.5
Missing	71	2.3

Ventilation, Mean no. windows/room (SD) (continuous)	0.69 (0.51)	
Ventilation (No. windows/room)		
>1	308	10.1
≤1	2722	89.3
Missing	18	0.6
Median density, persons/home (IQR)	6 (4 - 8)	
Household size (persons/home)		
1 – 5	1400	45.9
6 – 10	1335	43.8
>10	313	10.3

Definition of abbreviations: BCG = bacillus Calmette-Guerin; BMI = body mass index; IQR = interquartile range.

*Percentages refer to within–characteristic column totals among contacts of HIV-seropositive and -seronegative tuberculosis index patients. Percentages may not total 100% because within-column percentages were rounded to the nearest integer.

† We used Pearson chi-square tests to derive P value for all categorical variables. For continuous variables, we used Wilcoxon rank sum tests for comparison of two-sample medians. ‡ Nutritional status was assessed for each contact through BMI measurements for adults greater than or equal to 18 years of age and through weight-for-age z scores for child contacts. Individuals were classified as underweight if their z score was less than 22 or a BMI less than 18.5, normal weight if z scores were between

22 and 2 or their BMI was greater than or equal to 18.5 and less than 25, and overweight if z scores were greater than 2 or BMI was greater than or equal to 25.

x Evaluated through BCG scar, verified by medical records when available.

jj Includes other relatives, such as grandparents, grandchildren, aunts, uncles, and cousins. Also includes nonrelatives living in the household.

Table 2. Frequency and proportion of incident tuberculosis disease among household contacts in Kampala, Uganda (N=2855)

Variable	Contacts with incident disease (%)	No. Household Contacts	p-value
N	61 (2.1)	2855	–
Household contact characteristics			
Age group, years			<0.01
0 – 4	10 (2.0)	513	
5 – 14	13 (1.3)	1018	
15 – 24	11 (1.6)	684	
25 – 34	14 (4.2)	331	
35 – 44	11 (6.4)	172	
≥45	2 (1.5)	137	
Sex			0.52
Female	32 (2.0)	1614	
Male	29 (2.3)	1241	

Education level			0.71
None	14 (2.1)	663	
Primary	25 (1.9)	1294	
Secondary or higher	22 (2.5)	898	
Tuberculin skin test positive			0.18
Negative	15 (1.6)	923	
Positive	46 (2.4)	1908	
BCG vaccinated			0.34
No	18 (2.7)	660	
Yes	38 (1.9)	2020	
Unknown	5 (2.9)	174	
Cigarette smoker			0.011
No	54 (2.0)	2720	
Yes	7 (5.2)	134	
Relation to index case			<0.01
Other	14 (1.5)	911	

Sibling	3 (2.4)	126	
Child	13 (1.2)	1078	
Parent	10 (2.9)	340	
Spouse	20 (5.1)	394	
Know another tuberculosis case			0.70
No	47 (2.0)	2318	
Yes	7 (2.6)	266	
Don't know	7 (2.6)	271	
Past active tuberculosis			<0.01
No	56 (2.0)	2810	
Yes	5 (12.2)	41	
Nutrition status			0.15
Overweight	8 (1.3)	606	
Normal	43 (2.2)	1936	
Underweight	10 (3.3)	308	
Weight loss			<0.01

No	45 (1.7)	2668	
Yes	16 (8.7)	183	
Alcohol usage			0.003
No	45 (1.8)	2472	
Yes	16 (4.2)	382	
HIV serostatus (only HIV tested included)			<0.01
Seronegative	38 (1.7)	2208	
Seropositive	23 (10.1)	227	
HIV status (testing with self-report)			<0.01
Negative	38 (1.6)	2335	
Positive	23 (9.8)	234	
Closeness to index case			<0.01
Different room	24 (2.2)	1101	
Share room, not bed	15 (1.3)	1184	
Share bed	20 (3.7)	536	
Index case characteristics			

Age group, years			0.26
18 – 29	38 (2.7)	1389	
30 – 39	13 (1.5)	860	
40 – 49	7 (1.8)	383	
≥50	3 (1.9)	155	
Sex			0.08
Male	24 (1.7)	1384	
Female	37 (2.7)	1350	
Cigarette smoker			0.932
No	49 (2.2)	2222	
Yes	12 (2.3)	515	
Sputum smear status			
Negative			
Positive			
Lung cavitationll			0.06
Noncavitary disease	18 (1.6)	1127	

Cavitary disease	43 (2.7)	1590	
Duration of cough			0.22
<30 days	2 (1.1)	181	
≥30 and <60 days	18 (3.2)	557	
≥60 and <90 days	13 (2.3)	567	
≥90 days	25 (2.0)	1282	
HIV serostatus			0.97
Positive	26 (2.2)	1199	
Negative	35 (2.3)	1537	
Household characteristics			
Housing type			0.99
Single family household	30 (2.1)	1419	
Multifamily household	30 (2.1)	1416	
Charcoal or smoke exposure			0.68
None	1 (1.0)	103	
Outside household	15 (2.3)	647	

Inside household	44 (2.2)	2038	
Ventilation, windows/room (continuous)	–	–	
Ventilation (No. windows/room)††			0.32
>1	4 (1.4)	296	
≤1	57 (2.2)	2541	
Family size, persons/home (continuous)	–	–	
Family size (No. in household)			0.98
>10	6 (2.0)	300	
6 – 10	27 (2.1)	1267	
1 – 5	28 (2.2)	1288	

We used Pearson chi-square tests to derive P value for all categorical variables. For continuous variables, we used Wilcoxon rank sum tests for comparison of two-sample medians

*Percentages refer to within–characteristic column totals among contacts of HIV-seropositive and -seronegative tuberculosis index patients. Percentages may not total 100% because within-column percentages were rounded to the nearest integer

The model uses a modified Poisson regression with robust error variance allowing for estimation of relative risks and adjustment for household clustering of contacts

‡ Nutritional status was assessed for each contact through BMI measurements for adults greater than or equal to 18 years of age and through weight-for-age z scores for child contacts. Individuals were classified as underweight if their z score was less than 22 or a BMI less than 18.5, normal weight if z scores were between 22 and 2 or their BMI was greater than or equal to 18.5 and less than 25, and overweight if z scores were greater than 2 or BMI was greater than or equal to Evaluated through BCG scar, verified by medical records when available.

Table. Univariate model for incident tuberculosis disease among household contacts, Kampala, Uganda (N=2855)

Variable	Crude Relative Risk (95% CI)	*P*
Household contact characteristics		
Age group, years		0.004
0 – 4	1.53 (0.67 – 3.44)	
5 – 14	1 (Referent)	
15 – 24	1.26 (0.59 – 2.69)	
25 – 34	3.31 (1.57 – 7.01)	
35 – 44	5.01 (2.28 – 11.01)	
≥45	1.14 (0.26 – 5.04)	
Sex		0.53
Female	1 (Referent)	
Male	0.85 (0.51 – 1.41)	
Education level		0.61
None	1 (Referent)	
Primary	0.91 (0.48 – 1.75)	
Secondary or higher	1.16 (0.60 – 2.25)	
Tuberculin skin test positive		0.18
Negative	1 (Referent)	
Positive	1.48 (0.83 – 2.64)	
BCG vaccinated		0.54

No	1 (Referent)	
Yes	0.69 (0.40 – 1.22)	
Unknown	1.05 (0.41 – 2.71)	
Cigarette smoker		0.01
No	1 (Referent)	
Yes	2.63 (1.26 – 5.50)	
Relation to index case		0.008
Other	1 (Referent)	
Sibling	1.55 (1.69 – 6.46)	
Child	0.78 (0.37 – 1.65)	
Parent	1.91 (0.83 – 4.41)	
Spouse	3.30 (1.69 – 6.46)	
Know another tuberculosis case		0.42
No	1 (Referent)	
Yes	1.30 (0.59 – 3.02)	
Don't know	1.27 (0.60 – 2.71)	
Past active tuberculosis		<0.0001
No	1 (Referent)	
Yes	6.12 (2.59 – 14.44)	
Nutritional status		0.06
Overweight	1 (Referent)	
Normal	1.68 (0.74 – 3.83)	
Underweight	2.46 (0.93 – 6.53)	

Weight loss		<0.0001
No	1 (Referent)	
Yes	5.18 (2.95 – 9.12)	
Alcohol usage		0.003
No	1 (Referent)	
Yes	2.30 (1.33 – 3.97)	
HIV serostatus (only HIV tested included)		<0.0001
Seronegative	1 (Referent)	
Seropositive	5.89 (3.66 – 9.48)	
HIV status (testing with self-report)		<0.0001
Negative	1 (Referent)	
Positive	6.04 (3.75 – 9.73)	
Closeness to index case		0.23
Different room	1 (Referent)	
Share room, not bed	0.58 (0.31 – 1.09)	
Share bed	1.71 (0.95 – 3.10)	
Index case characteristics		
Age group, years		0.19
18 – 29	1 (Referent)	
30 – 39	0.55 (0.30 – 1.02)	
40 – 49	0.69 (0.30 – 1.49)	
≥50	0.71 (0.23 – 2.19)	

Sex		0.08
Male	1 (Referent)	
Female	1.58 (0.95 – 2.62)	
Cigarette smoker		0.86
No	1 (Referent)	
Yes	1.06 (0.58 – 1.93)	
Sputum smear status		
Negative		
Positive		
Lung cavitationll		0.05
Noncavitary disease	1 (Referent)	
Cavitary disease	1.69 (0.99 – 2.89)	
Duration of cough		0.46
<30 days	1 (Referent)	
≥30 and <60 days	2.92 (0.71 – 12.02)	
≥60 and <90 days	2.07 (0.49 – 8.70)	
≥90 days	1.76 (0.44 – 7.07)	
HIV serostatus		0.85
Positive	1 (Referent)	
Negative	1.05 (0.64 – 1.73)	
Household characteristics		
Housing type		0.99
Single family household	1 (Referent)	

Multifamily household	1.00 (0.60 – 1.65)	
Charcoal or smoke exposure		0.52
None	1 (Referent)	
Outside household	2.22 (0.30 – 16.66)	
Inside household	2.39 (0.30 – 18.71)	
Ventilation, windows/room (continuous)	0.98 (0.53 – 1.82)	0.96
Ventilation (No. windows/room)††		0.31
>1	1 (Referent)	
≤1	1.66 (0.62 – 4.44)	
Family size, persons/home (continuous)	0.96 (0.90 – 1.03)	0.71
Family size (No. in household)		0.87
>10	1 (Referent)	
6 – 10	1.07 (0.41 – 2.77)	
1 – 5	1.09 (0.42 – 2.81)	

Table. Polychoric relational matrix of variables with a P value<0.2 in univarate analysis of incident tuberculosis disease in household contacts of tuberculosis cases, Kampala, Uganda

	incdis	agegroup	ind_sex	hiv	ind_age	tbpast	ind_cavitary	alcoholuse	nutritionalstatus	ppd	smoker	relative
incdis	1											
agegroup	0.126	1										
ind_sex	0.123	-0.037	1									
hiv_sero	0.455	0.409	-0.039	1								
ind_age	-0.081	0.035	-0.233	0.087	1							
tbpast	0.360	0.354	0.014	0.320	-0.111	1						
ind_cavitary	0.127	-0.030	-0.011	-0.164	-0.288	0.017	1					
alcoholuse	0.190	0.653	-0.121	0.465	-0.012	0.264	0.020	1				
nutritionalstatus	-0.151	0.226	-0.040	-0.014	-0.004	-0.095	0.006	0.139	1			
ppd	0.084	0.237	-0.019	0.025	-0.037	0.129	0.243	0.260	0.063	1		
smoker	0.222	0.523	0.028	0.341	-0.011	0.288	-0.030	0.624	-0.081	0.240	1	
relative	-0.151	-0.281	0.135	-0.380	-0.163	-0.053	0.064	-0.216	-0.028	-0.201	-0.116	1

Table 4. Multivariate model 1 for incident tuberculosis disease among household contacts, Kampala, Uganda

Variable	Adjusted Relative Risk (95% CI)	*P*
Household contact characteristics		
Past active tuberculosis		0.03
No	1 (Referent)	
Yes	2.96 (1.13 – 7.78)	
Nutritional status		0.06
Overweight	1.52 (0.77 – 2.98)	
Normal	1 (Referent)	
Underweight	0.62 (0.28 – 1.35)	
HIV serostatus		<0.0001
Seronegative	1 (Referent)	
Seropositive	5.87 (3.50 – 9.83)	
Index case characteristics		
Lung cavitationll		0.017
Noncavitary disease	1 (Referent)	
Cavitary disease	1.92 (1.12 – 3.28)	

¥ Model selection was done using model fit with the Akaike information criterion. Complete case analysis was applied using only available information on all participants during model selection.

Table 5. Multivariate model 2 for incident tuberculosis disease among household contacts, Kampala, Uganda amongst household contacts <20 years of age, interaction between nutritional status and age

Variable	Adjusted Relative Risk (95% CI)	*P*
Household contact characteristics		
Past active tuberculosis		0.06
No	1 (Referent)	
Yes	6.87 (0.89 – 53.11)	
Nutritional status		0.78
Overweight	0.88 (0.26 – 3.00)	
Normal	1 (Referent)	
Underweight	0.76 (0.26 – 2.20)	
HIV serostatus		0.04
Seronegative	1 (Referent)	
Seropositive	3.94 (1.10 – 14.17)	
Index case characteristics		
Lung cavitationll		0.19
Noncavitary disease	1 (Referent)	
Cavitary disease	1.78 (0.75 – 4.22)	

¥ Model selection was done using model fit with the Akaike information criterion. Complete case analysis was applied using only available information on all participants during model selection.

Table 6. Multivariate model 3 for incident tuberculosis disease among household contacts, Kampala, Uganda amongst household contacts ≥20 years of age, interaction between nutritional status and age

Variable	Adjusted Relative Risk (95% CI)	*P*
Household contact characteristics		
Past active tuberculosis		0.26
No	1 (Referent)	
Yes	1.96 (0.61 – 6.36)	
Nutritional status		0.02
Overweight	2.79 (1.16 – 6.71)	
Normal	1 (Referent)	
Underweight	0.54 (0.20 – 1.49)	
HIV serostatus		<0.0001
Seronegative	1 (Referent)	
Seropositive	5.56 (2.83 – 10.91)	
Index case characteristics		
Lung cavitationll		0.04
Noncavitary disease	1 (Referent)	
Cavitary disease	2.04 (1.01 – 4.15)	

¥ Model selection was done using model fit with the Akaike information criterion. Complete case analysis was applied using only available information on all participants during model selection.

Aim 3, Section 3: Validation of two recommended clinical algorithms to detect undiagnosed tuberculosis disease in child contacts of tuberculosis cases: a prospective cohort study from sub-Saharan Africa

INTRODUCTION.

Current tuberculosis control interventions lack the ability to effectively identify diseased children. Active tuberculosis case finding through household contact tracing of children has been widely recommended as a supplementary control intervention in high-burden settings however has rarely been implemented due to resource intensiveness, high number needed-to-test to identify a case, and lack of diagnostic capability. Two clinical algorithms – the World Health Organization's symptom-based screening approach and the Chan Risk Score – have been proposed to increase yield and effectiveness. However, prospective validation of these screening methods has rarely been investigated and their usefulness in sub-Saharan Africa is unclear.

METHODS.

This was a prospective cohort study of newly diagnosed adults with tuberculosis disease and their child household contacts in Kampala, Uganda. Field workers administered an extensive questionnaire to all cases and contacts including information on all tuberculosis symptoms and demographic characteristics. Microbiological and clinical testing were also performed on all child contacts to derive sputum smear, culture, HIV, tuberculin skin test, and lung cavitation disease results. To evaluate the WHO's symptom-based algorithm we calculated the number needed to screen to detect

a tuberculosis case for individuals with each symptom and calculated the increased effectiveness of finding a child household contact with tuberculosis disease in those with any symptom compared to those with no symptoms. For the Chan Risk Score, we calculated the risk of coprevalent and incident tuberculosis disease by each risk factor included in the score and then by all risk factors. We calculated area under the receiver operating characteristics curve (AUC) for both algorithms.

RESULTS.

In all, 1212 household contacts were enrolled, of which, 65 (4.6% had tuberculosis disease at baseline and 9 (0.8%) developed tuberculosis over the follow-up. 321 children (26.5%) had at least one symptom and chronic cough was most common (N=193, 15.9%). The likelihood of coprevalent disease was highly correlated with increasing number of included symptoms (P_{trend}<0.001). The number needed to screen to detect one coprevalent child case among those with ≥1 symptom and no symptoms was 6.7 and 111.1, respectively. The NNS to detect one incident case among those with ≥1 symptom and no symptoms was 45.5 and 333.3, respectively. Screening only symptomatic contacts detected 85.7% and 66.7% of all coprevalent and incident cases. Out of all tuberculosis cases, 42 (64.6%) were microbiologically confirmed with either a sputum smear or culture positive test result. The Chan Risk Score had low predictive power (AUC=0.54) and no included characteristics in the model were predictive in our cohort (sex of index, AUC=0.52; TST induration status, AUC=0.54; sputum smear status of index, AUC=0.50).

DISCUSSION.

This is the first study to investigate the validity of World Health Organization's symptom-based algorithm and the Chan Risk Score in sub-Saharan Africa. The Chan Risk Score demonstrated poor predictive value in detecting new children with tuberculosis in our Ugandan cohort while the World Health Organization's symptom-based algorithm was highly efficient and detected substantially more cases than those with no symptoms.

INTRODUCTION.

Recent modeling estimates have suggested that the global burden of pediatric tuberculosis is higher than previously thought by experts and global health organizations.[282-284] Despite this, current tuberculosis control interventions lack the ability to effectively identify diseased children. Over 60% of pediatric cases are undetected globally indicating a substantial lack of prioritization of child case detection.[283,285] Untreated children younger than 15 years of age with tuberculosis have been reported to have fatality rates as high as 25% and reaches above 40% in those younger than 5 years old.[286-288] However, anti-tuberculosis treatment is extremely effective in children and case-fatality rates are >1% among treated children.[286] Specific, effective, and validated interventions to dramatically increase case detection amongst children are urgently needed.

Active tuberculosis case finding through household contact tracing of children has been widely recommended as a supplementary control intervention.[23,40,289,290] Despite high-yield in detecting new, undiagnosed cases, child contact tracing has rarely been implemented in high-burden settings due to resource intensiveness, monetary cost to the patient and tuberculosis program, high number needed-to-test to identify a case, and limited diagnostic testing such as chest radiograph and tuberculin skin testing.[25,130,291] Due to this, alternatives have been proposed to improve implementation of contact tracing to sustain the high tuberculosis disease yield of this intervention but limiting the number of children needed for disease screening and follow-up. Two clinical algorithms – the World Health Organization's symptom-based screening approach and the Chan Risk Score – have been proposed to increase yield and effectiveness of

childhood contact tracing.[135,292,293] However, prospective validation of these screening methods has been rare and their usefulness in settings with a high HIV prevalence is unclear. The Chan Risk Score has never been validated outside of Taiwan. Furthermore, the 2012 WHO guidelines to National Tuberculosis Programs on management of child tuberculosis contacts gives a strong recommendation for the symptom-based clinical algorithm to screen child contacts but stipulates that this is based on “very low quality evidence”.[292,293]

Using prospective data from a large Uganda cohort of child contacts of tuberculosis cases, we validated the effectiveness of the World Health Organization’s symptom-based screening approach and the Chan Risk Score clinical algorithms to detect new, coprevalent and incident tuberculosis disease in exposed children.

METHODS.

STUDY POPULATION AND SETTING.

The study design has been described previously.[5,290,294] Briefly, we identified newly diagnosed tuberculosis patients ≥18 years old from the National Tuberculosis and Leprosy Program at Old Mulago Hospital in Kampala, Uganda from 1995 through 2006. Index cases were microbiologically confirmed through a positive culture test and defined as the first eligible case of pulmonary tuberculosis in a household with one or more contacts.

Upon enrollment, index cases were evaluated through a physical examination and medical history. Information was collected on age, sex, room where they sleep, cigarette smoking status, chest radiograph, and duration of cough. Extent of disease through radiographic imaging results was graded independently by an experienced clinician using the National Tuberculosis Association classification system with sub-groupings for cavitary and non-cavitary disease.[295] Sputum samples were also collected for laboratory testing of mycobacterial culture and microscopic assessment.

Households with index cases were visited by trained field workers within two weeks of the tuberculosis index case's diagnosis. Household contacts were defined as any individual spending at least seven consecutive days in the same household as the index case in the three months preceding diagnosis. Household members were invited to participate and complete a baseline socio-demographic questionnaire and physical examination collecting data on age, sex, height, weight, cigarette smoking status, alcohol usage (yes or no), relationship to the index case (spouse, parent, child, sibling, or other), education level, past active tuberculosis, and household characteristics

(crowding, housing structure, ventilation, or smoke exposure). Bacillus Calmette-Guérin (BCG) vaccination was assessed through inspecting BCG scars and confirmed with medical records when possible. Children were classified as underweight if their z-score was less than -2, normal weight if z-scores were between -2 and 2, and overweight if z-scores were greater than 2.[250]

Index cases and household contacts between 5 and 15 years old were offered HIV testing with an enzyme-linked immunosorbent assay (Cambridge BiosScience, Worcester, Massachusetts). Parents gave informed consent for child contacts. Children under five years of age were offered HIV testing if the mother was living with HIV. If the mother was negative, the child was presumed to also be negative. Contacts with HIV or less than six years old without active tuberculosis disease were offered a six-month course of isoniazid preventative therapy.

Coprevalent tuberculosis disease was defined as the identification of tuberculosis disease at the baseline visit or within three months of the initial evaluation. The identification of tuberculosis disease amongst contacts was conducted using a multi-pronged approach. At baseline, posteroanterior chest radiographs were taken on all participants and were examined independently by two experienced pulmonary physicians. Household contacts were evaluated for active tuberculosis disease through a medical examination, specimen microscopy, and mycobacterial culture. Subjects with any tuberculosis symptoms, which included cough, fever, night sweats, dyspnea, weight loss, lymphadenopathy, loss of appetite, were evaluated using similar methods. Contacts classified without tuberculosis at baseline were followed and assessed for active tuberculosis at six month intervals for two years. Household visits were also

performed if a contact became ill at a date between visits. All baseline information on contacts that developed tuberculosis within one year were re-evaluated and those with subtle, abnormal chest radiographs and nonspecific symptoms were re-classified by a physician as co-prevalent rather than incident disease even if after the three-month window.

STATISTICAL ANALYTICAL PLAN.

The prevalence of active tuberculosis disease from household contact tracing were estimated using standard contingency tables and stratified by index case, household contact, and household environmental risk factors.

We evaluated correlations among variables using polychoric correlation coefficients which measure correlation between ordered levels where the latent trait can be considered continuous and normally distributed. Two-sided p-values and 95% confidence intervals were used to assess statistical significance in all models.

ETHICAL CONSIDERATIONS.

Institutional review boards at the Uganda National Council for Science and Technology, the Uganda National AIDS Research Subcommittee, Case Western University, and Makerere University approved this study. Informed consent was obtained for all index cases and household contacts. Parents or guardians of child contacts provided written consent in addition to verbal assent from the children.

RESULTS.

DEMOGRAPHIC CHARACTERISTICS.

In all, 1212 household contacts were enrolled in the study. The median age of the contacts was 6 years of age (interquartile range [IQR], 3 – 10); 445 (36.7%) were below five years of age. Over half (51.7%) were female and 78% were BCG vaccinated. Only 1.2% and 0.5% were smokers and previously had tuberculosis. Almost 2/3^{rds} of participants had a tuberculin skin test induration ≥10 millimeters (N=787, 64.9%). Above 40% had between 1 and 5 household members and 79.8% had poor ventilation (≤1 window per room). Of all participants, 74 had tuberculosis disease; 65 (4.6%) at baseline and 9 (0.8%) developed tuberculosis over two years of follow-up.

VALIDATION OF WORLD HEALTH ORGANIZATION SYMPTOM–BASED SCREENING ALGORITHM.

Of all children, 321 (26.5%) had at least one symptom and chronic cough was most common (N=193, 15.9%). The prevalence of other symptoms ranged from 3.6% for poor appetite to 6.7% for malnutrition. Among contacts with symptoms, most had only one symptom (N=231, 19.1%) while only four contacts had more than three symptoms.

The likelihood of coprevalent disease was highly correlated with increasing number of symptoms (P_{trend}<0.01); The proportion with coprevalent tuberculosis disease was 0.9%, 11.3%, 21.4%, 37.5%, and 33.3% in children with 0, 1, 2, 3, 4, and 5 symptoms (Table 3). The number needed to screen to detect one coprevalent child case among those with ≥1 symptom and no symptoms was 6.7 and 111.1, respectively.

Screening only symptomatic contacts detected 85.7% of all coprevalent cases (Table 3).

Screening only symptomatic contacts detected 85.7% and 66.7% of all coprevalent and incident cases (Table 3). The NNS to detect one incident case among those with ≥1 symptom and no symptoms was 45.5 and 333.3, respectively. Out of all tuberculosis cases, 42 (64.6%) were microbiologically confirmed with either a sputum smear or culture positive test result (Figure 3).

VALIDATION OF CHAN RISK SCORE.

None of the four variables included in the Chan Risk Score were statistically significant predictors of coprevalent or incident tuberculosis disease (Table 2). Compared to children with a tuberculin skin test induration <10 millimeters, odds of tuberculosis disease in children was higher in those with a skin test induration10 – 14 millimeters (Relative Risk, 2.0 [95% CI, 1.1 – 3.8]), 15 – 19 millimeters (RR, 1.2 [95% CI, 0.6 – 2.4]), and ≥20 millimeters (RR, 1.6 [95% CI, 0.6 – 4.1]). TB disease did not differ based on the sex of the index case (RR, 1.0 [95% CI, 0.6 – 1.7]) or the sputum smear status of the index case (RR, 1.2 [95% CI, 0.6 – 2.4]). Compared to children with a score of 0 – 4, children with a score of 5 – 8 did not have a statistically higher rate of coprevalent tuberculosis (5.9% versus 4.7%, $P = 0.405$), incident tuberculosis (1.1% versus 0.5%, $P = 0.237$), or any tuberculosis event (6.9% versus 5.1%, $P = 0.227$) (Table 3). The Chan Risk Score had low predictive power (AUC=0.54, Figure 2) and no included characteristics had an AUC above 0.60 (sex of index, AUC=0.52; tuberculin skin test induration status, AUC=0.54; sputum smear status of index, AUC=0.50).

DISCUSSION.

Predicting future tuberculosis disease risk, especially in children, is convoluted.[296] However, our ability to successfully predict individuals that develop incident tuberculosis disease, and provide effective preventative therapy, will be critical to containing the tuberculosis epidemic in areas with high tuberculosis transmission.[297] To guide epidemiologists and clinicians in identifying high-risk children two algorithms using epidemiological and clinical characteristics have been developed: the World Health Organization's proposed symptom-based screen algorithm and the Chan Risk Score. Although showing promise in a few cross-sectional, observational studies, our study is the first, to our knowledge, to prospectively validate these scores in sub-Saharan Africa. In this setting with a high-burden of both tuberculosis and HIV, we found the WHO symptom-based screening method was highly predictive of new, undiagnosed children. If only symptomatic children were screened for tuberculosis, 85.7% and 66.7% of all coprevalent and incident tuberculosis child cases would be detected despite only screening 321 of 1212 total child contacts using this algorithm. The Chan Risk Score, however, had poor predictive power demonstrating an AUC only slightly higher than 0.50.

Two important studies in Indonesia and The Gambia recently investigated the validity of the WHO recommended tuberculosis symptom-based algorithm in children.[298,299] Triasih and colleagues (2015) found 21% of symptomatic children with coprevalent disease compared to 0% of asymptomatic children and concluded the algorithm was highly effective.[299] Our study expands upon these results in several ways. First, this algorithm has never been evaluated in settings with a HIV burden such as

Uganda, where tuberculosis burden is amongst the highest globally and laboratory testing is uncommon. HIV testing was not performed in most contacts in both studies. Second, contacts were often diagnosed clinically through symptoms and not confirmed with laboratory tests. Due to this, ascertainment bias may be possible in both studies and the predictive accuracy of this algorithm may have been inflated. In our study, all children and HIV-infected contacts were administered gastric lavage tests in addition to both chest radiographs, tuberculin skin testing, and clinical examinations. Therefore, we determined the efficacy of the algorithm with independent laboratory confirmation. Last, our study had an extensive two-year follow-up. Other studies evaluating the algorithm's ability had either cross-sectional study design[300] to predict coprevalent tuberculosis disease or had a shorter follow-up period[298,299] to predict incident tuberculosis. Due to this, incident tuberculosis cases in children may have been missed.

Implementing household contact tracing of tuberculosis cases programmatically has proven difficult in low-income, high-burden settings. Although widely recommended, National Tuberculosis Programs have not implemented household contact tracing as a supplementary strategy to routinely performed Directly Observed Therapy.[25,130,291] When tracing has been implemented the practice is usually incomplete with a large proportion of contacts not screened or tested. This lack of implementation is likely due to several interconnected explanations including resource intensiveness of the intervention, diagnostic access and cost, patient cost, and high number needed to screen and test to detect or prevent a tuberculosis case. Using methodologies or algorithms that increase efficiency of household contact tracing to detect contacts at

most-risk for primary progressive disease is essential to encourage programs with few resources can invest in implementation of household contact tracing.

In 2013, Chan and colleagues derived and validated a predictive risk score to detect coprevalent and incident childhood tuberculosis disease using a comprehensive dataset of tuberculosis child contacts in Taiwan.[135] In addition to the WHO recommended algorithm, this is amongst the only scores to be derived to detect childhood tuberculosis. This score was successfully externally validated in a Taiwanese cohort of child tuberculosis contacts however the algorithms use in medium or high-burden settings is unclear. In our child cohort, the score did not successfully predict either coprevalent or incident tuberculosis well. There was a small, nonsignificant statistical difference between children with a high score (score 5 – 8, 6.9%) and those with a low score (score 1 – 4, 5.1%) to detect disease. Risk factors for development of tuberculosis in low- and high-incidence areas are substantially different and differences between Taiwan and Uganda likely explain why this score did not validate. For example, HIV infection is a nonfactor in Taiwan, even in impoverished regions, however is >5% in Uganda and plays a substantial and critical factor influencing the tuberculosis epidemic in this region.[290] Another potential reason for discrepancies between our results and those of Chan and colleagues is the definition of “contact”. In general, tuberculosis contact investigated are not standardized and most studies use slight variations to define contact. Chan and colleagues defined contact as an “eight-hour exposure to the tuberculosis index case in one day or a 40-hour cumulative exposure” but stipulated that the main objective was to target family and household contacts.[135] Therefore, we feel our household contact cohort serves as an appropriate and suitable validation cohort.

Our study shows little use in settings with high tuberculosis transmission rates and a high burden of HIV but may be useful in other countries with similar epidemiological characteristics as Taiwan. The Chan Risk Score should be externally validated in high-income, low tuberculosis burden settings where HIV prevalence is low.

There are a few limitations to this analysis. First, we are unable to definitively say whether contacts acquired disease due to the household exposure or from some other individual in the community without molecular genotyping such as whole-genome sequencing. However, we did not aim to determine transmission events in the household but rather to evaluate the yield of disease in our setting using the two specified algorithms. Second, although most contacts were given sputum tests, some older child contacts did not and therefore we would not detect cases of asymptomatic, subclinical disease amongst these contacts. However, when we partitioned our sample by children under 6 (all of whom were laboratory tested for tuberculosis regardless of symptoms) our results were consistent suggesting that this is unlikely to substantially influence our findings.

In conclusion, in this sub-Saharan African setting with a high-burden of both HIV and tuberculosis and substantial ongoing *M. tuberculosis* transmission, we found that the Chan Risk Score demonstrated poor predictive value in detecting new children with tuberculosis while the World Health Organization's symptom-based algorithm was highly efficient and detected substantially more cases than those with no symptoms. Programmatic evaluation of this symptom-based algorithm is necessary in high-burden settings but, if validated, could substantially impact tuberculosis case detection in children in sub-Saharan Africa.

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EVALUATION OF WORLD HEALTH ORGANIZATION SYMPTOM-BASED SCREENING APPROACH

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Figure 5. ROC curve for WHO symptom-based screening to predict incident tuberculosis amongst child contacts of tuberculosis cases

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Figure 7. ROC curve for WHO symptom-based screening to predict coprevalent tuberculosis amongst child contacts of tuberculosis cases

Figure 8. ROC curve for WHO symptom-based screening to predict incident tuberculosis amongst child contacts of tuberculosis cases

Figure 9. ROC curve for World Health Organization symptom-based screening to predict tuberculosis (either coprevalent or incident) amongst child contacts of tuberculosis cases

Table 1. Demographic characteristics of 1212 child household contacts of tuberculosis index cases

Variable	Frequency	Percent*
Household contact characteristics		
N	1212	100
Mean age, years (SD)	6.8 (±4.4)	
Median age, years (IQR)	6 (3 – 10)	–
Age group, years		
0 – 4	445	36.7
5 – 9	394	32.5
10 – 15	373	30.8
Sex		
Male	582	48.3
Female	622	51.7
BCG vaccinated††		
Yes	940	77.6
No	227	18.7
Unknown	45	3.7
Cigarette smoker		
Yes	15	1.2
No	781	64.4
Missing	416	34.3
Relation to index case		

Parent	10	0.8
Child	741	61.1
Sibling	61	5.0
Other[c]	396	32.7
Missing	4	0.3
Past active tuberculosis		
Yes	6	0.5
No	1195	98.6
Missing	11	0.9
Closeness to index case		
Share bed	117	9.7
Share room, not bed	630	52.0
Different room	445	36.7
Missing	20	1.7
Index case characteristics‡		
Median age, years (IQR)	30 (25 – 38)	–
Age group, years		
18 – 29	536	44.2
30 – 39	419	34.6
40 – 49	197	16.3
≥50	60	5.0
Sex		
Male	609	50.3

Female	603	49.8
Cigarette smoker		
Yes	267	22
No	933	77
Missing	12	1.0
Sputum smear status		
Positive	943	77.8
Negative	269	22.2
Lung cavitation§		
Cavitary disease	708	58.4
Noncavitary disease	479	39.5
Missing	25	2.1
Median cough duration, days (IQR)	84 (45 – 140)	–
Duration of cough, days		
<30 d	76	6.3
≥30 and <60 d	258	21.3
≥60 and <90 d	278	22.9
≥90 d	578	47.7
Missing	22	1.8
HIV serostatus		
Positive	580	47.9
Negative	631	52.1
Missing	1	0.1

Household characteristics		
Housing type		
Multi-family household	565	46.6
Single family household	642	53.0
Missing	5	0.4
Charcoal or fire smoke exposure		
Inside household	259	21.4
Outside household	866	71.5
None	74	6.1
Missing	13	1.1
Ventilation (No. windows/room)**		
>1	240	19.8
≤1	967	79.8
Missing	5	0.4
Median density, persons/home (IQR)	6 (5 – 8)	
Household size (persons/home)		
1 – 5	512	42.2
6 – 10	552	45.5
>10	148	12.2

* Percentages refer to within characteristic column totals among household contacts of tuberculosis index patients. Percentages may not total 100% because within column percentages were rounded to the nearest integer

‡ These are the number and percent of household contacts exposed to the index case characteristic in the left-hand column.

§ Radiographic imaging results were graded by an experienced clinician using the 1961 National Tuberculosis Association classification system.

**Windows must be to the outside.

†† Evaluated through BCG scar, verified by medical records when available

Table 2. Symptoms and diagnostic results in 1212 household contacts of tuberculosis cases

Variable	Frequency	Percent
Participant symptom characteristics		
Symptoms in World Health Organization algorithm		
Poor appetite	43	3.6
Chronic cough*	193	15.9
Weight loss	70	5.8
HIV-infection	49	4.0
Moderate or severe malnutrition§	81	6.7
Children with ≥1 symptom	321	26.5
Number of symptoms		
0	891	73.5
1	231	19.1
2	70	5.8
3	16	1.3
4	3	0.3
5	1	0.1
Diagnostic measures		
Tuberculin skin test positive (≥5 millimeters)	930	76.9
Tuberculin skin test positive (≥10 millimeters)	787	64.9
Tuberculosis disease diagnosis at baseline	56	4.6

Tuberculosis diagnosis during follow-up	9	0.8
Sputum culture positive	35	2.9
Sputum smear positive	15	1.2
Cavitary disease	8	0.7
Chest radiograph findings		
Minimal	66	5.5
Moderately advanced	39	3.2
Far advanced	10	0.8

* Chronic cough was defined as a cough that lasted 21 days or longer

§ Nutritional status was assessed for each contact through BMI measurements for adults ≥18 years of age and through weight-for-age z-scores for child contacts. Individuals were classified as underweight if their z-score was <-2 or a BMI <18.5, normal weight if z-scores were between -2 and 2 or their BMI was ≥18.5 and <25, and overweight if z-scores were >2 or BMI was ≥25.

Table 3. Yield of coprevalent and incident tuberculosis disease in 1212 household contacts of tuberculosis cases, stratified by the WHO symptom-based screening approach

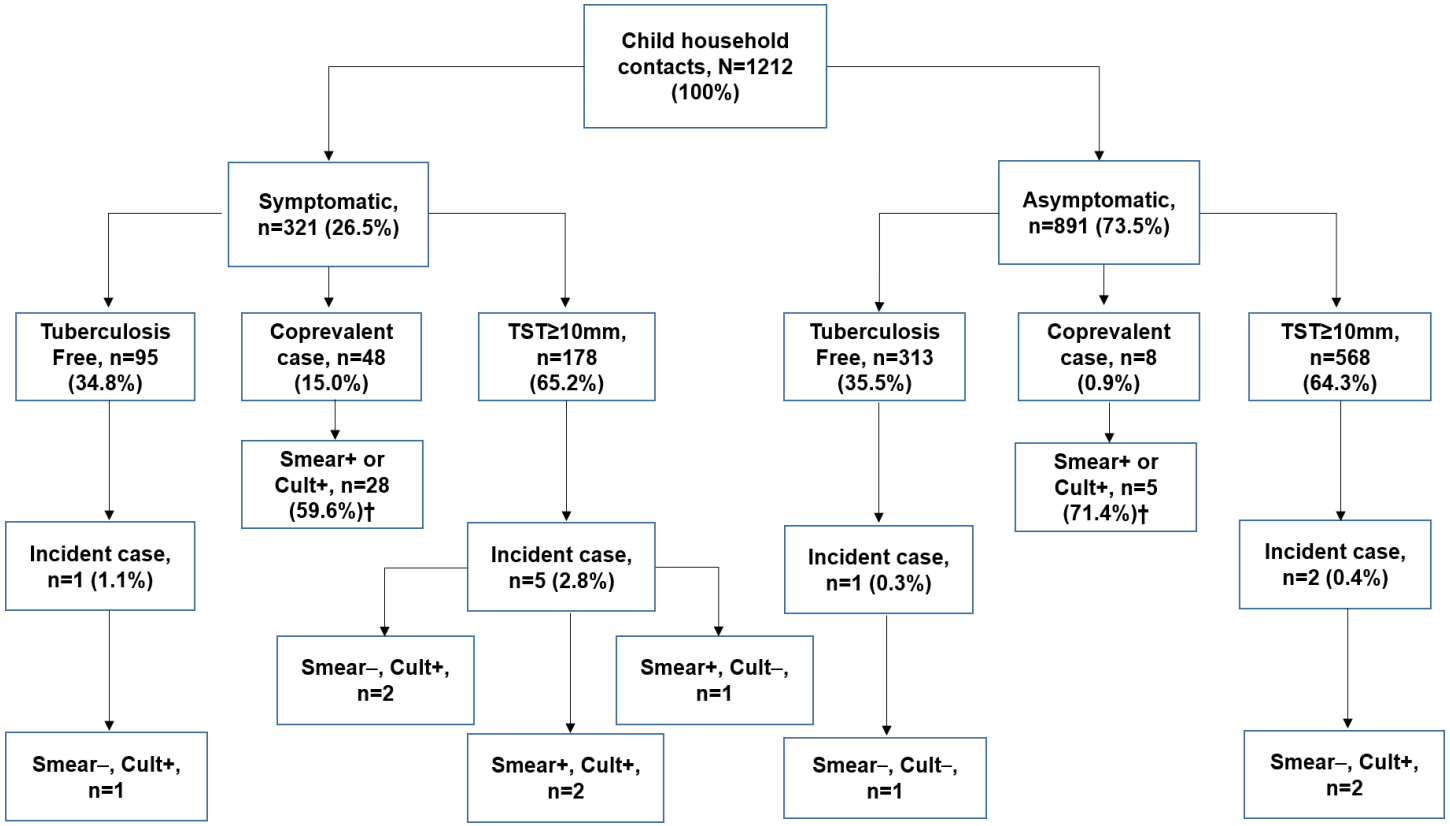
Variable	Coprevalent tuberculosis†			Incident tuberculosis†		
	Contacts with tuberculosis (% prevalence)	NNS to detect one case	Percent of all cases detected	Contacts with tuberculosis (% incidence)	NNS to detect one case	Percent of cases detected
All contacts	56 (4.6)	21.7	–	9 (0.8)	125	–
Symptoms in WHO Report						
Poor appetite	10 (23.3)	4.3	17.9	1 (3.0)	33.3	11.1
Chronic cough*	41 (21.2)	4.7	73.2	5 (3.3)	30.3	55.6
Weight loss	11 (15.7)	6.4	19.6	2 (3.4)	29.4	22.2
HIV-infection	7 (14.3)	7.0	12.5	1 (2.4)	41.7	11.1
Moderate or severe malnutrition	9 (11.1)	9.0	16.1	4 (1.4)	71.4	44.4
Children with ≥1 symptom	48 (15.0)	6.7	85.7	6 (2.2)	45.5	66.7
Number of symptoms						

0	8 (0.9)	111.1	14.3	3 (0.3)	333.3	33.3
1	26 (11.3)	8.8	46.4	2 (1.0)	100	22.2
2	15 (21.4)	6.7	26.8	4 (7.3)	13.7	44.4
3	6 (37.5)	2.7	10.7	0 (0)	NA	0
4	1 (33.3)	3.0	1.7	0 (0)	NA	0
5	0 (0)	NA	0	0 (0)	NA	0
Tuberculin skin test positive (≥5 mm)	49 (5.3)	18.9	87.5	9 (1.0)	100	100
Tuberculin skin test positive (≥10 mm)	41 (5.2)	19.2	73.2	7 (0.9)	111.1	77.8

† Coprevalent tuberculosis disease was defined as the identification of tuberculosis disease at or within 3 months of the baseline household visit. Incident tuberculosis disease was defined as diagnosis of tuberculosis disease at subsequent household follow-up visits, conducted at 6-month intervals for 2 years. Individuals with coprevalent disease were excluded from analyses of incident disease

* Chronic cough was defined as a cough that lasted 21 days or longer

Flowchart of tuberculosis-related outcomes from World Health Organization symptom-screening algorithm for child household contacts – Kampala, Uganda



† Amongst 48 symptomatic child contacts with coprevalent disease, 19 (40.4%) were smear and culture negative, 20 (42.6%) were smear negative and culture positive, 5 (10.6%) were smear positive and culture negative, and 3 (6.4%) were smear and culture positive. Amongst 8 asymptomatic child contacts with coprevalent disease, 2 (28.6%) were smear and culture negative, 4 (57.1%) were smear negative and culture positive, 1 (14.3%) was smear positive and culture negative, and 0 (0%) were smear and culture positive.

Figure 2. Flowchart of tuberculosis-related outcomes from World Health Organization symptom-screening algorithm for child household contacts, stratified by the age of the child contact – Kampala, Uganda

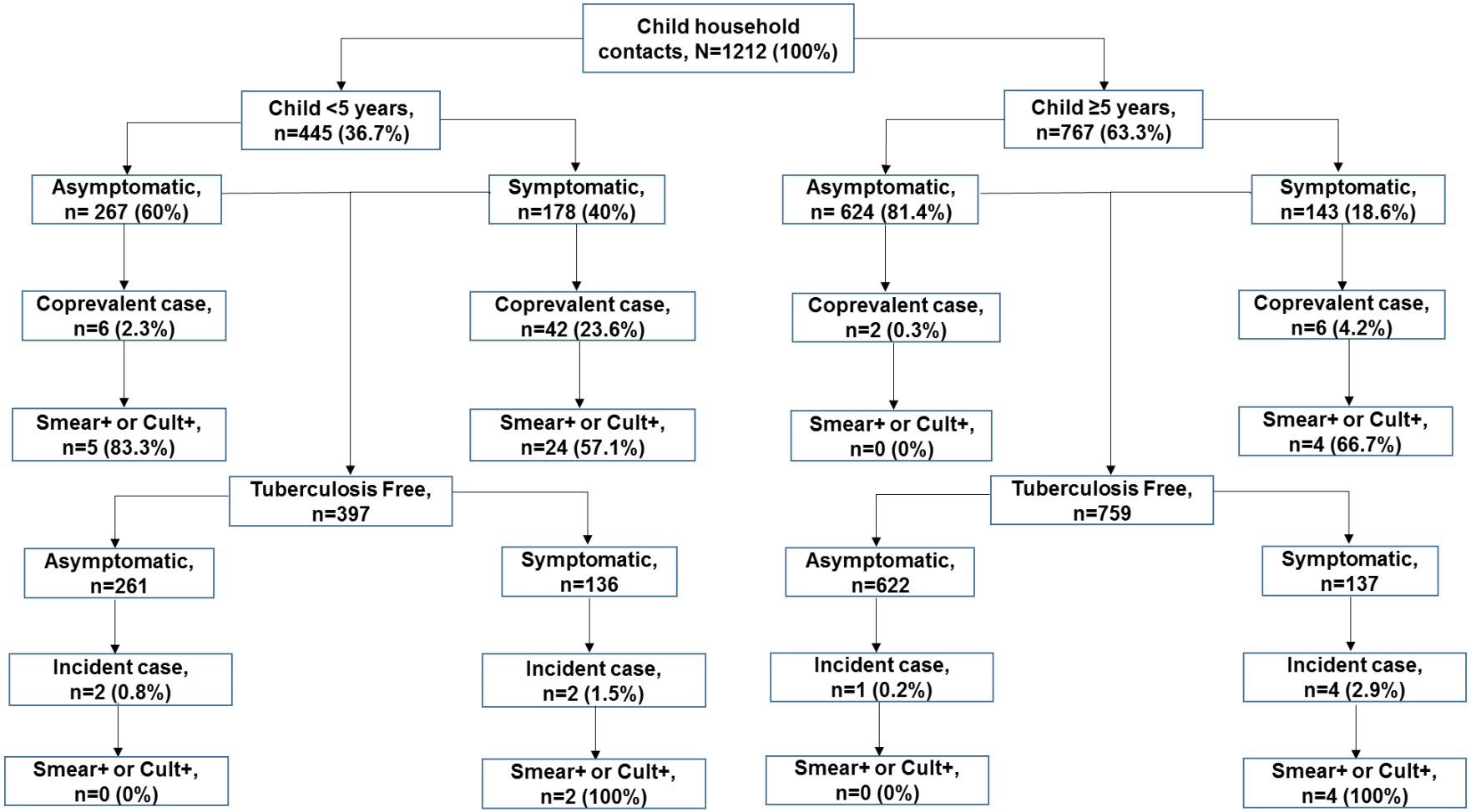
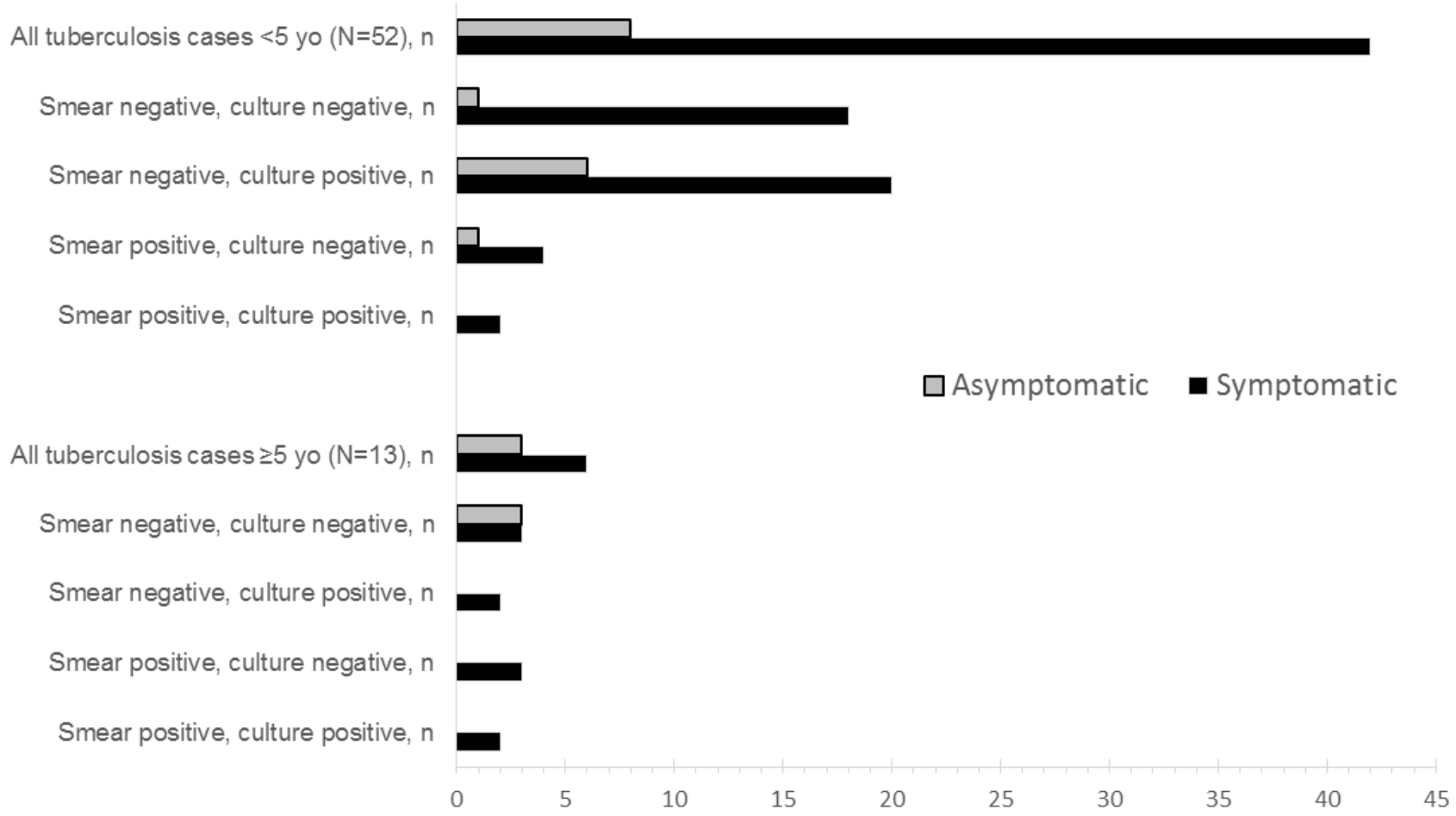
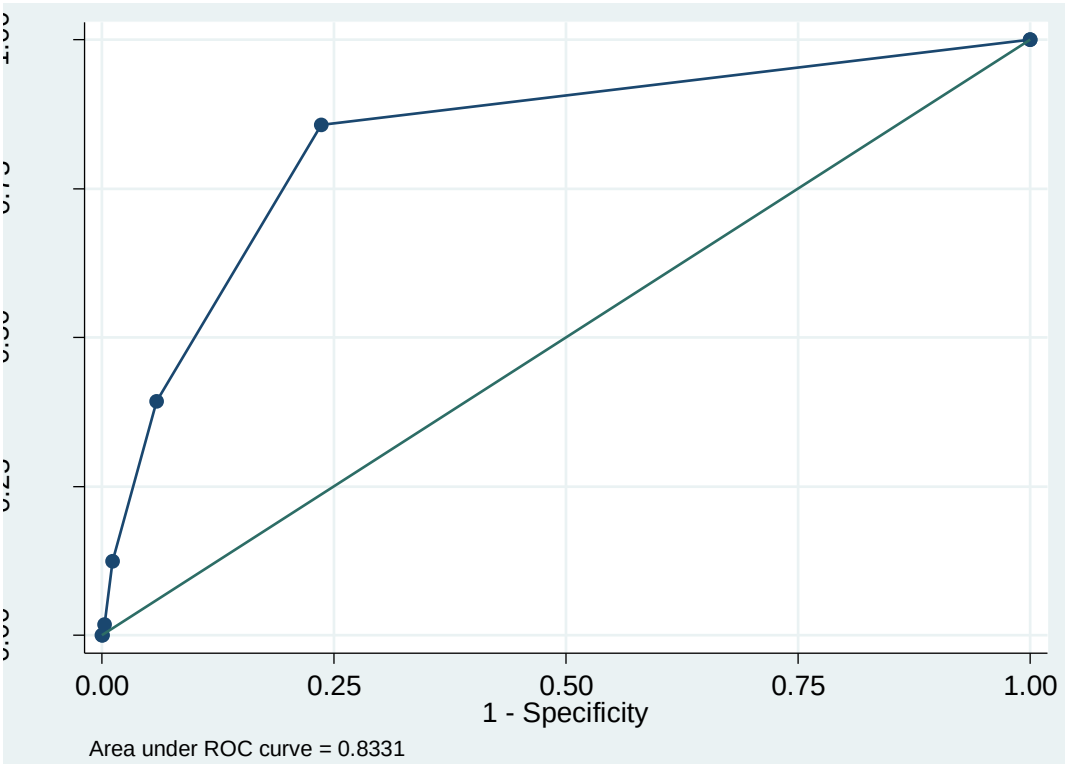


Figure 3. Microbiological confirmation of child household contacts that developed tuberculosis disease, stratified by the age of the child†



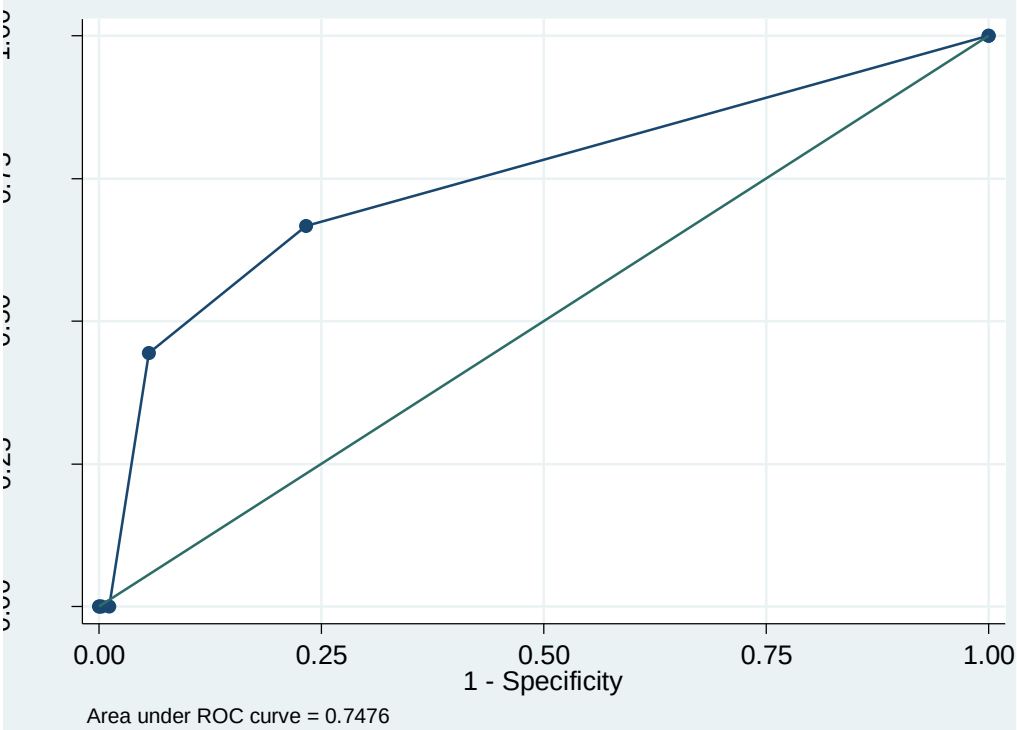
† In all, out of 65 total tuberculosis cases that were developed in child household contacts in the study, 42 (64.6%) were microbiologically confirmed with either a smear or culture positive test.

Figure 4. Receiver operating characteristic curve for World Health Organization symptom-based screening to predict coprevalent tuberculosis amongst child contacts of tuberculosis cases†



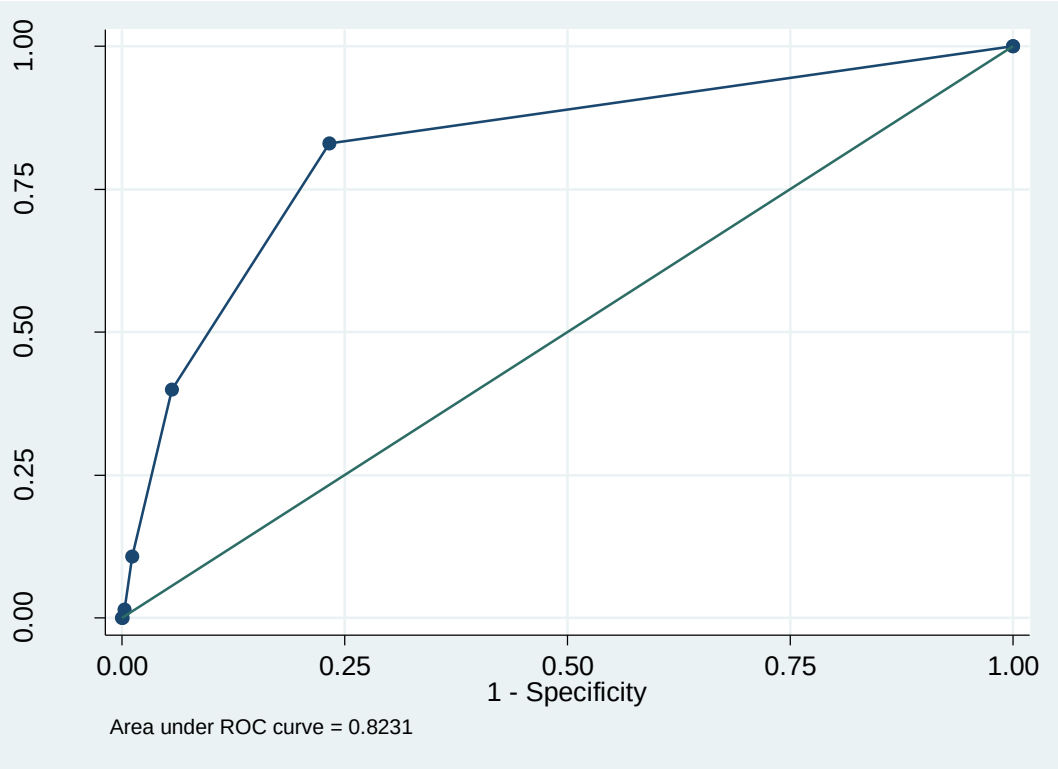
† Area under the curve is equal to 0.83 (95% CI, 0.78 – 0.89).

Figure 5. Receiver operating characteristic curve for World Health Organization symptom-based screening to predict incident tuberculosis amongst child contacts of tuberculosis cases†



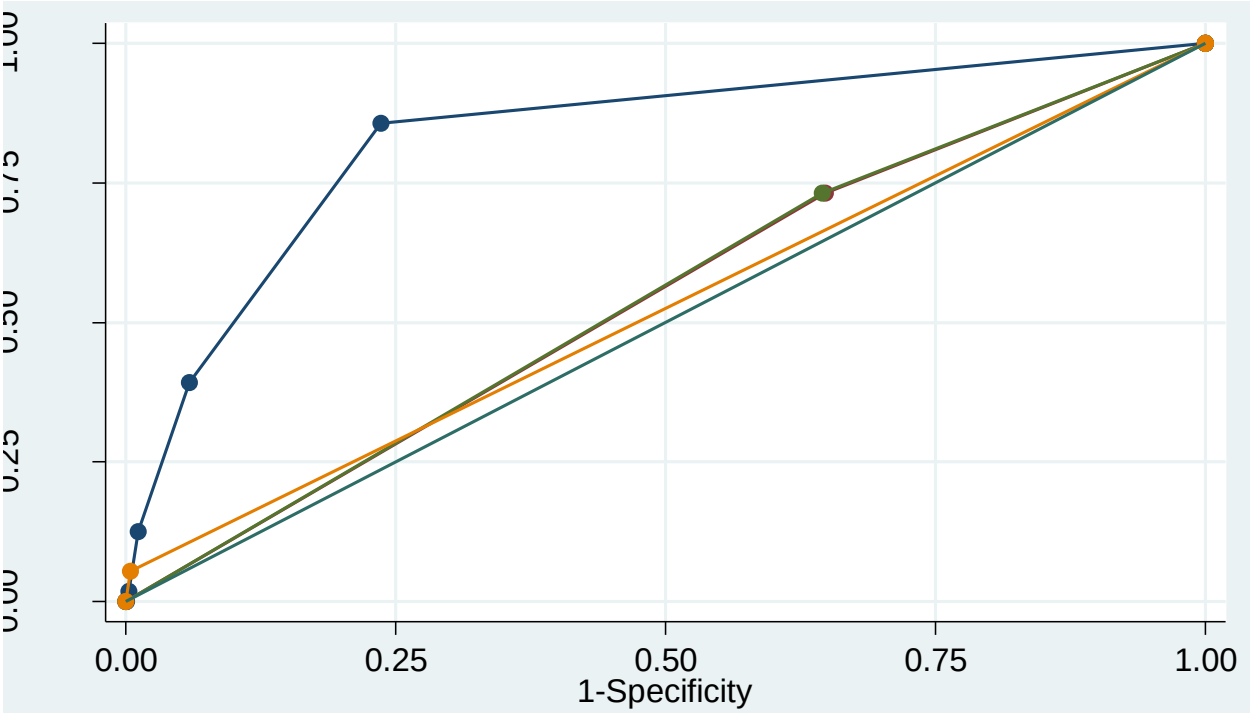
† Area under the curve is equal to 0.75 (95% CI, 0.57 – 0.93).

Figure 6. Receiver operating characteristic curve for World Health Organization symptom-based screening to predict any tuberculosis (incident or coprevalent) amongst child contacts of tuberculosis cases†



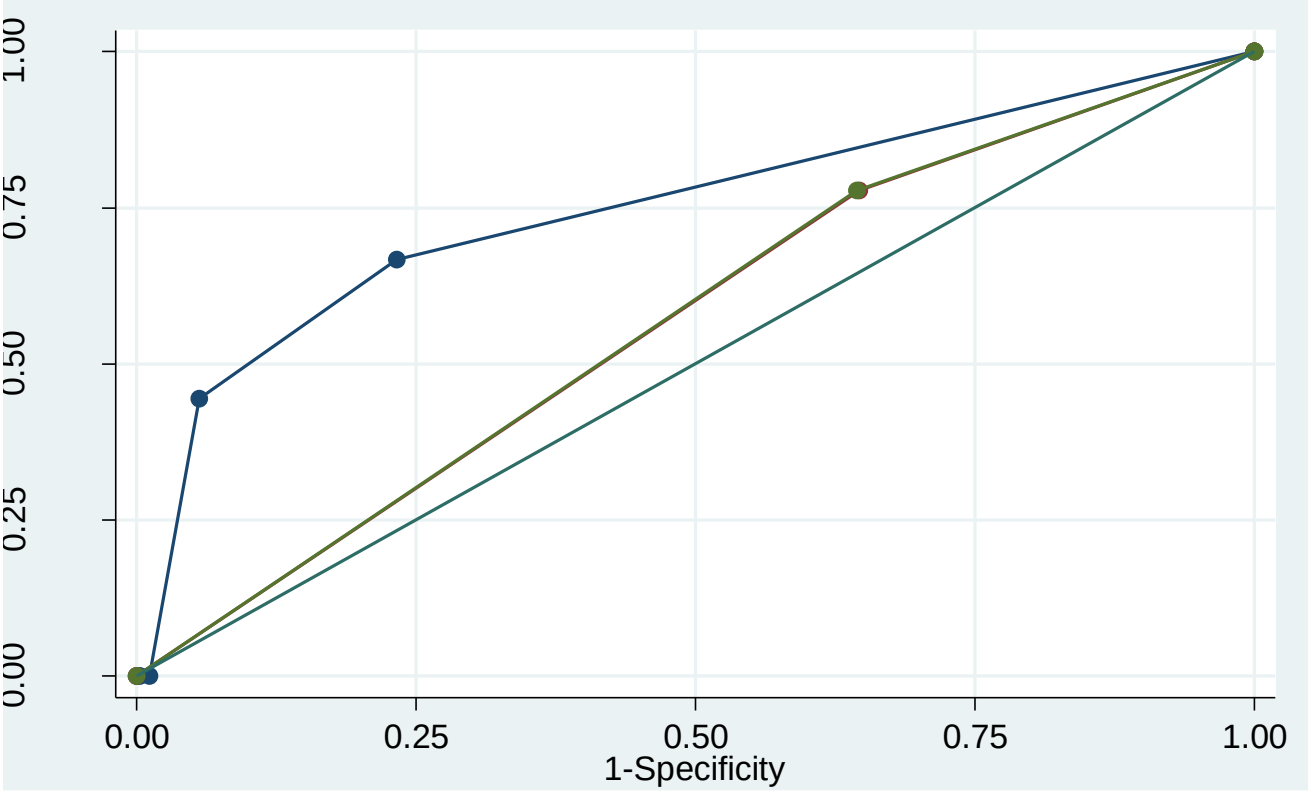
† Area under the curve is equal to 0.82 (95% CI, 0.77 – 0.87)

Figure 7. Receiver operating characteristic curve for World Health Organization symptom-based screening to predict coprevalent tuberculosis amongst child contacts of tuberculosis cases



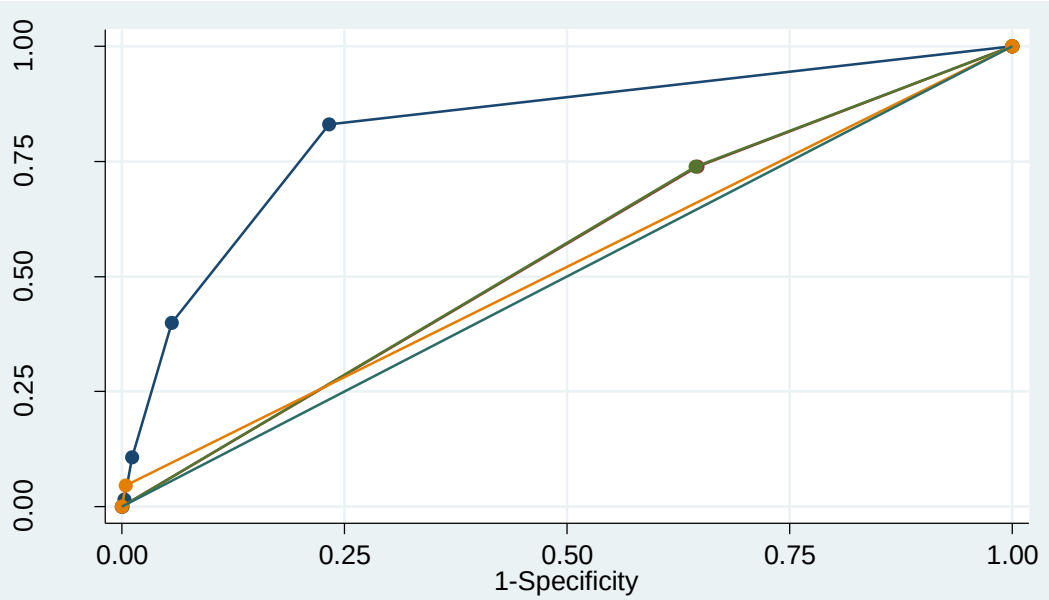
† The blue line is equal to the World Health Organization symptom screening algorithm (AUC, 0.82 [95% CI, 0.77 – 0.87]). The green line represents algorithm using a tuberculin skin test ≥10 millimeters (AUC, 0.54 [95% CI, 0.48 – 0.60]). The orange line represents algorithm using a positive cavitary chest radiograph test (AUC, 0.52 [95% CI, 0.49 – 0.55]). The red line represents algorithm using either a tuberculin skin test ≥10 millimeters or a positive cavitary chest radiograph test (AUC, 0.54 [95% CI, 0.48 – 0.60]).

Figure 8. Receiver operating characteristic curve for World Health Organization symptom-based screening to predict incident tuberculosis amongst child contacts of tuberculosis cases



† The blue line is equal to the World Health Organization symptom screening algorithm (AUC, 0.75 [95% CI, 0.57 – 0.93]). The green line represents algorithm using a tuberculin skin test ≥10 millimeters (AUC, 0.56 [95% CI, 0.42 – 0.71]). The red line represents algorithm using either a tuberculin skin test ≥10 millimeters or a positive cavitary chest radiograph test (AUC, 0.57 [95% CI, 0.42 – 0.71]). An algorithm using only a positive cavitary chest radiograph test did not vary and was not included.

Figure 9. Receiver operating characteristic curve for World Health Organization symptom-based screening to predict tuberculosis (either coprevalent or incident) amongst child contacts of tuberculosis cases



† The blue line is equal to the World Health Organization symptom screening algorithm (AUC, 0.82 [95% CI, 0.77 – 0.87]). The green line represents algorithm using a tuberculin skin test ≥10 millimeters (AUC, 0.55 [95% CI, 0.49 – 0.60]). The orange line represents algorithm using a positive cavitary chest radiograph test (AUC, 0.52 [95% CI, 0.50 – 0.55]). The red line represents algorithm using either a tuberculin skin test ≥10 millimeters or a positive cavitary chest radiograph test (AUC, 0.55 [95% CI, 0.49 – 0.60]).

TABLES AND FIGURES

EVALUATION OF CHAN PREDICTIVE RISK SCORE

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Table 1. Baseline Characteristics of Validation Cohort of Child Contacts from Uganda.

Variable	No. of Contacts	Percent
N	1032	100
Household Contact Characteristics		
Gender		
Male	516	50.0
Female	516	50.0
Age, years		
< 5	436	42.3
5-9	392	38.0
10-12	204	19.8
BCG vaccination		
Yes	813	78.8
No	184	17.8
Missing	32	3.1
TST induration, millimeters		
<10	446	43.2
10 – 14	209	20.3
15 – 19	296	28.7
≥20	81	7.9
Relationship with the index case†		
Household	1032	100.0

Outside household	0	0.0
Index case characteristics‡		
Age, years		
≥50	115	5.9
<50	1826	94.1
Gender		
Male	526	51.0
Female	506	49.0
Sputum smear status		
Positive	802	77.7
Negative	230	22.3
Lung Cavitation status		
Cavitary disease	603	58.4
Noncavitary disease	408	39.5
Missing	21	2.0
Residence in high-incidence area		
Yes	1032	100.0
No	0	0.0

In Taiwan, enhanced surveillance criteria of either an 8-hour exposure to index cases within 1 day or a 40-hour cumulative exposure is used to define the contacts (17). The household family members are the main targets. The contact investigations are

also routinely conducted in the congregate settings, such as schools, healthcare facilities, and prisons In Taiwan, enhanced surveillance criteria of either an 8-hour exposure to index cases within 1 day or a 40-hour cumulative exposure is used to define the contacts (17). The household family members are the main targets. The contact investigations are also routinely conducted in the congregate settings, such as schools, healthcare facilities, and prisons.

† Contact in the Chan et al study was defined as an eight hour exposure to the tuberculosis index case in one day or a 40 hour cumulative exposure. The main objective of surveillance of contacts in Taiwan is to target family contacts in the household.

‡ These are the number and percent of household contacts exposed to the index case characteristic in the left-hand column. Specific individual characteristics of tuberculosis index cases are included in Table 1.

Table 2. Univariable model assessing risk factors for disease in Kampala, Uganda

Variable	No. Contacts	No. with disease (% Prevalence)	Univariable Model	
			Relative Risk (95% CI)	*P* value
N	1032			
Household Contact Characteristics				
Gender				
Male	516	31 (6.0)	1 (Referent)	
Female	516	32 (6.2)	1.0 (0.6 – 1.7)	0.922
Age, years				
10 – 12	204	1 (0.8)	1 (Referent)	
5-9	392	9 (2.3)	3.0 (0.4 – 23.7)	0.297
< 5	436	52 (11.9)	17.2 (2.4 – 124.9)	0.005
BCG vaccination				
No	184	18 (9.8)	1 (Referent)	
Yes	813	45 (5.5)	0.5 (0.3 – 0.9)	0.031
Missing	32	0 (0.0)	–	

TST induration, millimeters				
<10	446	21 (4.7)	1 (Referent)	
10 – 14	209	19 (9.1)	2.01 (1.1 – 3.8)	0.033
15 – 19	296	17 (5.7)	1.23 (0.6 – 2.4)	0.535
≥20	81	6 (7.4)	1.58 (0.6 – 4.1)	0.347
Index case characteristics‡				
Age, years				
≥50	47	0 (0.0)	1 (Referent)	
<50	985	63 (6.4)	–	
Gender				
Male	526	32 (6.1)	1 (Referent)	
Female	506	31 (6.1)	1.0 (0.6 – 1.7)	0.97
Sputum smear status				
Negative	230	12 (5.2)	1 (Referent)	
Positive	802	51 (6.4)	1.2 (0.6 – 2.4)	0.535
Lung Cavitation status				

Noncavitary disease	408	12 (2.9)	1 (Referent)	
Cavitary disease	603	50 (8.3)	3.0 (1.6 – 5.7)	0.001
Missing	21	1 (4.8)	1.7 (0.2 – 13.3)	0.64

Table 3. Chan Score Implemented in Ugandan Cohort of Household Child Contacts of Tuberculosis cases (N = 1032)

Chan Score	No. Contacts with Each Score	Proportional Risk of All Disease among Contacts (N events/N total)†	Proportional Risk of Co-prevalent disease cases (N events/N total)†	Proportional Risk of Incident disease cases (N events/N total)†
8	31	0.1290 (4/31)	0.1290 (4/31)	0 (0/27)
7	159	0.0692 (11/159)	0.0377 (6/159)	0.0327 (5/153)
6	240	0.0583 (14/240)	0.0583 (14/240)	0 (0/226)
5	133	0.0752 (10/133)	0.0677 (9/133)	0.0081 (1/124)
4	187	0.0481 (9/187)	0.0428 (8/187)	0.0056 (1/179)
3	224	0.0536 (12/224)	0.0491 (11/224)	0.0047 (1/213)
2	58	0.0517 (3/58)	0.0517 (3/58)	0 (0/55)
1	0	–	–	–
0	0	–	–	–
P for trend‡		0.212	0.528	0.071
High (5–8)	563	0.0693 (39/563)	0.0586 (33/563)	0.0113 (6/530)
Low (0–4)	469	0.0512 (24/469)	0.0469 (22/469)	0.0045 (2/447)

P for trend‡		0.227	0.405	0.237
High (5–7)	532	0.0658 (35/532)	0.0545 (29/532)	0.0119 (6/503)
Low (0–4)	469	0.0512 (24/469)	0.0469 (22/469)	0.0045 (2/447)
P for trend‡		0.327	0.585	0.21

Abbreviations: No., number.

†Co-prevalent tuberculosis disease was defined as the identification of tuberculosis disease at or within three months of the baseline household visit. Incident tuberculosis disease was defined as diagnosis of tuberculosis disease at subsequent household follow-up visits, conducted at six month intervals for two years. Individuals with co-prevalent disease were excluded from analyses of incident disease.

‡ The Cochran–Armitage test was used to evaluate trends within groups.

Figure 1. Distribution of Chan Predictive Risk Score among Ugandan Child Contact Cohort.

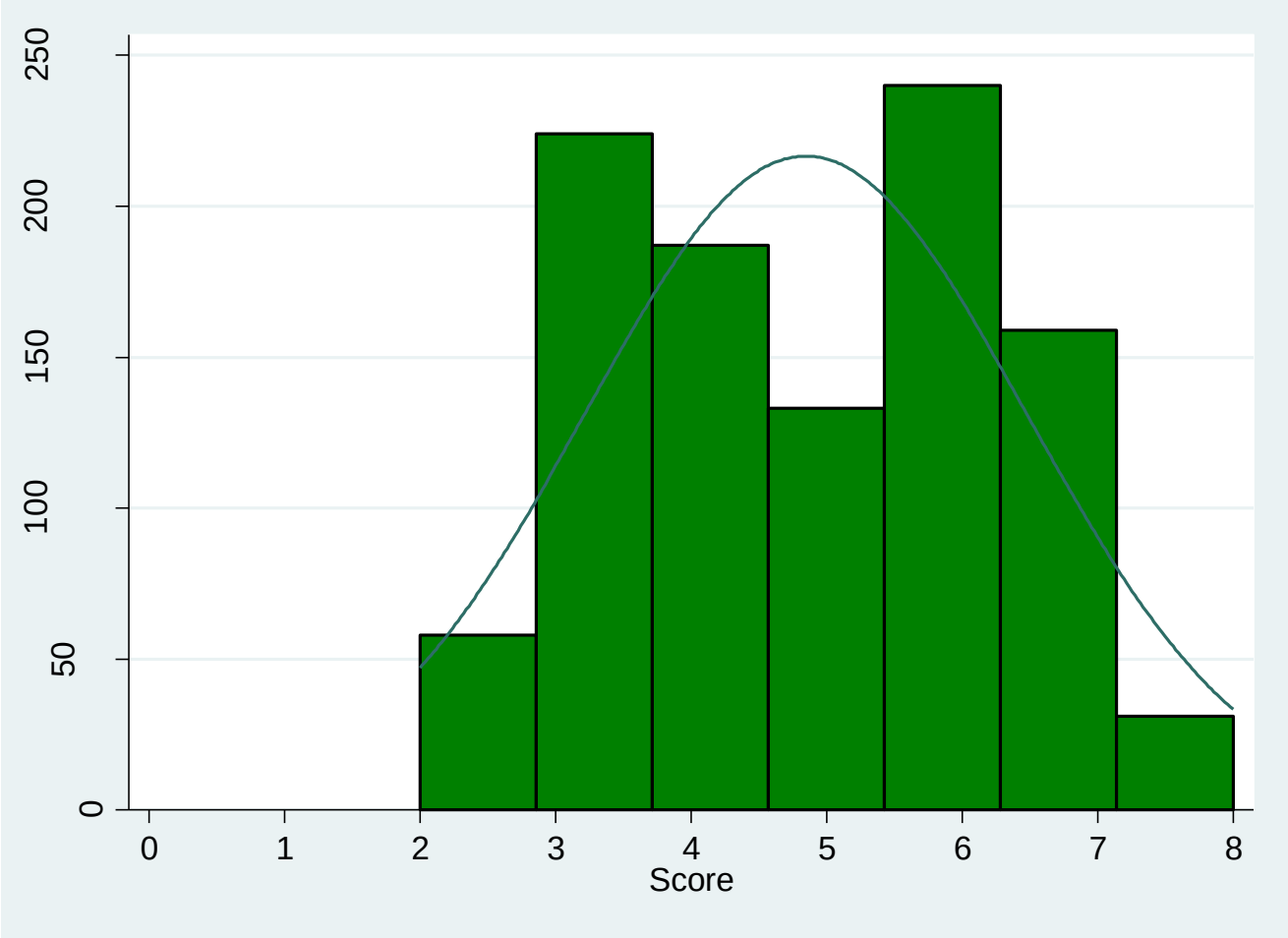
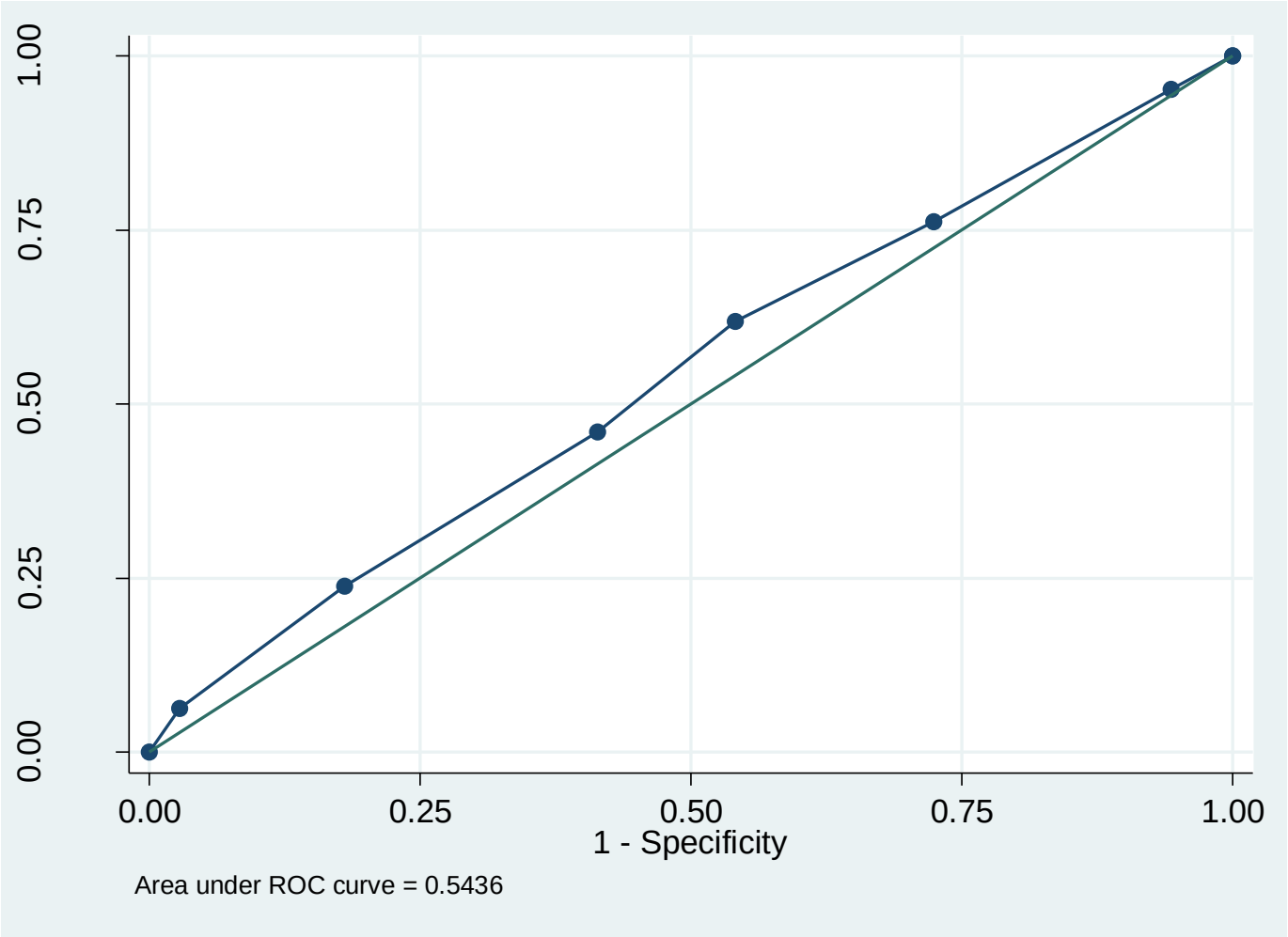
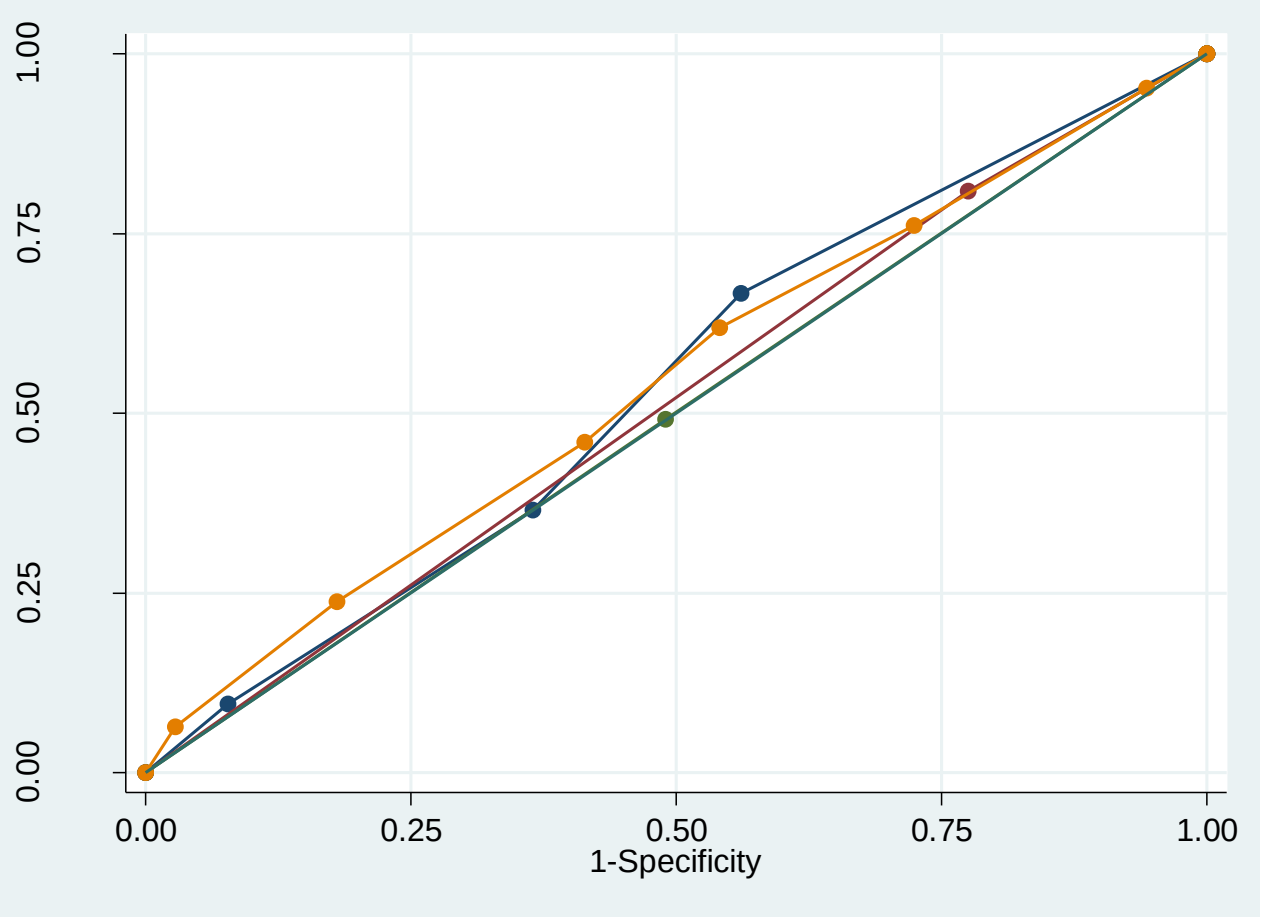


Figure 2. Receiver Operating Characteristic Curve for Chan Prediction Risk Score for Tuberculosis among Child Contacts in a Ugandan Cohort.



† Represents the area under the curve for the Chan Prediction Risk Score in the Uganda child contact cohort.

Figure 3. Receiver operating characteristic curve for different characteristics used in the Chan Prediction Risk Score for Tuberculosis Among Child Contacts in a Ugandan Child Contact Cohort (N = 1032).



† The green line represents the area under the curve for the sex of the index case (AUC = 0.52). The blue line represents the area under the curve for the tuberculin skin test induration status of the child contact (AUC = 0.54). The purple line represents the area under the curve for the sputum smear status of the index case (AUC = 0.50). The Orange line represents the area under the curve for the entire Chan Predictive Risk Score (AUC = 0.54).

CHAPTER 9.

SYNTHESIS, HEALTH POLICY IMPLICATIONS, AND FUTURE DIRECTIONS.

HEALTH POLICY IMPLICATION OF RESULTS.

Tuberculosis disease has recently become the deadliest infectious disease on the planet, leading to almost two million deaths annually. Most of these cases and deaths occur in low-income settings, such as sub-Saharan Africa, where National Tuberculosis Programs have limited resources to fight the epidemic. New, supplementary interventions must be highly effective, efficient, and culturally competent. Due to this, there is an increasing urgency to create effective global health policy directly impacting tuberculosis incidence and mortality. Evidenced-based research is needed to inform policy creation. This dissertation is concentrated on providing epidemiological evidence to advancing health policy improving tuberculosis control in two major areas: improving case-detection of undiagnosed tuberculosis disease and preventing new tuberculosis cases.

To inform current epidemiological knowledge, we first reviewed the literature and gathered and collated all available studies investigating active case finding of household contacts of tuberculosis disease and control groups. We did this in an effort to evaluate the increased effectiveness of household contact tracing of tuberculosis cases as a case-finding tool compared to surveying the general population. Our result, despite high heterogeneity, are clear. Household contact tracing is an incredibly high-yield program intervention and detects substantially more new, undiagnosed tuberculosis cases than

surveying the general population. Even hospital control groups, which technically should be at more risk than the general population, had much lower yield for both latent tuberculosis infection and tuberculosis disease than household contacts of tuberculosis cases. Previous policy conclusions on household contact tracing was based on a meta-analysis of household contact studies; however this meta-analysis did not include control groups of any kind and this substantially limits potential conclusions.

To fill this epidemiological knowledge gap, we conducted a systematic review and meta-analysis including studies containing both a household contact and a control group of any kind to compare the effectiveness of household contact tracing to other groups without such exposure to individuals with tuberculosis. The fact that both exposed and unexposed groups allow for matching by neighborhood; in addition the groups had to be matched by age. Although household contact tracing is widely recommended by global policy experts and infectious disease epidemiologists, there is a lack of evidenced-based research supporting this intervention at a population level.

In 2012, the World Health Organization came up with a comprehensive review of household contact tracing of tuberculosis cases in middle- and low-income settings. Many recommendations coming out of this review supported the inclusion of household contact tracing to current tuberculosis control programs however the majority of the synthesis of the results were deemed as low or very low “quality of evidence”.

FUTURE DIRECTIONS.

There are several further advances that are needed to supplement the evidence-base for active case finding through household contact tracing of tuberculosis cases. Although this dissertation attempted to investigate household contact tracing through

several different methodologies, including a systematic review of the literature, applying predictive risk scores to improve effectiveness, evidence on the population-level impact of household contact tracing on overall tuberculosis prevalence, incidence, and mortality are lacking. The ZAMSTAR study, including almost one million participants in South Africa and Zambia, found a set of household interventions (including household contact tracing) had epidemiologically important but nonsignificant improvements on overall population-level transmission (adjusted rate ratio, 0.45, 95% CI, 0.20 – 1.05) and prevalence (adjusted prevalence ratio, 0.82, 95% CI, 0.64 – 1.04). Although not technically statistically significant these results should encourage epidemiologists, public health practitioners, and policy makers to improve household contact tracing as we have done in this dissertation.

One area that may further improve our risk score is to create a household-based risk score, rather than an individual-based score as we have presented. A household-based score may be most efficient when discussing active case finding (finding coprevalent tuberculosis cases) rather than identifying contacts that may progress to primary progressive disease. This household-based score would be based on the overall risk profile of the household; prioritizing households with multiple high-risk contacts rather than visiting any contact at high-risk for coprevalent tuberculosis disease. In this way, an individual-based score may suggest visiting more households than a household-based score would. From a practical viewpoint, there are several issues to point out regarding the differences between these two methodological types of scores. Methods would need to be put into place when creating household scores to adjust for households with very high-risk contacts and no other high-risk contacts. In this

scenario, the household score may be medium-to-low but missing a high-risk contact may be unethical.

SUPPLEMENTARY APPENDIX.

TABLES AND FIGURES.

Table 2. Frequency and proportion of co-prevalent, incident, and any disease among household contacts*

Variable	No. of Household Contacts	Contacts with co-prevalent disease (%)	Contacts who developed incident disease (%)	All contacts with disease (%)
N	1941	81 (4.2)	34 (1.8)	115 (5.9)
Household contact characteristics				
Age group, years				
0 – 4	438	48 (11.0)	4 (1.0)	52 (11.7)
5 – 14	721	7 (1.0)	4 (0.6)	11 (1.5)
15 – 24	397	12 (3.0)	7 (1.8)	19 (4.8)
25 – 34	200	7 (3.5)	11 (5.7)	18 (9.0)
35 – 44	102	6 (5.9)	6 (6.3)	12 (11.8)
≥45	83	1 (1.2)	2 (2.4)	3 (3.6)
Sex				
Male	854	41 (4.8)	17 (2.1)	58 (6.8)
Female	1070	39 (3.6)	17 (1.7)	56 (5.2)

Tuberculin skin test result†				
Positive	1379	61 (4.4)	31 (2.4)	92 (6.7)
Negative	531	19 (3.5)	3 (0.6)	22 (4.1)
Tuberculin skin test induration, mm				
<5	460	18 (3.9)	3 (0.7)	21 (4.6)
5 – 9	223	9 (4.0)	4 (1.9)	13 (5.8)
10 – 14	407	20 (4.9)	7 (1.8)	27 (6.6)
15 – 19	604	20 (3.3)	13 (2.2)	33 (5.5)
≥ 20	224	13 (5.8)	7 (3.3)	20 (8.9)
BCG vaccinated††				
Yes	1358	53 (3.9)	20 (1.5)	73 (5.4)
No	510	27 (5.3)	13 (2.7)	40 (7.8)
Unknown	65	0 (0)	1 (1.5)	1 (1.5)
Cigarette smoker				
Yes	1414	5 (4.6)	6 (5.8)	11 (10.2)

No	108	56 (4.0)	24 (1.8)	80 (5.7)
Relation to index case				
Spouse	256	11 (4.3)	16 (6.5)	27 (10.6)
Parent	72	4 (5.6)	2 (2.9)	6 (8.3)
Child	819	45 (5.5)	7 (0.9)	52 (6.4)
Sibling	202	4 (2.0)	6 (3.0)	10 (5.0)
Other [c]	585	16 (2.7)	3 (0.5)	19 (3.3)
Know another tuberculosis case				
Yes	189	11 (5.8)	3 (1.7)	14 (7.4)
No	1507	59 (3.9)	28 (1.9)	87 (5.8)
Unknown	228	10 (4.4)	3 (1.4)	13 (5.7)
Current cough				
Yes	287	60 (20.9)	20 (8.8)	80 (27.9)
No	1225	18 (1.5)	13 (1.1)	31 (2.5)
Past active tuberculosis				
Yes	26	3 (11.5)	1 (4.4)	4 (15.4)

No	1900	77 (4.1)	33 (1.8)	110 (5.8)
Nutritional status‖				
Underweight	56	4 (7.1)	5 (9.6)	9 (16.1)
Normal	1703	74 (4.4)	27 (1.7)	101 (5.9)
Overweight	168	3 (1.8)	2 (1.2)	5 (3.0)
Anorexia				
Yes	93	21 (22.6)	7 (9.7)	28 (30.1)
No	1837	57 (3.1)	27 (1.5)	84 (4.6)
Alcohol usage				
Yes	258	7 (2.7)	10 (4.0)	17 (6.6)
No	1673	73 (4.4)	24 (1.5)	97 (5.8)
HIV serostatus				
Positive	201	22 (11.0)	16 (8.9)	38 (18.9)
Negative	1461	56 (3.8)	18 (1.3)	74 (5.1)
Closeness to index case				
Share bed	338	25 (7.4)	15 (4.8)	40 (11.8)

Share room, not bed	821	35 (4.3)	7 (0.9)	42 (5.1)
Different room	744	18 (3.4)	11 (1.5)	29 (3.9)
Index case characteristics‡				
Age group, years				
18 – 29	896	44 (4.9)	21 (2.5)	65 (7.3)
30 – 39	635	32 (5.0)	7 (1.2)	39 (6.1)
40 – 49	295	4 (1.4)	4 (1.4)	8 (2.7)
≥50	115	1 (0.9)	2 (1.8)	3 (2.6)
Sex				
Male	1013	43 (4.2)	15 (1.6)	58 (5.7)
Female	926	15 (1.5)	19 (2.1)	57 (6.2)
Cigarette smoker				
Yes	423	19 (4.5)	11 (2.7)	30 (7.1)
No	1497	61 (4.1)	23 (1.6)	84 (5.6)
Sputum smear status				
Negative	1489	17 (3.8)	4 (0.9)	21 (4.7)

Positive	450	64 (4.3)	30 (2.1)	94 (6.3)
Chest radiograph findings§				
Normal	100	2 (2.0)	1 (1.0)	3 (3.0)
Minimal	178	3 (1.7)	2 (1.1)	5 (2.8)
Moderately advanced	643	26 (4.0)	10 (1.6)	36 (5.6)
Far advanced	992	50 (5.0)	21 (2.2)	71 (7.2)
Lung cavitation§				
Cavitary disease	1121	59 (5.3)	25 (2.4)	84 (7.5)
Noncavitary disease	767	20 (2.6)	8 (1.1)	28 (3.7)
Duration of cough				
<30 days	540	4 (3.39)	1 (0.9)	5 (4.2)
≥30 and <90 days	858	31 (3.6)	16 (1.9)	47 (5.5)
≥90 days	923	44 (4.8)	15 (1.7)	59 (6.4)
HIV serostatus				
Positive	917	37 (4.0)	16 (1.8)	53 (5.8)
Negative	1018	44 (4.3)	18 (1.9)	62 (6.1)

Household characteristics				
Housing type				
Multifamily household	889	52 (5.9)	16 (1.9)	68 (7.7)
Single family household	1038	29 (2.8)	18 (1.8)	47 (4.5)
Charcoal or smoke exposure				
Inside household	412	10 (2.4)	10 (2.5)	20 (5.1)
Outside household	1358	66 (4.9)	23 (1.8)	89 (7.0)
None	131	4 (3.1)	0 (0)	4 (3.1)
Ventilation (No. windows/room)**				
>1	401	12 (3.0)	4 (1.0)	16 (4.0)
≤1	1526	69 (4.5)	30 (2.1)	99 (6.5)
Family size (No. in household)				
1 – 5	877	49 (5.6)	22 (2.7)	71 (8.1)
6 – 10	829	26 (3.1)	10 (1.3)	36 (4.3)
>10	235	6 (2.6)	2 (0.9)	8 (3.4)

Abbreviations: HIV = human immunodeficiency virus, TB = tuberculosis, BCG = Bacillus Calmette-Guerin, No. = number, IQR = interquartile range, NA = not applicable, mm = millimeters.

* Percentages refer to within characteristic column totals among household contacts of tuberculosis index patients. Percentages may not total 100% because within column percentages were rounded to the nearest integer. Co-prevalent tuberculosis disease was defined as the identification of tuberculosis disease at or within three months of the baseline household visit. Incident tuberculosis disease was defined as diagnosis of tuberculosis disease at subsequent household follow-up visits, conducted at six month intervals for two years. Individuals with co-prevalent disease were excluded from analyses of incident disease.

† A positive tuberculin skin test was defined as an induration ≥10 millimeters for HIV seronegative contacts and ≥5 millimeters for HIV seropositive contacts per American Thoracic Society recommendations.

‡ These are the number and percent of household contact exposed to the index case characteristic in the left-hand column.

§ Radiographic imaging results were graded by an experienced clinician using the 1961 National Tuberculosis Association classification system.

ll Nutritional status was assessed for each contact through BMI measurements for adults ≥18 years of age and through weight-for-age z-scores for child contacts. Individuals were classified as underweight if their z-score was <-2 or a BMI

<18.5, normal weight if z-scores were between -2 and 2 or their BMI was ≥18.5 and <25, and overweight if z-scores were >2 or BMI was ≥25.

**Windows must be to the outside.

†† Evaluated through BCG scar, verified by medical records when available.

Table 3. Univariate model for incident tuberculosis disease among household contacts, Kampala, Uganda (N=1941)

Variable	Contacts with incident disease (%)*	No. Household Contacts	p-value†	Relative Risk (95% CI)†	AUC
N	34 (1.8)	1860	--	--	--
Household contact characteristics					
Age group, years			<0.0001		0.70
0 – 4	4 (1.0)	397		1.79 (0.44 – 7.19)	
5 – 14	4 (0.6)	707		1 (Referent)	
15 – 24	7 (1.8)	385		3.25 (0.95 – 11.19)	
25 – 34	11 (5.7)	193		10.62 (3.34 – 33.75)	
35 – 44	6 (6.3)	96		11.72 (3.24 – 42.31)	
≥45	2 (2.4)	82		4.39 (0.79 – 24.37)	
Sex			0.483		0.53
Male	17 (2.1)	813		1 (Referent)	
Female	17 (1.7)	1031		0.79 (0.40 – 1.55)	

Education level			0.168		0.59
None	7 (1.2)	602		1 (Referent)	
Primary	16 (1.9)	855		1.64 (0.67 – 4.01)	
Secondary or higher	11 (2.8)	396		2.46 (0.94 – 6.39)	
Tuberculin skin test positive‡			0.011		0.60
Negative	3 (0.6)	520		1 (Referent)	
Positive	31 (2.4)	1318		4.15 (1.26 – 13.64)	
Tuberculin skin test induration, mm			0.136		0.61
<5	3 (0.7)	442		1 (Referent)	
5 – 9	4 (1.9)	214		2.79 (0.62 – 12.57)	
10 – 14	7 (1.8)	387		2.70 (0.69 – 10.50)	
15 – 19	13 (2.2)	584		3.33 (0.94 – 11.76)	
≥20	7 (3.3)	211		5.02 (1.29 – 19.62)	
BCG vaccinated‡‡			0.249		0.55
No	13 (2.7)	483		1 (Referent)	
Yes	20 (1.5)	1305		0.56 (0.28 – 1.14)	

Unknown	1 (1.4)	72		0.56 (0.07 – 4.39)	
Cigarette smoker			0.005		0.57
No	24 (1.8)	1358		1 (Referent)	
Yes	6 (5.8)	103		3.44 (1.37 – 8.61)	
Relation to index case			<0.0001		0.70
Other	3 (0.5)	569		1 (Referent)	
Sibling	6 (3.0)	198		5.90 (1.46 – 23.80)	
Child	7 (0.9)	774		1.72 (0.44 – 6.69)	
Parent	2 (2.9)	68		5.72 (0.93 – 34.84)	
Spouse	16 (6.5)	245		13.18 (3.80 – 45.67)	
Current cough			<0.0001		0.57
No	13 (1.1)	1207		1 (Referent)	
Yes	20 (8.8)	227		8.87 (4.35 – 18.12)	
Unknown	1 (0.2)	425		0.21 (0.03 – 1.65)	
Know another tuberculosis case			0.951		0.52
No	28 (1.9)	1456		1 (Referent)	

Yes	3 (1.7)	178		0.87 (0.26 – 2.91)	
Don't know	3 (1.4)	218		0.71 (0.21 – 2.36)	
Past active tuberculosis			0.350		0.51
No	33 (1.8)	1823		1 (Referent)	
Yes	1 (4.4)	23		2.47 (0.32 – 18.84)	
Nutrition status**			0.004		0.57
Underweight	5 (9.6)	52		6.31 (2.33 – 17.11)	
Normal	27 (1.7)	1629		1 (Referent)	
Overweight	2 (1.2)	165		0.73 (0.17 – 3.09)	
Anorexia			<0.0001		0.59
No	27 (1.5)	1780		1 (Referent)	
Yes	7 (9.7)	72		6.99 (2.94 – 16.65)	
Alcohol usage			0.006		0.58
No	24 (1.5)	1600		1 (Referent)	
Yes	10 (4.0)	251		2.72 (1.29 – 5.77)	
HIV Serostatus			<0.0001		0.58

Negative	18 (1.3)	1405		1 (Referent)	
Positive	16 (8.9)	179		7.56 (3.78 – 15.12)	
Unknown	0 (0.0)	276		–	
Closeness to index case			<0.0001		0.61
Different room	11 (1.5)	726		1 (Referent)	
Share room, not bed	7 (0.9)	786		0.84 (0.23 – 1.51)	
Share bed	15 (4.8)	313		3.27 (1.49 – 7.21)	
Index case characteristics§					
Age group, years			0.293		0.57
18 – 29	21 (2.5)	852		1 (Referent)	
30 – 39	7 (1.2)	603		0.46 (0.20 – 1.10)	
40 – 49	4 (1.4)	291		0.55 (0.19 – 1.62)	
≥50	2 (1.8)	114		0.71 (0.16 – 3.05)	
Sex			0.341		0.54
Male	15 (1.6)	970		1 (Referent)	
Female	19 (2.1)	888		1.39 (0.70 – 2.76)	

Cigarette smoker			0.139		0.55
No	23 (1.6)	1436		1 (Referent)	
Yes	11 (2.7)	404		1.72 (0.83 – 3.56)	
Sputum smear status			0.150		0.56
Negative	4 (0.9)	1425		1 (Referent)	
Positive	30 (2.1)	433		2.31 (0.81 – 6.58)	
Chest radiograph findings‖			0.792		0.56
Normal	1 (1.0)	98		1 (Referent)	
Minimal	2 (1.1)	175		1.12 (0.10 – 12.53)	
Moderately advanced	10 (1.6)	617		1.60 (0.20 – 12.62)	
Far advanced	21 (2.2)	942		2.21 (0.29 – 16.62)	
Lung cavitation‖			0.045		0.59
Noncavitary disease	8 (1.1)	747		1 (Referent)	
Cavitary disease	25 (2.4)	1062		2.23 (1.00 – 4.96)	
Duration of cough			0.880		0.50
<30 days	1 (0.9)	114		1 (Referent)	

≥30 and <90 days	16 (1.9)	830		2.22 (0.29 – 16.91)	
≥90 days	15 (1.7)	879		1.96 (0.26 – 14.99)	
HIV serostatus			0.962		0.50
Positive	16 (1.8)	880		1 (Referent)	
Negative	18 (1.9)	974		1.02 (0.52 – 2.01)	
Household characteristics					
Housing type			0.839		0.51
Single family household	18 (1.8)	1009		1 (Referent)	
Multifamily household	16 (1.9)	837		1.07 (0.54 – 2.12)	
Charcoal or smoke exposure			0.205		0.57
Inside household	10 (2.5)	402		1.41 (0.66 – 2.98)	
Outside household	23 (1.8)	1292		1 (Referent)	
None	0 (0)	127		--	
Ventilation (No. windows/room)††			0.209		0.55
>1	4 (1.0)	389		1 (Referent)	
≤1	30 (2.1)	1457		2.02 (0.71 – 5.78)	

Family size (No. in household)			0.069	0.61
1 – 5	22 (2.7)	828	1 (Referent)	
6 – 10	10 (1.3)	803	0.46 (0.22 – 0.98)	
>10	2 (0.9)	229	0.32 (0.08 – 1.38)	

Abbreviations: HIV = human immunodeficiency virus, BCG = Bacillus Calmette-Guerin, No. = number, IQR = interquartile range, NA = not applicable, mm = millimeters, AUC = area under the curve.

* Percentages refer to within characteristic column totals among household contacts of tuberculosis index patients. Percentages may not total 100% because within column percentages were rounded to the nearest integer. Co-prevalent tuberculosis disease was defined as the identification of tuberculosis disease at or within three months of the baseline household visit.

† Calculated using the $\chi 2$ test or Fisher's exact test as appropriate. All odds ratios were derived from a generalized additive mixed-effects logistic regression model adjusting for household clustering of contacts. For participants in the same household, an exchangeable working correlation structure is stipulated.

‡ A positive tuberculin skin test was defined as an induration ≥10 millimeters for HIV seronegative contacts and ≥5 millimeters for HIV seropositive contacts per American Thoracic Society recommendations.

§ These are the number and percent of household contact exposed to the index case characteristic in the left-hand column.

ll Radiographic imaging results were graded by an experienced clinician using the 1961 National Tuberculosis Association classification system** Nutritional status was assessed for each contact through BMI measurements for adults ≥18 years of age and through weight-for-age z-scores for child contacts. Individuals were classified as underweight if their z-score was <-2 or a BMI <18.5, normal weight if z-scores were between -2 and 2 or their BMI was ≥18.5 and <25, and overweight if z-scores were >2 or BMI was ≥25.

†† Windows must be to the outside.

‡‡ Evaluated through BCG scar, verified by medical records when available.

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