DRIVERS OF ONGOING TUBERCULOSIS TRANSMISSION IN AFRICAN CITY: INSIGHTS INTO SOCIAL BEHAVIORS AND ENVIRONMENT

by

TRANG HO THU QUACH

(Under the Direction of Christopher Whalen)

ABSTRACT

Statement of the Problem: Over 25 years of efforts the global TB epidemic remarkably improved in reducing suffering and death by enhancing access to diagnosis and treatment but failed to drive down tuberculosis epidemic. The goal of End TB Strategy to eliminate disease cannot be achieved if one TB case transmits and produces one or more cases among susceptible contacts. Therefore, an explicit focus on halting transmission is a critical component that is necessary for the success of End TB Strategy **Goal:** To understand factors driving on-going TB transmission in an urban African setting in order to expand control strategies to interrupt TB transmission at population-level. **Aims:** To measure the extent of TB transmission in the community by cumulative incidence of TB infection, and identify social behaviors and community-based settings associated with TB transmission **Methods:** We conducted a prospective, community-based cohort study of adults without TB infection in Kampala, Uganda from 2014 to 2016. All participants were retested with TST to evaluate incident infection after one year of following up. We visited participants for every 3 months to assess risk of acquiring a new TB infection and measure the amount of time spent in settings by using standardized questionnaires. **Results:** At least 29% of participants had recent contact with TB patients**.** The annual risk of infection was high (11.8%).

Smokers, heavy alcohol users, and persons who contacted with TB patients before enrollment and during follow up were as high risk of getting TB infection as HIV-infected (20% per year). Being older, being men, non-religious Roman Catholic, contacting with TB patients before enrollment and during follow up, and spending time at worship centers and schools increased risk of acquiring LTBI, while attending drug shop and staying at own home lowered the risk. **Conclusions:** TB transmission occurs at high rate in urban African settings as high proportion of population contacted with TB patients. Smokers, heavy alcohol users, and persons who contacted with TB patients before enrollment and during follow up should be treated for TB infection. Worship centers and schools are environments that could be targeted for TB control programs.

INDEX WORDS: Annual risk of TB infection, Cumulative incidence, Incidence density, Latent tuberculosis Infection, Risk factors, Social behaviors, Sex difference, Settings, Locations.

DRIVERS OF ONGOING TUBERCULOSIS TRANSMISSION IN AFRICAN CITY: INSIGHTS INTO SOCIAL BEHAVIORS AND ENVIRONMENT

by

TRANG HO THU QUACH

PharmD, Ho Chi Minh City University of Medicine and Pharmacy, Vietnam, 2014

MPH, University of Georgia, 2018

A Dissertation Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2021

DRIVERS OF ONGOING TUBERCULOSIS TRANSMISSION IN AFRICAN CITY:

INSIGHTS INTO SOCIAL BEHAVIORS AND ENVIRONMENT

by

TRANG HO THU QUACH

Major Professor: Christopher C. Whalen
Committee: Juliet N. Sekandi
Kevin K. Dobbin
Luke Naeher

Electronic Version Approved

Ron Walcott
Vice Provost for Graduate Education and Dean of the Graduate School
The University of Georgia
August 2021

ACKNOWLEDGEMENT

I thank to my parents who always advised me to choose education. My parents devoted themselves to give me well-rounded education and trained me to be patient, resilient, forethoughtful, and hard working.

I would like to acknowledge Vietnam Education Foundation (VEF) scholarship and Dr. Cordero that gave me a golden opportunity to study the M.P.H program at University of Georgia where I met and receive the support from great peoples. I thank to all of my friends and colleagues at University of Georgia, who were always welcome and supportive. I thank to all professors who taught me and gave me solid knowledge in the field.

I thank my dissertation committee members: Dr. Christopher Whalen, Juliet Sekandi, Kevin Dobbin, and Luke Naeher for all of your time and helpful feedback at every stage of this process. To all my colleagues and friends in the Epidemiology In Action (EIA) research group directed by Dr. Whalen. I was enriched in public health research weekly by EIA meeting.

I am forever grateful to Dr. Whalen who were advised me over past 5 years. Thank you for being patient, supportive, generous, and kind to me. I could not be here and had these accomplishments without your support and kindness.

Finally, I thank to my husband and son who give loves and supports to me. I could not have endured the challenges of being a Ph.D. student, wife, and mom without their support.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Impact of Tuberculosis on Public Health

Tuberculosis (TB) was a leading cause of mobility and mortality from a single infectious agent with an estimated 10 million cases and 1.4 million deaths in 2019 (WHO, 2020b). This makes TB the tenth leading cause of death, ranking above human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) in the world. TB and HIV have found a lethal synergy. HIV patients showed an increased likelihood of TB acquisition by up to 18-fold and TB-HIV coinfection was estimated to made up to 8.2 percent of all TB cases in 2019 (WHO, 2018b). The impact of these diseases on one another is bidirectional: (1) HIV increases risk of TB infection and disease progression, (2) TB slows CD4 recovery and increases progression to AIDS and death among the HIV infected. Approximately 15% of TB deaths in 2019 was contributed by HIV-infected patients (WHO, 2018b). The consequences of this dual burden was not only increased deaths due to TB, but also a larger pool of patients with active TB disease capable of spreading infection. It is more worrying that the emergence of multi-drug resistant TB complicates the picture further. In 2019, 206,030 people developed multi-drug or rifampicin resistant TB, a 10% increase from 186 883 in 2018 (Grabowski et al., 2017).

Over 90% of the TB cases and deaths occurred in low and middle income countries (WHO, 2018b). TB and poverty are closely linked (WHO, 2005). Malnutrition, overcrowding, poor air circulation and sanitation associated with poverty increase the probability of acquiring infection and developing active TB disease. Poverty and TB form a vicious cycle. TB exacerbates the poverty by decreasing capacity to work and adding treatment expenses. Poor people tend to live in close and unhygienic quarters where TB flourishes. The poor receive inadequate healthcare, which prevents them from the early diagnosis. Treatment, if received at all, is often erratic or simply incorrect. The poor are also less likely to seek care from healthcare professionals, and are 2 to 3 times more likely to self-medicate than other income groups. Self-medication facilitates the emergence of TB drug-resistance and further increases the impacts on the poor and the risks to others in society (WHO, 2005).

TB halts work in the formal and informal economies, as well as within household. It is documented that approximately 3-4 months of work lost annually due to disease, and lost earnings of 20 to 30% of household income. Families of persons who died from the disease lost about 15 years of income. In summary, every twelve months, TB causes somewhere nearly $ 12 billion to disappear from the global economy (WHO, 2005).

Latent tuberculosis infection (LTBI) has been defined as a state with persistent immune responses to *Mycobacterium tuberculosis (Mtb)* antigens without evidence of manifestation of clinical symptoms (Mack et al., 2009). Approximately 25% of the world's population is infected with TB, representing a large reservoir of people at risk of progression to active TB disease (WHO, 2018b). About 5-10% of people with LTBI progress to active TB disease at some points in their lifetime, with the majority developing TB disease within 2-5 years of initial infection unless they were diagnosed and treated with antibiotic drugs (D. B. Young, Perkins, Duncan, & Barry, 2008).

According to WHO report 2020, Uganda was one of 30 high TB/HIV burden countries. The overall incidence rate was estimated at 200 per 100,000 population, of which 40% were estimated to be co-infected with HIV (WHO, 2018b). These statistics suggest that TB burden in

Uganda was fueled by both progressions from latent tuberculosis infection (LTBI) to active TB, with a huge part due to HIV-infection, and ongoing transmission of *Mtb*.

WHO Methods Used to Estimate TB Incidence

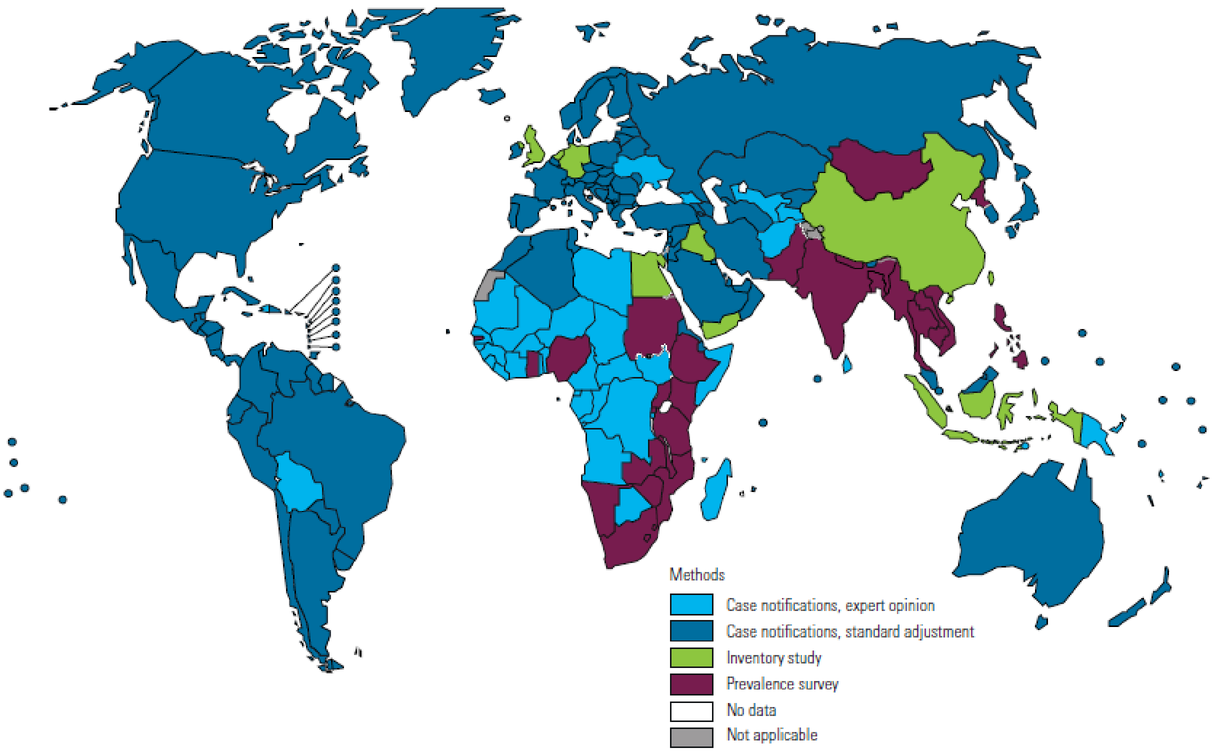

Figure 1. 1 Main methods used by WHO to estimate TB incidence

TB incidence has never been measured through population based surveys at national level because this requires long-term studies among large cohorts of people with high costs and challenging logistics. Methods currently used by WHO to estimate TB incidence can be grouped into four major categories (Glaziou, Sismanidis, Zignol, & Floyd, 2020). Understanding how WHO measures TB incidence worldwide can help us have an appropriate interpretation.

<u>Results from TB prevalence surveys:</u> Incidence is estimated using prevalence survey results and estimates of the distribution characteristics of duration of disease, accounting for the impact of HIV coinfection and ART. This method is used for 29 countries, of which 28 have

national survey data and one – India – has a survey in one state. The 29 countries accounted for 66% of the estimated global number of incidence cases in 2019 (Glaziou et al., 2020). The limitation of this method are (1) there is the insufficient power of surveys to estimate the number of prevalent TB cases on treatment with great precision; (2) cases found on treatment during the survey do not have a bacteriological status at onset of treatment in most surveys; (3) literature reviews have provided estimates of duration of disease in untreated TB cases from pre-chemotherapy era (before 1950s). The best estimate of the mean duration of untreated disease in HIV-negative individuals is about three years. There are few data on the duration of disease in HIV-positive individuals.

Notification in high-income countries adjusted by a standard factor to account for under-reporting, under-diagnosis and overdiagnosis/overreporting: This method is used for 139 countries that include all high-income countries except Germany, the Netherlands and the United Kingdom, plus some upper-middle income countries with low levels of underreporting, including Brazil, China and the Russian Federation (Glaziou et al., 2020). These 139 countries accounted for 6% of the estimated global number of incident cases in 2019. TB surveillance systems from countries in the high-income group were assumed to perform similarly well on average. The exceptions were the Repulic of Korea, where the under-reporting of TB cases has recently been measured using annual inventory studies and France where the estimated level of under-reporting was communcated by public health authorities, based on unpublished survey results. In the United Kingdom and the Netherlands, incidence was ontained using capture-recapture modelling. Surveillance data in this group of countries are usually internally consistent.

Results from inventory/capture-recapture studies: An inventory study aims at quantifying the level of under-reporting of detected TB cases. This method is used for 8 countries: China, Egypt, Germany, Indonesia, Iraq, the Nertherlands, the United Kingdom, and Yemen. They accounted for 17% of estimated global number of incident cases in 2019 (Glaziou et al., 2020). The surveillance gap (proportion of unreported incident cases) in the UK and the Netherlands was assumed time invariant. In Yemen, trends in incidence were derived from results of two consecutive tuberculin survey. In Egypt and Iraq, trends were derived using the fourth method.

Case notification data combined with expert opinion about case detection gaps: Expert opinion, elicited in regional workshops or country missions, is used to estimate levels of under-reporting and under-diagnosis. Trends are estimated using either mortality data, surveys of the annual risk of infection or exponential interpolation using estimates of case detection gaps for three years. This method is considered generally unreliable and used when other methods are not applicable due to missing or poor quality data. This method is used for 39 countries that accounted for 11% of the estimated gloable number of incident cases in 2019 (Glaziou et al., 2020). Limitations of the method based on eliciting expert opinion about gaps in case detection and reporting included a generally small number of interviewed experts; lack of clarity about vested interests when eliciting expert opinion; lack of recognition of over-reporting (due to over-diagnosis, e.g. in some countries implementing a large-scale systematic population screening policy that may result in many people with abnormal chest X-ray but no bacteriological confirmation of TB disease being notified or treated as new TB cases); incomplete data on laboratory quanlity and high proportion of patients with no bacteriological confirmation of diagnosis are a potential source of error in estimates.

Heterogeneity in TB Distribution

After estimating TB incidence in every country, global TB incidence was estimated by global number of TB incidence dividing by world population. Similarly, TB incidences in six epidemiological WHO regions were estimated by number of TB incidence in a region dividing by population in that region.

TB occurs in every part of the world and varied substaintally by region. Globally in 2019, an estimated 10.0 million people fell ill with TB, equivalent to 130 cases per 100,000 population. Most of the estimated number of cases in 2019 occurred in the WHO regions of South-East Asia (44%), Africa (25%) and Western Pacific (18%). Smaller proportion of cases occurred in the WHO regions of Eastern Mediterranean (8.2%), the Americas (2.9%), and Europe (2.5%). The 30 high TB burden countries accounted for 86% of all estimated incident cases worldwide, and eight of these countries accounted for two thirds of the global total: India (26%), Indonesia (8.5%), China (8.4%), the Philippine (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%). In 2019, 54 countries had a low incidence of TB (<10 cases per 100 000 population per year), mostly in WHO region of the Americas and European region. There were 150-400 cases per 100 000 population in most of the 30 high TB burden countries, and more than 500 cases in the Central African Republic, the Democratic People’s Republic of Korea, Lesotho, the Philippines, and South Africa (Figure 1. 2) (WHO, 2020b).

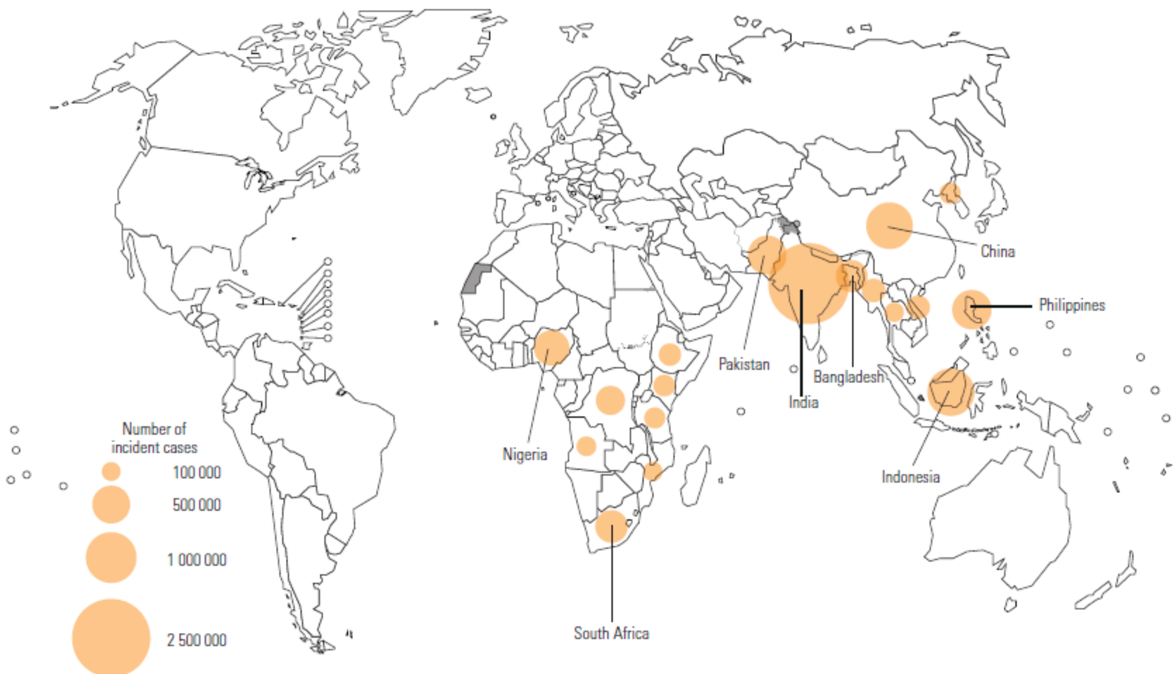

Figure 1. 2 Estimated TB incidence in 2019, for countries with at least 100 000 incident cases

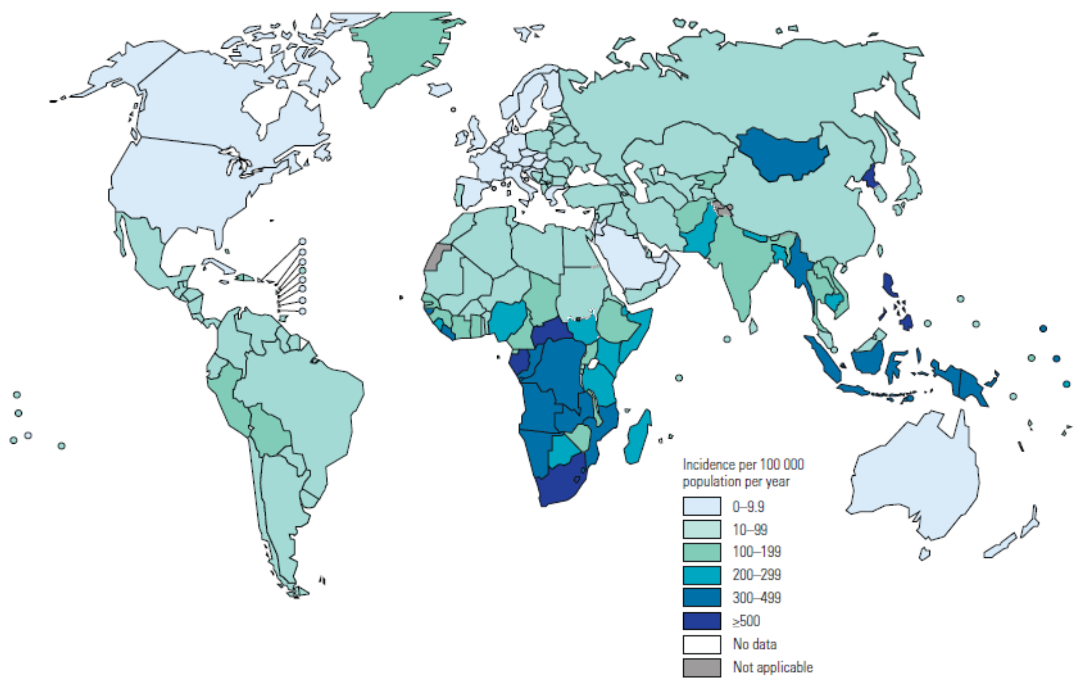

Figure 1. 3 Estimated TB incidence rates, 2019

TB Controls Achievements and Challenges

Over decades of efforts to control the global TB epidemic remarkably improved outcomes in regard to TB mobility and mortality by enhancing access to diagnosis and treatment. It is estimated that 43 million lives saved between 2000 and 2015 (WHO, 2016). Concerning the targets set by Global Plan to Stop TB 2011 – 2015, a 47% drop in TB mortality rates was achieved, compared to the 50% target. HIV-related TB death downed by 32% in the last decade.

However, all efforts had little effect on incidence rates and failed to drive down the TB epidemic. In fact, TB incidence declined by only 18% in 2014 compared to the level of the year 2000. In addition, there have been numerous challenges. Treatment for MDR-TB has increased with almost all cases detected in 2014 started treatment, and MDR-TB has been a public health crisis because of only one in four MDR-TB cases detected and one in two cases cured. The devastating synergy between TB and HIV co-infection was so huge burden on public health, which requires antiretroviral treatment, treatment of latent TB infection, and other key interventions, that the resources still need further scale-up and availability for TB control failed to restrain new TB cases caused by HIV infection. Of the 10 million new and relapsed cases in 2019, around 7 million (70%) were officially reported to national authorities and the WHO (WHO, 2018b). The 3 million gap are missed by health systems, raising serious concern on optimal clinical and public health management. This is mainly attributed to incomplete compliance of private providers in some countries, while economic barriers to primary care access might determine underdiagnosed TB in low-income countries. These challenges will impose a huge financial and political burden on the TB control.

Human population movement has played an important role in spread of disease. Because of global health disparities and prevalence differences, health systems and policies in low burden countries have been challenged to protect the host populations from the risk of TB transmission and to reduce the impact on their healthcare systems. For an example, a high income and low burden like the US where migration accounted for a significant part of population growth. It has been concerned that immigrants could bring TB disease into the country. Nearly all (91%) of the reported tuberculosis patients among Asians and Pacific Islanders were foreign-born, and 52% of all Hispanic tuberculosis patients were foreign-born (Cdc., 1990). As a result, the US developed public health screening systems and border control health policies to control TB among migrants and prevent TB transmission to resident population (MacPherson, Gushulak, & Macdonald, 2007). Universal health coverage should be ensured for refugees and migrants. However, the WHO European Region is the only one in the world with a consensus document on the minimum package of cross-border TB control and care interventions (WHO, 2021). Tuberculosis in migrants and refugees pose a challenge to cross-border management of TB cases with communications among clinicians from different countries in terms of sharing information for clinical management and contact tracing.

WHO End TB Strategy and Its Targets for 2035

The new era of the fight against TB was conceived as a component of the sustainable development goals for 2030, which was adopted by the United Nations General Assembly. In 2014, the End TB Strategy was first approved. The strategy provides a unified response to ending TB deaths, disease, and suffering. The strategy builds on three strategic pillars underpinned by four key principles.

Principles:

1. Government stewardship and accountability, with monitoring and evaluation
2. Strong coalition with civil society organization and communities

3. Protection and promotion of human rights, ethics, and equity
4. Adaptation of strategy and targets at country level, with global collaboration

Pillars and components:

1. Integrated, patient-centered care and prevention
    - Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high risk groups.
    - Treatment of all people with TB including drug-resistant TB, and patient support
    - Collaborative TB/HIV activities, and management of co-morbidities
    - Preventive treatment of persons at high risk, and vaccination against TB
2. Bold policies and supportive systems
    - Political commitment with adequate resources for TB care and prevention
    - Engagement of communities, civil society organizations, and public and private care providers
    - Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control.
    - Social protection, poverty alleviation, and actions on other determinants of TB
3. Intensified research and innovation
    - Discovery, development and rapid uptake of new tools, interventions, and strategies
    - Research to optimize implementation and impact, and promote innovations

Three main targets have been set for 2035:

(i) a 95% decline in TB mortality,

(ii) 90% reduction in TB incidence or down from > 1000 per million population to less than 100 cases per million population globally, and

(iii) the complete abolition of any catastrophic costs for TB patients and their families.

A rate of decline of 10% per year is thought to be achievable, as this was observed during 1950s and 1960s in Western Europe, where comprehensive tuberculosis control efforts, which included infection control and treatment of *Mtb* infection and all forms of tuberculosis, were intensified, and universal health coverage and socioeconomic development were expanded.

Importance of Research to Fill Gaps of TB Transmission

Interrupting tuberculosis transmission is central to achieving the reductions in tuberculosis incidence required to meet the End TB targets. The ability to stop new cases hinges directly on the capacity to halt transmission because when a TB case is replaced by one or more cases among susceptible contacts, tuberculosis epidemics continued (Whalen, 2016). As with so much of tuberculosis care, our current tools for halting transmission have around for decades: active case finding, contact investigations, BCG vaccination for infants, and targeted testing, and treatment for latent tuberculosis infection. These interventions have proven quite successful in decreasing the tuberculosis burden, but have been shown some limitations. For example, in Sub-Saharan Africa, transmission in the community is often so intense that household members and other known contacts only account for a minority of transmission events. As a result, contact investigation is unlikely to interrupt TB transmission on its own on high burden contexts, even though it may prevent a high absolute number of cases. Another example is that BCG vaccination is only partially effective, which provide some protection against severe forms of pediatric non-pulmonary TB, but is unreliable against adult pulmonary TB which accounts for most of the TB disease and transmission worldwide. With current approaches to eliminate TB, TB epidemic continues in spite of an available, cost-effective and broadly implemented vaccine for infants – Bacille Calmette-Guerin (BCG) – and the carefully managed use of drugs for those who do become infected through directly observed therapy (DOTs). Consequently, TB incidence is falling at about 2% per year and between 2015 and 2019 the cumulative reduction was 9%. This was less than half way to the End TB Strategy milestone of 20% reduction between 2015 and 2020. Additionally, the global rate of decline in tuberculosis incidence was projected to increase to 4% - 5% by 2020 and then to 10% per year by 2025 to meet the WHO End TB Strategy targets.

A critical component of what will be necessary for success has been too often neglected: an explicit focus on halting transmission. Although our understanding of tuberculosis transmission and disease progression has improved substantially over the intervening century of tuberculosis research, many gaps remain. Gaps in our understanding of the biology and local determinants of transmission underscore just how little we know about transmission and how that ignorance may be undermining our efforts to end TB. Over decades, household contact investigations are the key components of tuberculosis control program because the majority of transmission is thought to occur among close household contacts. However, recent studies suggest that the proportion of transmission that actually occurs in household in high burden countries was less than 20% (Martinez, Shen, et al., 2017). Given that a minority of transmission occurs among household contacts in high burden countries, the majority of transmission presumably occurs in a variety of community-based settings. Therefore, there are important gaps in understanding of locations or settings where TB transmission occurs. It is important to conduct a cohort study to estimate incidence of TB infection in general population from unknown exposures. WHO emphasized that to achieve the goal of 2035, it requires expanding the scope and research for TB prevention and pursuing new scientific knowledge and innovations that can dramatically change TB prevention and care. Our limited understanding about TB transmission dynamics of TB in the high risk environment constrains the ability to design and evaluate public health intervention in the community.

While we must continue to deploy tools that are currently available and maximize the benefit from interventions that are known to be effect, we must also mobilize to develop new tools that can maximize interrupting tuberculosis transmission. Addressing research gaps in TB transmission while simultaneously scaling up current available effective tuberculosis control interventions to interrupt tuberculosis transmission can maximize impact on reducing tuberculosis incidence and mortality and thereby reach the Ending TB targets. The purpose of this proposal was to understand factors that drive the ongoing TB transmission in high TB burden community.

Research Questions for Specific Aims

Aim 1:

Estimate incidence of latent TB and HIV infection in an urban African city and identify participants' characteristics associated with incidence of TB infection

Aim 2:

Identify social behaviors associated with incidence of TB infection

Aim 3:

Identify type of community settings where TB transmission more likely occurs (e.g. worship center, school, bar, transport sites, etc.)

CHAPTER 2

LITERATURE REVIEW

Natural History of Tuberculosis Disease

Tuberculosis (TB) is caused by bacteria (Mycobacterium tuberculosis) that most often affect the lungs. TB is spread from person to person through the air. When people with lung TB cough, sneeze or spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected (WHO, 2020a). TB is not spread by shaking someone’s hand, sharing food or drink, touching bed linens, or toilet seats, sharing toothbrushes, and kissing. Not everyone infected with TB bacteria becomes sick. As a result, two TB-related conditions exist: latent TB infection (LTBI) and TB disease.

TB bacteria can live in the body without making people sick. This is called latent TB infection. In most people who breath in TB bacteria and become infected, the body is able to fight the bacteria to stop them from growing. People with LTBI have no clinical symptoms, cannot spread TB bacteria to others, and may develop TB disease if they do not receive treatment for LTBI.

Many people who have LTBI never develop TB disease. In these people, TB bacteria remain inactive for a lifetime without causing disease. However, in other people, especially people who have a weak immune system, the bacteria become active, multiply and cause TB disease.

When a person breathes in TB bacteria, the bacteria can settle in the lungs and begin to grow. If the immune system cannot stop them from growing, then TB bacteria are active and multiplying in your body. This is called TB disease. From lung, they can move through the blood to other parts of the body, such as the kidney, spine, and brain. TB disease in the lungs or throat can be infectious. This means that the bacteria can be spread to other people. TB in other parts of the body, such as kidney or spine, is usually not infectious.

Many people who have LTBI never develop TB disease. Some people develop TB disease soon after becoming infected (within weeks) before their immune system can fight the TB bacteria. Other people may get sick years later when their immune system becomes weak for other reasons. That’s why people whose immune systems are week, especially those with HIV infection, the risk of developing TB disease is much higher than for people with normal immune systems.

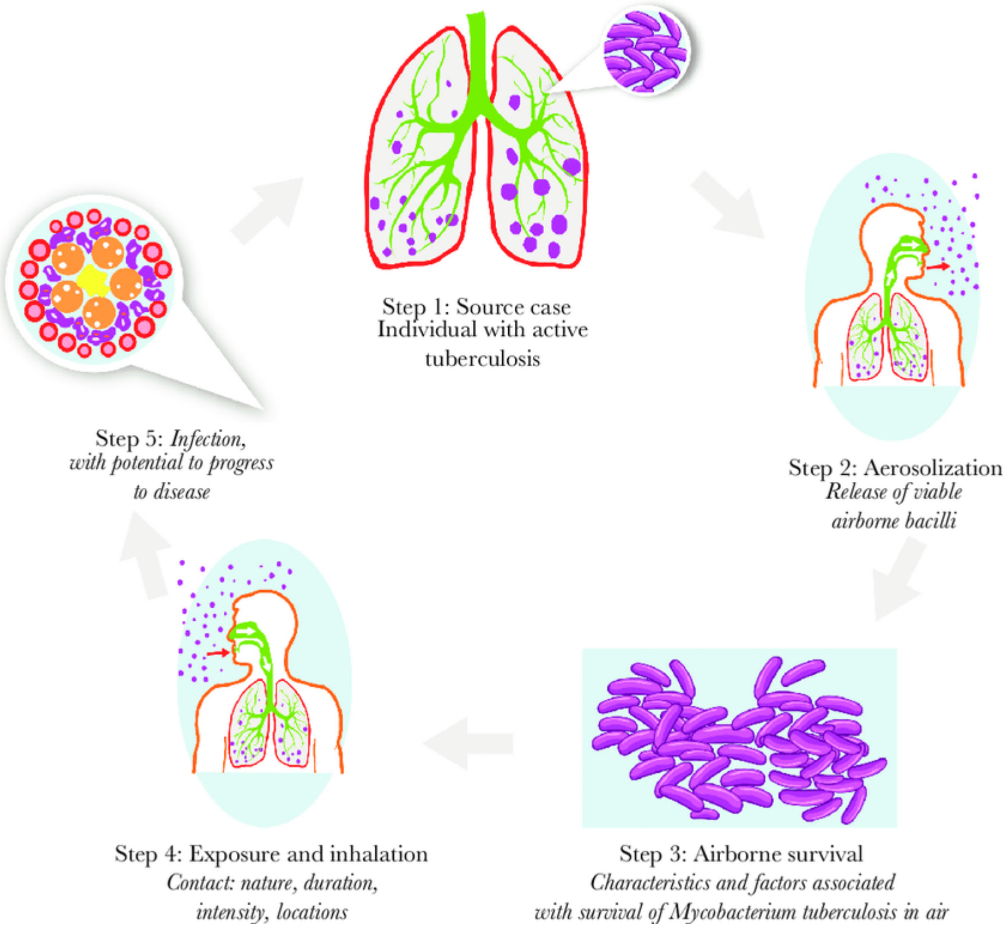

Figure 2. 1 Cascade of Tuberculosis transmission

In traditional perspectives, it is thought that tuberculosis has two stages of the disease: latent TB infection and active TB disease. However, recent research has clearly demonstrated that human TB infection from latent TB infection to active disease exists other stages which a continuous spectrum of metabolic bacterial activity and antagonistic immunological responses occurs. With contemporary prospective, TB disease was recognized with 4 stages including latent TB infection, incipient TB, subclinical TB, and active TB (Drain et al., 2018). Following the establishment of latent infection, the pathways by which disease may naturally progress include (1) latency, (2) rapid or (3) slow progression through incipient and subclinical disease to active TB, or (4) a period of cycling through incipient and subclinical states that may precede the development of symptomatic disease or eventual disease resolution (Drain et al., 2018). The revised process of TB disease provides opportunities for the development of diagnostic and interventions to prevent progression to active TB disease and transmission of TB bacilli.

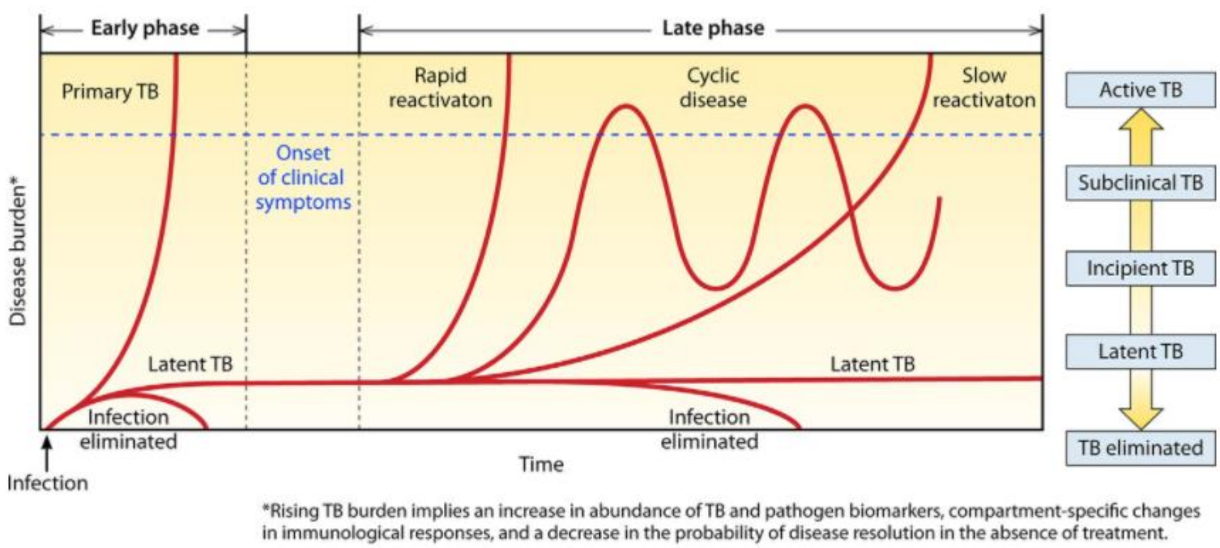

Figure 2. 2 Pathways of tuberculosis disease progression

Annual risk of Tuberculosis Infection

The annual risk of tuberculosis infection (ARTI) is an epidemiological index derived from surveys or cohort study to measure the extent of TB transmission in the community. It is the probability of acquiring new TB infection or reinfection over a period of one year. ARTI trend are a critical indicator for progress in tuberculosis control in the community. The annual risk of infection can be estimated using (1) direct methods that rely on the follow up of initially uninfected individuals over one-year period or (2) indirect methods that typically rely on statistical analysis of data on the prevalence of latent tuberculosis infection. To be specifically, the indirect method estimated the annual risk of infection by the formula ARTI = 1 – $(1 - p)^{1/b}$ (p is the prevalence of infection and b is the mean age of individuals who underwent TST) (Cauthen, Pio, & Ten Dam, 2002). ARTI estimated by indirect methods is problematic and controversy (Borgdorff, 2002). The annual risk of infection estimated from cross-sectional studies was substantially biased because some assumptions for estimating annual risk of infection from prevalent TB infection violated. These assumptions are (1) it is assumed that ARTI was independent of the age of the person at risk of infection while exposure to TB is likely to change as people grow older; (2) ARTI was constant over time, which may not be the case since the surveys were done in different age groups and it estimated the ARTI for every year of the age.

ARTI from cross-sectional study ranged from 0.35% in Saudi Arabia to 7.9% among children aged at 15 years in South Africa (table 2.1). The estimated ARTI among prospective cohort study was much higher than ARTI from cross-sectional studies, with range of 13.0% to 14.5 % by TST. There is a big discrepancy in ARTI measured by TST or IGRA in prospective cohort study in China (Table 2.1).

Table 2. 1 Annual risk of tuberculosis infection in general population

Author, year	**Study design and population**	**Test used**	**Sample size**	**Annual risk of tuberculosis infection (ARTI)**
Annual risk of TB infection from surveys				
Balkhy, 2017 (Balkhy et al., 2017)	Cross-sectional study, population-based sample in adults in Saudi Arabia	TST and IGRA	1369	ARTI by TST: 0.36% ARTI by IGRA: 0.35%
Malacarne, 2016 (Malacarne et al., 2016)	Cross-sectional study, in indigenous population in Brazil (including children and adults)	TST	263	ARTI: 2.4%
Adetifa, 2015 (Adetifa et al., 2015)	Multi-cluster survey in children aged 6-11 years in Gambia	TST	13386	ARTI: 0.75%
Wood, 2010 (Wood et al., 2010)	Cross-sectional study among people aged 5-40 years, in South Africa	TST	1061	ARTI among children aged ≤ 5 years old is 3.9% and increased throughout out childhood to maximum of 7.9% at age 15 years old.
Rao, 2008 (Rao et al., 2008)	Cross-sectional study, among children aged 1-9 years old, in India	TST	4802	ARTI: 1.3%
Annual risk of infection from prospective cohort studies				
Gao, 2016 (Gao et al., 2016)	Prospective cohort study, in 2013, in adults in 4 sites of rural China	TST (≥ 10 mm), and IGRA	11422	TB infection incidence after one year follow up: 14.5% TB infection incidence after one year follow up: 3.1%
Adrews, 2015 (Andrews et al., 2015)	Prospective cohort study in adolescents aged 12-18 years old in South Africa	TST and IGRA	5357	ARTI by IGRA: 14% ARTI by TST: 13%

Risk Factors for prevalent and incident latent TB infection

Studies investigated the burden of LTBI have mainly focused on special populations such as children, household contacts of TB cases, healthcare workers, migrants and prisoners. In comparison, very few community-based or population-based studies have been conducted to examine risk factors associated with LTBI in general population.

This section will review risk factors associated with both prevalent and incident LTBI in general population. A search on Medline was performed to find all papers in this topic. The following search terms were used ((Latent tuberculosis infection[Title] OR tuberculosis infection[Title] OR LTBI[Title]) AND (General population[Title/Abstract] OR population-based[Title/Abstract] OR community[Title/Abstract] OR Community-based[Title/Abstract])) NOT (Health care worker*[Title] OR Prison[Title] OR homeless[Title] OR children[Title] OR child[Title] OR student[Title] OR active tuberculosis[Title] OR Pediatric[Title] OR migrants[Title] OR Health care workers[Title] OR Systematic-review[Title] OR Healthcare workers[Title] OR patients[Title] OR students[Title] OR kidney[Title] OR workers[Title]).

In summary, there were 13 articles (equivalent to 9 studies) investigated the risk factors of prevalent and incident LTBI on general population. Of 13 articles, 12 articles identified risk factors associated with prevalent LTBI, and only 1 article investigated risk factor associated with incident LTBI (Table 2.2). ***Except for one prospective cohort study, all studies were cross-sectional studies.*** Out of 13 articles, three were from NHANES data in 2011-2012 and 1999-2000. Studies conducted by Gao et al. and Zhang et al. were the same study, but investigated some different risk factors. Three were conducted in Asia, three in Africa, and three in America. All studies collected data from 1999 to 2014, except for one study. This particular study analyzed the data from 1951 to 1996 on Aboriginal population, Canada.

Risk factor for prevalent TB infection

This section discussed risk factors of prevalent LTBI found from 12 articles corresponding to 8 studies. Since tuberculin skin test cannot distinguish between recent and remote TB infection and is generally positive for decades, the prevalence is expected to be high. The prevalence of LTBI ranged from 5% in US (Mancuso, Diffenderfer, Ghassemieh, Horne, & Kao, 2016) to 49% in Uganda (Kizza et al., 2015). The risk factors identified in the cross-sectional studies were affected by the risk of acquiring new infection and survival of the infection until tested, while the risk factors identified from cohort study purely illustrated risk factors associated with acquisition of TB infection.

The risk factors for prevalent LTBI identified from cross-sectional studies are not equivalent to or exchangeable to the risk factors for incident LTBI identified from cohort studies. Using prevalence rate ratio or prevalence odds ratio in cross-sectional studies as an estimation of incidence ratio is subject to bias when the purpose is to investigate the etiology or identify risk factors that influence the development of LTBI. Prevalence is a function of incidence and time. Since LTBI is lifelong, using prevalent LTBI to determine risk of infection actually conflates the risks of acquiring infection with the risks of surviving with the infection. Further, the prevalence rate ratio tends to underestimate the strength of association. The magnitude of this bias depends on both prevalent rate ratio and the magnitude of prevalent rates. The magnitude can be big when the prevalent rates are high (> 10%) and the prevalent rate ratio is high.

The unmodified risk factors for prevalent TB infection were being older, being male, and being a specific ethnicity (African American/Hispanic/Mexican American vs. White). The modified risk factors included birthplace (US vs. foreign in NHANES study), having TB contact, having other diseases (diabetes and hepatitis B), having BCG vaccination, coughing > 3 weeks, smoking, and drinking. Some risk factors were only found to be statistically significant in one study such as higher BMI, larger family size, living with partner vs. not living with partner, poor living condition, leaving home for work or school, and being malnourished. There were risk factors which showed conflicts between studies such as level of education (Leo, 2017 and Gao, 2015) and social economic status (Ncayiyana 2016 and Malacarne 2016, Gao 2015).

Age and sex: Age was a consistent risk factors for prevalent LTBI in most studies. This may be explained by the cumulative exposure to TB patients overtime. Male gender was associated with higher prevalence of TB infection compared to women. This could be because men have more social activities than women and have more opportunities to exposure to TB patients.

Race/Ethnicity: African/Mexican American race were risk factor for prevalent LTBI in the US. There are many possible explanations for the difference in the observed association in prevalence of LTBI by race/ethnicity. There may be a true difference in how race/ethnicity affect the prevalence of LTBI or it could be due to innate or acquired characteristics. Poverty including limited access to quality health care, unemployment, housing, and transportation or language and cultural barrier can directly or indirectly increase the burden of LTBI in African/Mexican American. In addition, African American have the most severe burden of HIV of all racial/ethnic groups in the United States, which increase the risk of getting LTBI in this certain population.

Foreign-born vs. US-born: Foreign-born individuals have a higher age-specific prevalence of LTBI than US-born individuals. In a NHANES survey, researchers found that the mean age of immigration in foreign-born participants was 38 years old, foreign-born participants had a higher cumulative risk of LTBI due to higher burden of TB in their countries compared to the US. In 2010, 28% of the foreign-born population in the United States were born in Asia and 5 out of 10 leading countries of origin for immigration to the US were from Asia countries: China, Vietnam, India, Korea, and Philippines that have the highest burdens of TB disease worldwide. Asian individuals had the highest prevalence of LTBI among any of the groups studies (25% positive TST in Asian population compared to 5% positive TST in whole US population).

Having TB contacts: Of the 12 articles, 9 investigated the association between history of contacts with TB cases and LTBI. All articles showed that individuals who had contacts with TB patients had higher prevalence of LTBI than individuals who did not contact with TB patients. From a systematic review, a small proportion of TB transmission (<20%) was attributable to contacts with household TB cases (Martinez, Shen, et al., 2017). So, outside household or unknown TB contacts may play a large proportion of TB transmission.

Diabetes: The deadly link between diabetes and tuberculosis has been known for decades. One studies in Spain observed 69 (42%) of 163 patients had positive TST in diabetic patients (Negrato & Gomes, 2013). The double to triple higher proportion of LTBI or active TB were observed in diabetic patients compared to non-diabetic patients in many studies (Kim, Hong, Lew, Yang, & Lee, 1995; Martinez, Zhu, et al., 2017; Stevenson et al., 2007). Among Hispanic people aged 25-54 years, the tuberculosis risk which was attributable to diabetes was 25%, equivalent to that of HIV (Pablos-Mendez, Blustein, & Knirsch, 1997). In addition, there were two studies which provided evidence that the severity of diabetes (insulin dependence as indicators) predicted increased tuberculosis risk (Olmos et al., 1989; Swai, McLarty, & Mugusi, 1990).

Hepatitis: TB is considered as an immunodeficiency-related condition. There is a scare knowledge about the association between Hepatitis B or C and LTBI. Among 12 articles, only one study examined the association between hepatitis B and LTBI and this association was significant (Martinez, Zhu, et al., 2017). In literature, there were much more studies investigated the relation between hepatitis and active TB disease. It is acknowledged that liver cirrhosis (a consequence of hepatitis B and C) is associated with risk of active TB (Y.-T. Lin et al., 2014). It is observed that Hepatitis B and C and TB shared the same high risk populations such as homeless people, prisoners, and HIV patients. These diseases also have similar epidemiological risk factors (Awofeso, 2010; Reis et al., 2011). A nationwide cohort study analyzed healthcare data found that hepatitis C rather than hepatitis B was a risk factor associated with progression to active TB. This can be explained that hepatitis C core protein could bind and inhibit the tumor necrosis factor-alpha (TNF-α) receptor (Saito et al., 2006). As TNF-α is important cytokines for acute TB control (Kaufmann, 2002; Van Crevel, Ottenhoff, & Van Der Meer, 2002), the relation between HCV infection and TB disease can be speculated. Furthermore, HCV infection also has been linked to numerous diseases of immune dysfunction and possible mechanism known as B cell, T cell, natural killer cell, and dendritic cell dysregulation (King, Trabue, Yin, Yao, & Moorman, 2007).

Smoking: smoking was found to be a risk factor of acquiring LTBI in 4 out of 7 articles investigating this factor (Gao et al., 2015; Horne et al., 2012; Zhang et al., 2017). This adverse effect of smoking might explain the susceptibility of smoking population to TB infection. Smoking may attenuate host defense mechanisms. Nicotine could turn-off production of TNF-α by macrophages (Matsunaga, Klein, Friedman, & Yamamoto, 2002). Alveolar macrophage may have a key role in determining whether an individual develops LTBI following exposure to M. tuberculosis. It is found that macrophages from smokers may be less successful in controlling intracellular *M. tuberculosis* compared to never smokers (Shang et al., 2011).

Alcohol use: 3 out of 12 articles investigated the relation of alcohol use and LTBI. Only one study found that alcohol drinking lowered the risk of acquiring LTBI (Mack et al., 2009). The alcohol consumption was not clearly defined in the study conducted by Gao and his colleagues. A systematic review has shown that light to moderate alcohol consumption could help boost the immune system (Romeo et al., 2007). However, alcohol use disorder and addiction lowers and damages to the immune system. WHO reports that alcohol abuse increases the risk of tuberculosis disease threefold, and is also a strong risk factor for poor TB treatment adherence. People who abuse alcohol are less likely to eat regular or have healthy meals. Malnutrition adds additional risk to those who may contract TB. In conclusion, the effect of alcohol use might depend on the amount of drink daily and be affected by lifestyle of patients.

BCG vaccination: BCG is used in many countries with high prevalence of TB to prevent childhood tuberculous meningitis and military disease. However, BCG is generally considered to offer minimal or no protection effect when administered to previously unvaccinated adults (Colditz et al., 1995). The effect of BCG vaccination on interpretation of TST was controversial. Of 12 articles, BCG vaccination was examined in 6 articles. Four out of the six articles showed that BCG vaccinated individual had a higher prevalence of LTBI than individuals who did not vaccinated with BCG. BCG vaccination, especially if given in multiple doses, increased the likelihood of a positive TST and more recent BCG vaccination more likely increased the risk of TST positivity (Cook, Kuramoto, Noertjojo, Elwood, & Fitzgerald, 2006). It has been concerned that prevalence of LTBI may be overestimated by high rate of BCG vaccination in high burden countries. However, one study evaluated the effect of neonatal BCG vaccination on tuberculin skin test positivity in Uganda children exposed to infectious TB cases and found that BCG vaccination at birth had no important effect on the interpretation of the tuberculin skin test reactivity in Ugandan children (Musoke Mudido et al., 1999). In another study examining the distribution of TST test, they found a small effect of BCG vaccination on TST reading because the mean value of the lower distribution was 1.9 mm larger among vaccinated contacts compared with those who were not vaccinated (Woldu et al., 2021).

Public Transport: No articles investigate the role of transportation to prevent or incident TB infection. In settings with a high tuberculosis burden, TB transmission was argued to be more likely to occur outside household setting (Churchyard et al., 2017). Public transportation can be an important setting of transmission between age groups and may play a critical role in driving TB transmission in South Africa (Andrews, Morrow, Walensky, & Wood, 2014; Andrews, Morrow, & Wood, 2013). TB transmission via casual contacts in extra household setting has been documented, including while using public transportation such as buses, trains, airplanes (Edelson & Phypers, 2011; Mangili & Gendreau, 2005; Moore, Valway, Ihle, & Onorato, 1999; Yusuf et al., 1997). It is more likely that a passenger and his/her TB contacts shared the same public transportation. They were in speaking distance which enabled *Mtb* to transmit in such closed and limited space. This assumption is appropriate for what we found from literature. The annual risk of TB transmission was found to be high in public transport driver (20.3%), but low in the passenger on public transport (2.4%) (Hella et al., 2017). Being driver on public transport were a risk factor of tuberculosis disease (O. Horna-Campos, Bedoya-Lama, Romero-Sandoval, & Martin-Mateo, 2010) and time working in public transport was strongly associated with TB transmission in Peru (O. J. Horna-Campos et al., 2011). Cooperating with our findings, these evidences implied that TB occurred in public transportation, but only when passengers were proximity to TB cases or driver who spent a lot of time in this setting and had higher probability to be exposed to TB patients in speaking distance and the ideal condition in public transportation enabled *Mtb* transmit.

Air pollutants: There was a strong relationship between ambient air pollution exposures and TB incidence. The population attributable fraction to TB incidence by carbon monoxide was 1.6 to 12.2% and NO_x or NO_2 exposures was 1.2 to 9.8% (Y.-J. Lin et al., 2019). Indoor air pollution increased the risk of TB disease in a systematic review (H.-H. Lin, Ezzati, & Murray, 2007). The effect of air pollution on acquisition of LTBI was not understood.

Risk factors for incident LTBI

There was only one study investigated the risk factors associated with incident tuberculosis infection (Gao et al., 2016). This study investigated the prevalence of LTBI in a cohort at baseline and then retested subgroup of cohort who were negative in TST or IGRA test at baseline after one year of follow up. The incidence of TST conversion was 14.5% and IGRA conversion was 3.1%(Gao et al., 2016). This prospective cohort study only examined a limited number of factors. They found that being older, higher level of education and history of close contact with TB patients were risk factors for incident LTBI. Other factors including sex, income, smoking, alcohol use, BCG scar, and BMI were not statistically significant with acquisition of LTBI.

Table 2. 2 Studies investigated on burden of LTBI and associated risk factors in general population

Author, year	Study design, and population	Test used	Sample size	No. of LTBI (%)	Factors	Effect	Other factors†
Risk factors associated with prevalent LTBI							
Balkhy, 2017 (Balkhy et al., 2017)	Cross-sectional study 2010-2013, Saudi Arabia	TST and IGRA	1369	127 (9.3) by TST 124 (9.1) by IGRA	Increasing age	Increased risk	Family income, family size, region, marital status
					Being male	Increased risk	
					Divorced/widowed (vs. single or married)	Increased risk	
					Illiterates vs. primary/mid/high school University/above vs. primary/mid/high school	Increased risk	
					Smoking	Increased risk	
					Being retired (vs. military, civilian, housewife, student, unemployed)	Increased risk	
Leo, 2017 (Martinez, Zhu, et al., 2017)	NHANES survey 2011-2012, US	TST	4215	211 (5)	Increasing age	Increased risk	Sex, smoking, 2 hour plasma glucose, fasting plasma glucose, and BMI.
					Birthplace (Foreign vs. US)	Increased risk	
					Lower level of education	Increased risk	

					Household TB contact	Increased risk	
					Increasing family size	Increased risk	
					Increasing HbA1C	Increased risk	
					Diabetes vs. non-diabetes	Increased risk	
					Hepatitis B	Increased risk	
Zhang, 2017 (Zhang et al., 2017)	Cross-sectional study in rural residents, in 2013, in China	IGRA	21008	3954 (19)	Being male (aOR 1.26, 95% CI 1.14, 1.39)	Increased risk	Education, household income, alcohol use, and history of type 2 diabetes.
					Increasing age	Increased risk	
					Increasing BMI	Increased risk	
					Smoking	Increased risk	
					History of TB contact	Increased risk	
Ncayiyana, 2016 (Ncayiyana et al., 2016)	Cross-sectional study, from 2013 to 2014, in South Africa	TST	446	153 (34)	Being male (aOR 2.7, 95% CI 1.55, 4.7)	Increased risk	HIV infection, BMI, anemia, education, employment, smoking, alcohol use, secondary smoking, no. of room in house, ventilation, household density
					Increasing age	Increased risk	
					Marital status (living with partner vs. not living with partner)	Increased risk	
					Household contact with TB	Increased risk	
					Household SES	Increased risk	

					(High vs. Low)		
Malacarne, 2016 (Malacarne et al., 2016)	Cross-sectional study in 2011, on Brazilian Amazon	TST, cut off of positive 5 mm	263	106 (40)	Increasing age	Increased risk	Sex, household income, Education of head of household, No. of household residents, BCG, chest X-ray
					History of TB	Increased risk	
					Contact with TB patients	Increased risk	
					BCG vaccination	Increased risk	
					TB history in family	Increased risk	
					Malnourished	Increased risk	
					SES (Upper vs. lower)	Lower risk	
					Living condition (Better vs. poor)	Lower risk	
Gao, 2015 (Gao et al., 2015)	Baseline survey of the cohort study, in 2013, in rural China	TST (≥ 10 mm) and IGRA	21022	5878 (28) by TST 3955 (19) by IGRA	Being male (aOR 1.25, 95% CI 1.14, 1.36)	Increased risk	BMI
					Increasing age	Increased risk	
					Higher level of education	Increased risk	
					Family income per head (high vs. low)	Increased risk	
					Smoking	Increased risk	
					Alcohol use	Lower risk	
					Presence of BCG scar	Increased risk	

					History of close contact with TB patients	Increased risk	
Kizza, 2015 (Kizza et al., 2015)	Cross-sectional, from 2008 to 2009, in Kampala, Uganda	TST (≥ 10 mm)	283	140 (49)	Increasing age	Increased risk	Sex, education, marital status, religion, smoking, HIV infection, History of TB, and chronic cough.
					Leave home for school or employment	Increased risk	
Mancuso, 2015 (Mancuso et al., 2016)	NHANES survey from 2011 to 2012, in US	TST (≥ 10 mm)	6083	268 (4) by TST 292 (5) by IGRA	Race/ethnicity (Black/Hispanic vs. Non-Hispanic white)	Increased risk	Poverty
					Being male (aOR 1.6, 95% CI 1.2, 2.1)	Increased risk	
					Increasing age	Increased risk	
Horne, 2012 (Horne et al., 2012)	NHANES survey from 1999 to 2000, in US	TST (≥ 10 mm)	3843	339 (5)	Increasing age	Increased risk	Poverty, BCG, and education.
					Being male (aOR 1.78, 95% CI 1.19, 2.66)	Increased risk	
					Smoking	Increased risk	
					Birthplace (Foreign vs. US)	Increased risk	
					History of TB exposure	Increased risk	

					Race (Black/Mexican-American/ Other vs. White)	Increased risk	
Legesse, 2011 (Legesse et al., 2011)	Cross-sectional, in 2010, in the Amibara District of the Afar Region, Ethiopia.	TST (≥ 10 mm) and IGRA	587 by TST 570 by IGRA	183 (31) by TST 363 (62) by IGRA	Being male (aOR 1.8, 95% CI 1.2, 2.7)	Increased risk	Age, marital status, occupation, education (illiterate vs. literate), and contact with TB patients.
					Presence of BCG scar	Increased risk	
Doocy, 2008 (Doocy, Todd, Llainez, Ahmadzai, & Burnham, 2008)	A cluster survey in 8 Afghan provinces, in 2006, in Afghanistan	TST (≥ 10 mm)	11336	1700 (15)	Increasing age	Increased risk	Sex, ≥ 7 people sleeping per room, and cooking fire in sleeping room.
					Prior TB treatment/ contact	Increased risk	
					Presence of BCG scar	Increased risk	
					Cough duration > 3 weeks	Increased risk	
					Productive cough	Increased risk	
Cook, 2006 (Cook et al., 2006)	Cross-sectional study, Aboriginal Population Canada, from 1951 to 1996	TST (≥ 10 or 5 mm as positive in those without/with history of TB contact, respectively)	17615	4153 (25%)	Having TB contact	Increased risk	Age, sex, contact type with TB cases, age at first BCG, and time of first BCG
					BCG vaccination	Increased risk	
					No. of BCG vaccination (≥ 2 shots vs. 1 shot)	Increased risk	
					Time from most recent BCG to TST	Increasing time discrepancy, decreased risk	

Risk factors associated with incident LTBI							
Gao, 2016 (Gao et al., 2016)	Prospective cohort study from 2013 to 2015 in China	TST (≥ 10 mm) and IGRA	13580	1654 (14.5) by TST 390 (3.1) By IGRA	Increasing age	Increased risk	Sex, income, smoking, alcohol use, BCG scar, and BMI
					Middle/high school vs. primary school	Increased risk	
					History of close contact with TB patient	Increased risk	

† Other factors: the factors investigated in the studies, but show no statistically significant associated with LTBI

Locations, Settings, and Social Network Related to TB Transmission

TB transmission is generally categorized as having occurred in one of the following locations: (1) homes; (2) healthcare and congregate settings, including hospitals, clinics and prisons; and (3) community-based setting, including workplaces, public transport (For example, buses and trains) and other congregate locations where transmission may occur between individuals who may or may not know one another.

Homes: TB was transmitted between individuals by aerosols and that close contact, as with household members, was associated with a high likelihood of transmission. Several meta-analyses of contact investigations support the elevated risk of TB infection among household contacts, with approximately half of household contacts having TB infection (Fox, Barry, Britton, & Marks, 2013; Kakaire et al., 2020; Morrison, Pai, & Hopewell, 2008). The prevalence of LTBI among household contacts of TB cases was homogeneous because the overall secondary attack rate for tuberculosis infection was 47% and did not vary widely by age, HIV infection status, and BCG vaccination (Whalen et al., 2011). Similarly, the homogeneous risk of TB infection was confirmed in another study in 10 years later. The prevalence of LTBI among household contacts of TB cases did not vary by age (Kakaire et al., 2020). While household contact screening is high yield for identifying additional cases of TB infection and disease (J. Sekandi et al., 2014), a number of recent studies suggest that the proportion of transmission that actually occurs in the household may have been overestimated in high burden settings. Molecular studies suggest that only around 8% to 19% of transmission to adults occurs within-household, or between known social-contacts. In one study-based community in Cape Town, it was estimated that only 8% of tuberculosis resulted from transmission between household members (Middelkoop et al., 2014). In another, during the early years of the South African HIV epidemic, 19% of clustered tuberculosis could be attributed to household transmission (Verver et al., 2004). Elsewhere in KwaZulu-Natal South Africa, ‘prolonged or intimate contact’ was identified between only 12% of molecularly linked cases (Wilkinson et al., 1997). A recent meta-analysis that included 26 studies found that household exposure to TB cases significantly increased the odds of TB infection on individual level, but household contacts accounted for less than 20% of transmission at population level (Martinez, Shen, et al., 2017). A study compared household and extra-household contacts of both TB case index and control index in terms of prevalence of TB infection. The researcher found that most contacts of TB cases do not have adequate contact with index case to experience additional risk for infection, but appear instead to acquire infection through unrecognized exposures with other TB cases in the community (Kakaire et al., 2020). Modelling studies, in conjunction with social mixing and ventilation studies, also suggesting that a minority of TB transmission – with estimated ranging from 16% to 30% - occurs in household in high-burden settings such as South Africa (Andrews et al., 2014) and Peru (Brooks-Pollock, Becerra, Goldstein, Cohen, & Murray, 2011). Furthermore, a recent study that modelled social-contact behavior using data from Cape Town, South Africa, determined that household, repeated, and non-repeated contacts contributed 36%, 13%, and 51% of contact time, and 13%, 8%, and 79% of disease, respectively.

Nevertheless, home-based contact investigations have a proven record of success for identifying TB infection and disease among household contacts. Recent data indicated a prevalence of TB was 1-6% among household contacts (Guwatudde et al., 2003), while the prevalence of TB in general population in high burden countries was around 0.1 to 0.7% (J. Sekandi et al., 2014; Yuen et al., 2015). Therefore, the prevalence of TB among household contacts was at least 10-fold greater than that in the general population. Given that the majority of transmission occurs outside the household, the high yield of contact investigations suggests that household contacts may share other risk factors for TB – whether a shared risk of infection from a similar social milieu or shared risk of progression from infection to disease based on malnutrition or genetic predisposition. Additional benefits of household contact tracing, beyond the identification of co-prevalent cases of active TB, include the administration of TB preventive treatment, and antiretroviral therapy for HIV-infected individuals. Therefore, household contact investigation remains an essential element of TB control.

Healthcare and congregate settings: A systematic review of over 50 studies identified substantial risk of TB infection among healthcare workers ranging from 33% to 79% in various studies, with a pooled prevalence estimate of 54% (Joshi, Reingold, Menzies, & Pai, 2006). The prevalence of LTBI in healthcare workers increased by 1.5 (95% CI 1.0 to 2.2) to 2.4 (95% CI 1.1 to 5.0) times with employment duration of additional one year. The prevalence of LTBI was 3-fold higher with ≥ 10 years of employment. The annual risk of TB infection in healthcare workers ranged from 3.9% to 14.3%, after accounting for the incidence of TB infection in the general population.

Incarcerated persons also have elevated incidence of LTBI and TB, with a series of studies from Brazil indicating that during a 4-year period in a medium-size city in Brazil, 25% of TB cases occurred among prisoners, who represented < 1% of the population. It is showed that 54% of incident cases of TB among non-incarcerated community members could be connected with Mtb strains circulating in local prisons based on shared genotypes (Sacchi et al., 2015). With the genetic linkages observed and the high rates of TB disease among prisoners and ex-prisoners, the prison served as major reservoirs of TB for the general population. In another study, the prevalence of LTBI was around 8% in new prisoners for both sex (within the first month of incarceration), which indicated that large number of individuals who enter prison are susceptible to TB infection

(Carbone et al., 2015). This study estimated that prevalence among inmates increased by 5% with each year of incarceration.

Community-based settings: Given that a minority of transmission occurs among household contacts in high-burden settings, the majority of transmission presumably occurs in a wide range of community-based settings (e.g. marketplaces, worship center, public transport, etc.), between casual contacts or individuals not known to one another. Thus, interventions focused on households and nosocomial settings while important and high yield, will not be sufficient to interrupt the majority of transmission events. Interventions targeted to community-based settings with high rates of transmission, on the other hand, may translate into substantial reductions in TB infection incidence and active TB incidence. However, to date, there have been no studies designed to explicitly confirm the presence or locations of community transmission. Rather, the evidence for community-based transmission is garnered primarily from the lack of evidence for transmission in homes and hospitals.

A population-based genotyping study in China found limited evidence for epidemiologic links among clusters of genotypically related cases with only 15% of isolates being clustered and none of TB cases reported having contacts with other members within the same cluster (Wang et al., 2014). This study also identified small cluster sizes ranging from two to four TB cases. Low proportion of clustering combined with small cluster sizes can indicate a more important role of reactive disease compared with recent transmission. These findings underscored the role of casual contact or reactivation of latent TB as a driving factor maintaining the TB epidemic in rural China with high burdens of tuberculosis.

Tools to Study TB Transmission

Historically, annual case notification rates and prevalence surveys of LTBI, particularly among children and adolescents, have also been used to measure transmission. While these approaches cannot identify specific transmission events and locations, they provide valuable insight into population-level temporal trends in exposure to infection and can be used to estimate the impact of interventions to reduce transmission. TB transmission in low-burden settings has also been studied to uncover point-source outbreaks, where TB patients are interviewed about people contacted and places visited during their infectious period. In high burden settings, household contact surveys have been used to study rates of transmission between index cases and their household contacts (Fox et al., 2013; Guwatudde et al., 2003; Morrison et al., 2008). However, these approaches have some limitations, in that they presume transmission based upon an epidemiologic connection between two individuals and evidence of TB infection or disease in the contact. The advent of molecular epidemiology and sophisticated tools to characterize ventilation and aerosols, alongside the expansion of geospatial techniques have significantly enhanced our ability to study and understand transmission.

Molecular epidemiology (genotyping to WGS): Strains resulting from the recent transmission should belong to the same genotype (clustered), whereas those from reactivation will have a unique signature in the population. By identifying related Mtb strains, genotyping has been utilized to determine the likelihood of transmission between individuals.

One of the most common genotyping methods used are IS6110-RFLP, followed by mycobacterial interspersed repetitive unit-variable number tandem repeat (MIRU-VNTRs) typing and spoligotyping. IS6110-RFLP has been considered as the standard method for genotyping of Mtb in 1990s. It works on the principle of copy number variation of insertion sequence IS6110 in different clinical isolates. Despite its high discriminatory power, it has technical difficulties in data production and comparison of results or sharing the data among different laboratories.

Spoligotyping is considered the simplest, rapid, and cost-effective technique that has been used to define the predominant and growing number of important clinical Mtb clones or strains. However, spoligotyping has some limitations in differentiating the Bejing strains, which reduces its ability to explore transmission dynamics of Mtb in China.

MIRU-VNTR typing is currently widely used method, which consists of variable sizes of repeat regions in the genome. The discriminatory power of this method, as well as IS6110-RFLP, has been reported by using a combination of 15/24-loci spectrum. MIRU-VNTR typing offers high-throughput typing, is convenient, and allows easy sharing of digital data for comparison among different laboratories. However, many of VNTR loci in the standard 15-/24-loci spectrum have limited discriminatory power among the Beijing strains.

In low-burden settings population-based genotyping in the context of TB outbreaks has allowed for the identification of transmission that occurred not only between named contacts, but also between individuals not known to one another. For example, in two US-based outbreak investigations, genotyping facilitated the identification of epidemiologic links between individuals not known to one another but who frequented the same restaurants, bars or worship centers (Perri et al., 2011) (Ijaz, Yang, Matthews, Bates, & Cave, 2002). Although Mtb genotyping has been less used in high burden settings, presumably due to cost and limited laboratory capacity, there are several studies from high-burden setting where genotyping has enhanced our understanding of TB transmission. A study conducted in South Africa utilizing RFLP analysis indicate that the presence of an adult with infectious tuberculosis in the same house as a child with tuberculosis does not necessarily imply adult-to-child transmission. Young children may be infected from other TB cases in either community or the household harboring the same strains. Therefore, in contrast to low burden settings, where transmission events are relatively isolated and genotypically related cases are often presumed to represent transmission, genotyping may be less sensitive in high burden setting, where TB is endemic and many cases may share a genotype, especially in regions with specific dominant genotypes.

WGS of Mtb isolates has emerged as a powerful tool to advance our ability to study TB transmission and define outbreaks. In a systematic review, sensitivity of WGS to identify epidemiologically linked isolates is high, reaching 100% in eight studies with specificity (17% - 95%) highly dependent on the settings. By accounting for the sequential accumulation of SNPs, WGS has the potential to reveal microevolution and chains of transmission, not simply clusters of related cases. For example, WGS was used to investigate an extended TB outbreak in Canada and revealed two genetically distinct lineages of Mtb, despite identical MIRU-VNTR genotypes, suggesting two concomitant outbreaks (Gardy et al., 2011). In addition, the high resolution of WGS is particularly useful to confirm or exclude the possibility of direct transmission events defined by other typing methods (Luo et al., 2014). Also, WGS can be potentially used to distinguish between true relapses and re-infections.

The integration of WGS data with epidemiologic data about individuals' social interactions and movements can provide compelling evidence for transmission events by establishing the opportunity for transmission, based upon an epidemiologic connection, and a closely related Mtb strain. This understanding of where and between whom transmission is occurring can help inform more directed public health interventions to interrupt future transmission. In addition to enhancing our ability to construct transmission networks, population-level research can also help to address outstanding methodology questions about the interpretation of WGS data such as the appropriate

SNP threshold for identifying transmission, the mutation rate of Mtb in different settings, within-host evolution of Mtb and mixed infection with multiple strains.

Geospatial analysis: There has also been a dramatic increase in the use of geospatial data to understand disease patterns and transmission over the last several decades. Geospatial data can include a range of data types including: self-report of home residence, administrative data on neighborhoods and districts, health center, hospital location data and global positioning system (GIS) coordinates. In the context of TB, geospatial analyses have helped to identify areas of spatial aggregation and hotspots for TB transmission in numerous settings. Many studies have mapped TB patients' homes to identify spatial aggregation. These data can then be used to guide interventions or focus further investigation. For example, a study conducted in Mexico using both residential and healthcare center addresses and genotyping to identify the hotspot in the area (Blanco-Guillot et al., 2018). The local spatial analysis showed that hotspot for clustering was located in a municipality.

There are several TB outbreaks where individuals were asked about where they spend their time, providing a more comprehensive sense of their activity space, which enabled the identification of areas of transmission beyond their primary residence. In Houston US, individual bus route, including one route servicing the local hospital, were found to be risk factors for endemic Mtb clustered strains and the routes themselves geographically connect the census tracts previously identified as having endemic TB.

Mobile phone data and wearable GPS devices are another emerging and promising source for geospatial data. These devices have the potential to provide near-continuous data about an individual's movement patterns and interactions with other individuals, with the added advantage of not being subject to recall bias. However, these benefits must be balanced against some of the limitations from these data sources, including signal loss, cellular tower density, not wearing the device, access to cellphone data from multiple companies, and complicated analysis. Also, it is worth noting that structured interviewed have been compared to GPS devices or phone records in several studies, and that interviews provide reasonably accurate estimates of location visited (> 70% concordance) (Paz-Soldan et al., 2014; Williams, Thomas, Dunbar, Eagle, & Dobra, 2015). However, a challenge in characterizing movement patterns relevant to TB transmission is that individuals are often exposed to TB months to years prior to their development of active disease and then they are often ill for some months prior to diagnosis. There may be a discrepancy in an individual's movement patterns between when they are infected and diagnosed.

Social contacts and ventilation studies: Advances in indirect measures of transmission potential are also a significant advance in recent years. For example, studies of social contacts, where the amount of contact between individuals is quantified, demonstrate that residents spent a large proportion of their time indoors which did not vary across age strata, but type of locations and the number of contacts met in those locations varied markedly across age strata (Wood et al., 2012). Additionally, five main types of locations (own households, other households, school, workplaces, and transport) contributed the 97% of total indoor time and 80% of total indoor contacts in South Africa (Wood et al., 2012). Rate and types of social contacts vary by age and demography – for example, children and young adults are most likely to be infected from school and workplace contacts (Andrews et al., 2014). The findings of these studies should be viewed as hypothesis-generating for future studies to empirically confirm whether transmission is indeed occurring in community settings such as schools, workplaces, and public transport. Furthermore, it is likely that social contacts patterns vary across cultures, so it will be essential to characterize these patterns at local level to direct initial interventions or target further research.

Ventilation studies, with devices that quantify ambient CO_2 levels as a proxy for rebreathed air and transmission potential, and new technologies to characterize cough aerosol production also represent new directions to enhance transmission research. Room ventilation and social contact patterns predict whether other individuals are exposed to *M tuberculosis* that has been aerosolized. The Wells-Riley equation is used to model the transmission of respiratory pathogens, such as *M tuberculosis*, that are spread by crowd rather than close contact. Transmission risk in a defined space over time t is modelled as a Poisson process: Probability of transmission = $1 - e^{-Iqpt/Q}$

where I is the number of infectious individuals present, q is the rate at which infectious individuals produce quanta, p is the rate at which susceptible individuals breathe, and Q is the rate at which air from the space is exchanged with uncontaminated air (ventilation). Riley and colleagues defined quanta as "the number of infectious airborne particles required to infect which may be one or more airborne particles". The parameter q is often assumed or fitted to data.

The Wells-Riley equation has several important limitations. The equation assumes that air in the space is fully mixed and does not account for the heterogeneity in infectiousness or susceptibility of infection. Adaptations to the equation have been published. One widely used variant uses a rebreathed fraction, the fraction of inhaled air that has been exhaled previously by someone in the building (Rudnick & Milton, 2003). This process avoids the need to measure Q, which can be technically challenging. In many settings, spatial and temporal variations in CO_2 concentrations are substantial. Not obtaining contemporaneous CO_2 measurements from directly outside the buildings studied might be reasonable in the absence of alternative CO_2 sources and where wind speeds restrict local spatial and temporal variation in CO_2. The absence of such contemporaneous measurements would not be reasonable in other circumstances.

Ventilation studies have recently shown that there are a limited number of air exchanges in many locations where casual contact occurs, such as schools and churches (Andrews et al., 2014; Patterson et al., 2017; Taylor et al., 2016). In such spaces, the likelihood of transmission from an infectious person to others is increased, given the high proportion of rebreathed air. It is important to prospectively study transmission rates and rebreathed air to validate whether ambient CO_2 levels are accurate proxy for transmission potential.

Table 2. 3 Articles estimate the risk of TB infection in different settings

Authors, year	Country	Results
Hella, 2017 (Hella et al., 2017)	Tanzania	Using a modified Wells and Riley equation to estimate annual risk of TB infection is • 42% in prison inmates • 20% in drivers of public transportation • 5% for trader and 0.5% for customers • 2 % in passengers in public transport • Public school (4%), nightclubs (2%), and religious and social halls (1%)
Patterson, 2016 (Patterson et al., 2017)	South Africa	Hot spot analysis was performed to identified the communal buildings with high rebreathed air volumes. A clinic, two schools, and a library revealed the most intense clustering if high rebreathed air volumes. In conclusion, school is a TB transmission hot pot.
Taylor, 2016 (Taylor et al., 2016)	South Africa	The annual risk of TB infection was 17% for healthcare worker in a clinic waiting room and 11% for students in classrooms.
Chamie, 2015 (Chamie et al., 2015)	Uganda	Using molecular epidemiology, geospatial, and social network data from adult TB cases, they quantified person-time spent at high-risk locations across rural Ugandan community and

		determined the most likely sites of recent TB transmission to be healthcare and social venues.
Dodd, 2014 (Dodd et al., 2015)	Zambia and South Africa	This article models the incidence of TB infection among adults using data on infection incidence in children, disease prevalence in adults, and social contact patterns. Location and duration of contacts • Most close contact occurred at home (in Zambia 51% and South Africa 73%). • Close contacts occurred in other homes, outside, in work buildings, and in schools (12%, 9%, 5%, and 3%, respectively). • Casual contacts, 19% occurred in church, 16% in shops, 15% in work building, and 12% in other homes. Contact duration by location shows shorter contact episodes in shops, churches, and bar than at work or school Estimated incidence of *M. tuberculosis* infection • Annual infection incidence was 6% to 10% in South Africa and 3 to 7% in Zambia • The estimated overall percentage of infections due to contact with adult men was 57% in Western Cape and 66% in Zambia.
Andrews, 2013 (Andrews et al., 2014)	South Africa	This article uses extensions to the Well-Riley model of tuberculosis transmission, using exhaled carbon dioxide as a tracer gas, to describe transmission patterns, after accounted for social contact structure and role of environment. The annual risk of TB transmission overall was 6.6%. The risk varied from 4.4% among children aged 5-9 to 9.1% among young adults aged 15-19. The majority of tuberculosis transmission was estimated to occur outside of one's own household, for all age groups (percentage transmission with own household is 16%).

		School accounted for 25% of infection among children aged 0-14 years and 50% of infection among children aged 15-19%. There was 41% of TB transmission among adults occurred in workplaces. Public transit accounted for 8% to 35% of transmission in all age group.
Andrews, 2012 (Andrews et al., 2013)	South Africa	This article used a modified Well-Riley model for airborne disease transmission to estimate the risk of tuberculosis transmission on public transport. Among daily commuters, the annual risk of tuberculosis infection was 4-5% and was highest among taxi commuters.

Impacts of SAR-CoV-2 on studying TB transmission

COHSONET study was conducted from 2014 to 2018, which were 2 years before the SAR-CovV-2 pandemic. This part will discuss about how SAR-CoV-2 pandemic could affect the results of COHSONET study if it conducted amid the pandemic. Firstly, people were more likely to stay at home and reduced most of their social activities during the pandemic. This would increase TB transmission among household members of TB cases and decrease TB transmission in the community. As the majority of TB transmission occurs in the community, the pandemic would cause a decrease in annual risk of TB infection. Secondly, measuring the history of exposure to TB patients during follow up would be affected as participants were more likely to work at home if possible or could wear medical mask if working outside the home. This would modify the transmission process completely, which reduce airborne transmission for both TB and SAR-CoV-2. Thirdly, social behaviors regarding to drinking settings, healthcare facility attendance, transportation use, history of travelling would be changed. Peoples could not gather to drink or travel because of lockdown or restriction on mobility. They also did not visit healthcare facility for checking up their health except for urgent or necessary reasons. Public transportation could be closed during the pandemic. Fourthly, we could not measure the amount of time spent in community settings as they could spend all of their time at home. In conclusion, if our study conducted during the pandemic especially during lockdown, we would fail to measure both cumulative incidence of TB infection and exposures in daily life.

CHAPTER 3

INCIDENCE OF LATENT TUBERCULOSIS INFECTION IN AN AFRICAN CITY: POPULATION-BASED PROSPECTIVE COHORT STUDY [1]

[1] Quach HTT, Zalwango S, Sekandi NJ, Dobbin KK, Naeher L, Castellanos ME, Kakaire R, Kiwanuka N, Whalen CC. To be submitted to Lancet Public Health.

ABSTRACT

Objectives: This study was to estimate incidence of latent tuberculosis infection (LTBI) and HIV infection, and evaluate risk factors for new *Mycobacterium tuberculosis* infection.

Method: We conducted a prospective, community-based cohort study of adult aged from 17 to 60 without latent tuberculosis infection (LTBI) in Kampala, Uganda from 2014 to 2016. After one year of follow up, participants were retested with TST and HIV rapid test to evaluate new infection. Multivariate Poisson regression with robust error variance was used to identify risk factors for TB transmission.

Results: We enrolled 1681 participants. Of these, 406 (24%) were lost to follow up. Among 1275 with available follow up TST results, proportion of male was 58.6% and the median (IQR) of age was 24 (20 – 29). Overall annual risk of LTBI was 11.8% (95% CI 10.1% – 13.8%). Annual risk of LTBI among men was 15.2% (95% CI 12% – 18.4%) and among women was 9.4% (95% CI 7.3% – 11.5%). The annual risk of infection among former/current smokers was 22.7% (95% CI 10.3% – 35.1%), among heavy alcohol users was 19.7% (95% CI 10.4% – 29.0%), among HIV-infected individuals was 19.3% (95% CI 9.1% – 29.5%), and among participants who have been in contact with TB patient over one year before enrollment and during follow up was 20.5% (95% CI 7.8% – 33.2%). The prevalence of HIV infection was 4.7% at baseline. The cumulative incidence of HIV infection was 1.3% with median of 379 follow up days. In multivariate analysis, being older, male sex, non-religious Roman Catholic affiliation, and have been in contact with TB patients were risk factors associated with acquisition of TB infection. Sex difference in acquisition of TB infection was modified by ever knowing anyone with TB status or age groups.

Conclusion: TB transmission rate in African urban setting was high. Identification of high risk individuals and prophylaxis treatment for them is crucial component of ending TB. Preventive

therapy should be targeted on former/current smokers, heavy alcohol users, and subjects being contacts of TB patients for long period of time as these persons are at the same risk of acquiring TB infection as HIV-infected subjects.

INTRODUCTION

An estimated 10 million TB cases and 1.4 million deaths occurred worldwide in 2019 (WHO, 2020b). This makes TB the tenth leading cause of death, ranking above human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) in the world. According to WHO 2020, Uganda was one of 30 high TB/HIV burden countries. The prevalence of HIV infection in Uganda was 5.7% ("HIV and AIDS in Uganda," 2020). The overall incidence rate was estimated at 204 per 100,000 population, of which 40% were estimated to be co-infected with HIV (WHO, 2018b). These statistics suggest that TB burden in Uganda was fueled by both progressions from latent tuberculosis infection (LTBI) to active TB with a huge part due to HIV-infection and ongoing *Mycobacterium tuberculosis (Mtb)* transmission.

Latent tuberculosis infection has been defined as a state with persistent immune responses to *Mtb* antigens without evidence of manifestation of clinical symptoms (Mack et al., 2009). Nearly one fourth of the world's population is infected with LTBI, representing a large reservoir of people at risk of progression to active TB disease (WHO, 2018b). About 5-10% of people with LTBI progress to active TB disease at some points in their lifetime, with the majority developing TB disease within 2-5 years of initial infection unless they were diagnosed and treated with antibiotic drugs (D. B. Young et al., 2008). To date, studies on LTBI have mainly measured the burden or prevalence of LTBI on high risk population such as children, household contacts of TB cases, healthcare workers, and prisons (Chandrasekaran et al., 2018; Hanifa et al., 2009; Janagond et al., 2017; J. Young & O'connor, 2005), and very few studies were on general population or community (Kizza et al., 2015; Ncayiyana et al., 2016). In these studies, the burden of TB was estimated by the prevalence of LTBI from surveys or cross-sectional studies, ranging from 12% in Mexican children to 89% in gold miners in South Africa. There has been a lack of study on estimating annual risk of TB infection (ARTI) in general population which is a key epidemiological indicator of the extent of TB transmission in a community over one-year period. Annual risk of LTBI can be estimated by direct methods that derived from the follow up of susceptible TB infection cohort or indirect methods that derived from the prevalence of tuberculosis infection. Annual risk of TB infection measured by indirect methods were inaccurate and biased. There was a predominance of studies using indirect methods to measuring ARTI, compared to direct methods. In sub-Saharan Africa, the devastating synergy between TB and HIV co-infection was so huge burden on public health that the resources available for TB control failed to restrain new TB cases caused by HIV infection. We therefore estimated the incidence of LTBI and HIV infection in urban population, and examined the risk factors associated with new *Mtb* transmission in Kampala, Uganda.

METHODS

Study population and measurements

We performed a prospective study within a cohort of adult African individuals aged from 17 to 60 years old confirmed to be free from tuberculosis infection. Between June 2014 to June 2016, a cohort of 1681 individuals was recruited from residents of Rubaga division of Kampala, Uganda. The inclusion criteria were: Tuberculin skin test (TST) below 5 mm at baseline, age between 17 and 60 years, and no signs or symptoms of active tuberculosis. A standard evaluation was performed to assess risk of acquiring a new tuberculosis infection at baseline and quarterly visits. At one year, participants were retested with TST to detect new infection defined as TST conversion. We planned to recruit 2000 participants and follow them for one year. To estimate sample size of 2000 participants, we assumed that 5% of participants converted to TST positive. However, we were not able to enroll 2000 participants in reality, and thus had to increase the follow up time to ensure power of study. Participants who were negative with TST at the end of one year, were asked to extend their follow-up time to 2 years.

Demographic, social, and clinical characteristics were obtained through interviews performed by trained field workers using standardized questionnaires. History of exposure to TB patient was collected at baseline and for every 3 month visits. TST was performed by placing 5 tuberculin units of purified protein derivative on the left forearm of each participant using the Mantoux method. Two field workers independently read the diameter of induration within 48 to 72 hours. The diameter of the skin test induration was measured using the "ball-point" technique with digital calipers to reduce digit preference bias. HIV testing was performed following the Uganda Ministry of Health National Testing algorithms. All participants were administered a Determine HIV-1/2 and a HIV 1/2 STAT-PAK; a Uni-gold HIV test was performed if there were discrepant results for the initial tests.

In HIV-seronegative subjects, a TST conversion was defined as having a second tuberculin skin test reading of 10 millimeters or greater with an increase in reaction of six millimeters or greater from the first to the second reading. In HIV-seropositive subjects, TST conversion was defined as having a second tuberculin skin test reading of five millimeters or greater with an increase in induration of three millimeters or greater from the first to the second reading. If the above conditions were not met, subjects were classified as persistent skin test negative.

Analytic strategy

Baseline characteristics of the study population and the subset of subjects with available repeated TST results were summarized with proportions and measures of central tendency. The distribution of TST induration at follow up was categorized as 0 mm, 0.1 to 4.9 mm, 5 to 9.9 mm, 10 to 14.9 mm, and 15 mm or more and then summarized with proportions.

Incidence of TST conversion and HIV infections were estimated by two methods: simple cumulative incidence and incidence density. Cumulative incidence of TST conversion and HIV infection were estimated as proportion with 95% confidence intervals. To estimate cumulative incidence of TST over study period, we used TST results with the longest follow up time. To estimate annual risk of LTBI (cumulative incidence of TST conversion over 12 months of follow up), we restricted to TST results within 12-month period. A sensitivity analysis for cumulative of TST conversion was conducted by adjusting for loss to follow up, booster effect, and false-positive comparing to QFT-GIT. In the same study, we estimated that the prevalence of boosted TST reaction was 2% (J. N. Sekandi et al., 2018). Also, of TST converters with increment ≥ 15 mm, 79% had positive QFT-GIT and of TST converters with increment < 15 mm, 50% had positive QFT-GIT (Castellanos et al., 2018). In estimation of incidence density of TST/HIV, we used the date of retesting TST/HIV correspondingly or last date seen to obtain follow up time.

The Poisson regression model with robust error variance was used as it is a better approach for estimating relative risks for cohort studies with common binary outcome compared to using logistic regression (Zou, 2004). We performed univariate analysis to estimate crude relative risks for association between TST conversion and a set of variables. The factors that were associated with TST conversion in a univariate analysis with p-value ≤ 0.10 were included in multivariable regression analysis. The quasi-likelihood under the independence model criterion (QIC) was applied to compare models and determine the risk factors that showed the best model fit. Lower QIC value indicated a better model fit, but there was no test for statistical significance of the differences. To explore potential interactions, a global test for two-way interactions between factors included multivariate analysis and all baseline risk factors was performed and found to be significant at the 10% level. Multivariate analysis with potential interaction terms was tested with statistically significant level at the 5%. R version 3.6.1 was used for all analyses.

Ethical considerations

Written informed consent was obtained from all participants prior to study inclusion. Institutional review board clearance was obtained from Ethics Committee at Makerere University School of Public Health and the University of Georgia. Tuberculin converters were referred for evaluation of tuberculosis by study medical personnel. If tuberculosis was suspected, the participant was referred to the National Tuberculosis Control Program for treatment, otherwise they were offered isoniazid treatment by the study personnel.

RESULTS

Study population characteristics

From June 2014 to June 2016, we screened 8552 persons and found out 2338 eligible individuals. 1681/2338 (72%) participants aged 17 to 60 with TST < 5 mm were enrolled. A total of 406 (24%) with loss of follow up was identified by the end of study period (Figure 3.1). Except for history of having been contact with TB patient during follow up, characteristics of participants with available follow up TST results were the same as that of participants with loss of follow up. The participants with available TST results at follow up were more often to be in contact with TB patient during follow up than the participants without TST results at follow up (table S3.1).

Among 1275 participants, the median age was 24 years (IQR 20 – 29). The proportion of male was 41%. The prevalence of HIV-infection at baseline was 5%. Roman Catholic religion accounted for 40%. Most of participants were BCG vaccinated (92%) and have never smoked (96%). The proportion of participants consuming alcohol was 21% including 15% light users and 6% heavy users. In terms of exposing to TB patients, 21% of participants had ever known a TB patient and 9% of participants had ever lived with a TB patient. The proportion of participants who have been in contact with a TB patient either over one year before enrollment or during follow up, or both was 18% (Table 3.1).

Incidence of LTBI and HIV infection

Of 1275 participants with available repeated TST at the end of study, the TST indurations were 0 mm for 77.8% of participants, 0.1 to 4.9 mmm for 3.3% of participants, 5 to 9.9 mm for 3.9%, 10 to 14.9 mm for 9.7%, and 15 mm or more for 5.3% (Table 3.3). At the end of study, we detected 194 incident LTBI cases, which translated to a cumulative incidence of 15.1% (95% CI 13.2% - 17.2%) with median 379 days of follow up. There was no participant that was known to have developed TB disease. At the end of 12 months, repeated TST results were available for 1213 participants of whom 143 got TB infection, suggesting annual risk of infection of 11.8% (95% CI 10.1% - 13.8%) (Table 3.2). Annual risk of LTBI reduced to 10.0% after adjusted for booster effect, to 6.9% after adjusted for false-positive when comparing to QuantiFERON blood test, and to 5% after adjusted for both (Table S3.3).

When stratifying annual risk of infection by participants' characteristics, the highest annual risk of LTBI was found in former/current smoker (22.7%, 95% CI 10.3% - 35.1%), following by participants having contact with TB patients before enrollment and during follow up (20.5%, 95% CI 7.8 - 33.2%), heavy alcohol users (19.7%, 95% CI 10.4% - 29.0%), and HIV-infected participants (19.3%, 95% CI 9.1% - 29.5%). Male experienced a higher annual risk of LTBI compared to women (15.2%, 95% CI 12.0% - 18.4% vs. 9.4%, 95% CI 7.3% - 11.5%). As age increasing, the annual risk of infection increased with 15.4% (95% CI 11.1% - 19.7%) for age group 30 – 60 years old (Table 3.4).

At baseline, 79 (4.7%) HIV infected cases were identified. During study period, 417/1602 (24.8%) participants lost to follow-up or refused repeated HIV rapid test. Of 1185 susceptible individuals for HIV infection, 22 got infected, suggesting a cumulative incidence of 1.9% (95% CI 1.2, 2.8) with median 379 days of follow up (Table 3.2).

Factors associated with incident LTBI

The univariate analyses for predictive variables related to participants' characteristics are shown in table 3.5. Age, sex, monthly income, religion, smoking, alcohol users, and HIV infection status at baseline were associated with incident LTBI. Older age was significantly associated with higher risk of LTBI (22 – 29 years RR 1.85, 95% CI 1.29 – 2.65 and 30 – 60 years RR 2.27, 95% CI 1.55 to 3.34) compared to younger age 17 – 21 years old. Male had 1.47 times higher risk of acquiring LTBI (95% CI 1.14 – 1.91). Non-religious Roman Catholic had higher risk of acquiring LTBI (RR 1.45, 95% 1.09 – 1.92). HIV infection increased risk of developing LTBI (RR 1.66, 95% CI 1.05 – 2.62). Former or current smoker had a higher risk with RR 1.96 (95% CI 1.23 to 3.11). Compared to non-users of alcohol, only heavy users showed a statistically significant higher risk of acquiring LTBI (RR 1.66, 95% CI 1.08 – 2.55). However, in multivariate model, monthly income, smoking status, alcohol use, HIV infection status at baseline did not show a statistically significant association with development of LTBI. These associations were confounded by sex and therefore disappeared in multivariate models.

The univariate analyses for predictive variables related to history of exposure to TB patient were shown in table 3.6. Ever known TB patients, have been in contact with TB patients, sleep in the same bedroom with TB patients, and knew contact with TB receiving treatment were statistically significant association with TST conversion in univariate analysis. However, in multivariate model, knew contact with TB receiving treatment did not show a statistically significant association with development of LTBI. This association was confounded by have been in contact with TB patients and therefore disappeared in multivariate model. “have been in contact with TB patients” was highly correlated with “sleep in the same bedroom with TB patients”, so only “have been in contact with TB patients” was included in multivariate model. After adjusted for age, sex, religion, have been in contact with TB patients in both before enrollment and during follow was associated with acquisition of LTBI (aRR 1.81, 95% CI 1.13 – 2.90). Although ‘sleep in the same bedroom with TB patients’ was dropped in multivariate model, 40% of participants sleeping in the same bedroom with TB patients over one year before enrollment developed LTBI. Interestingly, we observed the gradient effect of variables related history of TB exposure on incident LTBI. History to TB exposure one year before enrollment was more predictable about incident LTBI than history of TB exposure during follow up (Figure 3.3).

Multivariate model including interactions was shown in table 3.8. The interactions between age and sex demonstrated the higher risk of acquiring LTBI in men compared to women in age group 22 to 29 (aRR 1.62, 95% CI 1.13 – 2.31) and age group 30 to 60 (aRR 1.65, 95% CI 1.04 – 2.61), but did not in age group 17 to 21 years old (aRR 0.96, 95% CI 0.5 – 1.84). Similarly, the higher risk of acquiring LTBI in men compared to women was found in group of participants who have never known anyone with TB (aRR 1.64, 95% CI 1.21 – 2.23), but not found in group of participants who have ever known anyone with TB (aRR 1.07, 95% CI 0.64 – 1.78) (Figure 3.2).

DISCUSSION

Among adults in African urban setting, annual risk of infection was high at 11.8% (95% CI 10.1% – 13.8%). The cumulative incidence of HIV infection was low, 1.9% (95% CI 1.2% - 2.8%) for average of 379 days of follow-up. Being older, male, non-religious Roman Catholic, and have been in contact with TB patients before enrollment and during follow up were risk factors for acquisition of LTBI. Higher risk of incident LTBI was not found in age group 17 to 21 years old or among participants who have ever known anyone with TB. This suggests that the difference between male and female in acquisition of LTBI was not attributable to biological differences.

The incidence of LTBI found in this study was lower than studies conducted in South Africa which reported incidence of LTBI ranging from 13% in adolescent (Andrews et al., 2015) to 38% in healthcare workers (Adams et al., 2015). In our study, the annual risk of infection in age group 17 to 21 was 6.8 (95% CI 4.3 to 9.3). One possible explanation for the differences could be that the burden of TB in South Africa is much higher than that of Uganda (360 per 100,000 vs. 200 per 100,000) (WHO, 2018b). Secondly, the study in South Africa was conducted among healthcare workers, a group with a higher risk of LTBI than the general population. These studies estimated the incidence of LTBI by consecutive screening for TB infection, which included both individuals with and without TB infection at enrollment. TST reversion phenomenon was an issue in the estimation of incidence in these studies.

In our study, loss of follow up might have bias in the estimation of cumulative incidence for LTBI. It is possible that participants without repeated TST results had lower incidence than participants with repeated TST results as people who have been in contact with TB patients during follow up were more likely to remain in the study than who have not. However, have been in contact with TB patient during follow up was not associated with acquisition of TB infection. Thus, selection bias due to loss of follow up less likely caused an overestimation in incidence of TB infection.

The accuracy of TST results could be affected by cross-reactivity with BCG and non-tuberculous mycobacteria, booster effect, and immunosuppression. Firstly, cross-reactivity with BCG could not happen as we only enrolled persons with negative TST and therefore persons with cross-reactivity with BCG were excluded at enrollment. Secondly, cross-reactivity with non-tuberculous mycobacteria could occur, but it less likely affects the estimation of cumulative incidence. The reason is that IGRA test is specific to infection of *Mycobacterium tuberculosis* and can avoid the cross-reactivity with non-tuberculous mycobacteria, but annual risk of TB infection in South Africa measuring by either TST or IGRA test was almost the same with 13% for TST and 14% for IGRA (Andrews et al., 2015). Thirdly, for booster effect, we estimated that the prevalence of boosted TST reaction was 2% (J. N. Sekandi et al., 2018). When adjusted for booster effect, the annual risk of infection was 10.0%. Lastly, although the cutoff value of the TST was adjusted from an induration of 10 mm to 5 mm to compensate for loss of sensitivity in HIV-infected participants, it is possible that skin test anergy could occur in HIV-infected persons with a substantially decreasing immunocompetence or an all-or-nothing switch to complete anergy. It is reported anergy was observed in 25% of HIV-infected patients with smear positive pulmonary TB (Cobelens et al., 2006). If I assume that 25% of HIV-infected had anergy skin test and take into account anergy to estimate annual risk of infection, the annual risk of infection was 13.2% instead of 11.8%.

To be extreme, the annual risk of infection was lowered to 8.5% if assuming no TST conversion among individuals without TST results at follow up, to 6.6% if continuing to adjust for booster effect, to 3.0% if continuing to adjust for false-positive comparing to QTF-GIT (table S3. 3). However, we believed that the annual risk of infection of 10.0% after adjusted for booster effect was the true estimation for TB transmission in urban African city for the following reasons: (1) selection bias effect on incidence of TB infection was less likely to occur. Therefore, we can estimate annual risk of infection on subgroup with available repeated TST results; (2) Although IGRA test is thought to be superior than TST test for some reasons and the concordance of TST and IGRA was moderate (Castellanos et al., 2018), proportions of population with TST or IGRA positive were similar in many studies (Andrews et al., 2015; Mancuso et al., 2016). Therefore, there is no need to adjust for false-positive comparing to IGRA test.

For HIV infection in Uganda, it was estimated to be 0.66 cases per 100 person-years in community from 2014 to 2016 (Grabowski et al., 2017) and 1.8 per 100 person-year in women at high risk for HIV infection from 2013 to 2017 (Kasamba, Nash, Seeley, & Weiss, 2019). In our study, this figure was 1.9% for 379 days of follow-up or 1.6 cases per 100 person-years, which was more double than study conducted by Grabowski et. al (Grabowski et al., 2017).

Results from our study illustrate that risk of LTBI was significantly associated with increasing age after adjusting for relevant covariates. This association was found in many cross-sectional studies in general population (Kizza et al., 2015; Zhang et al., 2017) (table 2.2). These articles explained that the major reason for this association can be from cumulative exposure to active TB patients over time. However, in our prospective cohort study, we can exclude this reason as all participants were TST negative at enrollment. Therefore, we suggest that the reasons behind the association between being older age and LTBI were more extra household contacts and mobility as age increased.

We noted that men were higher risk of incident LTBI than women (aRR 1.47, 95% CI 1.14, 1.91). The higher risk of prevalent LTBI among men was found in 7 cross-sectional studies in table 2.2. The association between sex and prevalent LTBI in these studies was measured by odds ratios and therefore overestimated the effect of sex on prevalent LTBI. The reason for higher risk of incident LTBI in men could be because men had more social activities than women and therefore had more opportunities to expose to TB patient. The two interactions (between sex and ever known anyone with TB, and between sex and age group) indirectly support this reason. When both men and women have ever known anyone with TB, they were at the same risk for getting LTBI. However, when participants have never known anyone with TB, men were at the higher risk or more likely to be expose to TB patients. This implied that the sex difference in incidence of TB infection was not because of biological difference between sex. Similarly, higher risk of getting LTBI among men was observed in age group 22 to 29 and 30 to 60 years old, but not in age group 17 to 21 years old. This can be explained that people from 17 to 21 years old were at the schooled-age. Thus, men did not have more social contacts or more opportunities to exposing to TB case than men. However, when age increased, men had more social activities and therefore were more likely to contact with TB case. This assumption was proven in a social network analysis that men were positioned within their networks to be exposed more often to TB cases (Miller et al., 2021). This phenomenon was observed in a cross-sectional study conducted in South Africa as the difference in prevalent LTBI between male and female was greatest among older participants (Wood et al., 2010).

Individuals with non-religious Roman Catholic had a higher risk of LTBI than Roman Catholic. The role of religion on TB transmission was limited. A study with small sample size investigated the risk factors for prevalent case of LTBI in Uganda showed that Roman Catholic had a lowest prevalence of LTBI compared to other religion although their estimate was insignificant (Kizza et al., 2015). The reason for lowest risk of getting LTBI in Roman Catholic individuals should be investigated in further study.

In our study, we found ‘have been in contact with TB patients’ had higher risk of acquiring LTBI. This association was found in many cross-sectional studies. Five out of 13 articles in table 2.2 showed ‘history of TB contact’ or ‘history of close contact with TB patients’ increased the risk of prevalent LTBI. Interestingly, we observed the gradient relative risk of acquiring LTBI when categorized history of TB exposure by periods of one year before enrollment and during follow up. The risk of getting LTBI was more predictable by history of TB exposure one year before enrollment than history of TB exposure during follow up. The reason for this could be that history of TB exposure over one year before enrollment was better indicator for participants being a member of TB patients' social network.

The strength of this study is that it estimated the annual risk of LTBI in a large cohort of the urban African community without LTBI. Most of previous studies estimated annual risk of LTBI by cross-sectional studies or multi-cluster survey. The annual risk of LTBI in these studies ranged from 0.35% among adults in Saudi Arabia to 3.9% among children aged less than or equal to 5 years old in South Africa. Obviously, estimating annual risk of LTBI by cross-sectional studies or by prevalent LTBI was substantially underestimated incidence of LTBI or TB transmission. Further, the annual risk of incident LTBI in our study was not underestimated because of TST reversion as other studies (Adams et al., 2015; Andrews et al., 2015). Also, this study examined a myriad of exposure and covariates to investigate risk factors associated with TB transmission. In terms of limitation, selection bias might exist because of 24% loss of follow up in this prospective cohort study although participants remaining in the study had the same distribution in most of characteristics as participants who lost to follow up.

This study provides a valuable insight into annual risk of LTBI or level of on-going TB transmission in a country with high burden of tuberculosis where BCG vaccination is routinely given. Our findings suggest that the annual risk of LTBI is high. Owing to the high ongoing TB transmission rate in African urban population, management strategy for TB transmission would be a crucial component of ending TB epidemics. Without identification and prophylaxis treatment, about 10% of incident LTBI cases will develop TB disease in the future and fueled TB epidemics.

According to the WHO guidelines for management of LTBI, people living with HIV and children below 5 years of age who are household contacts of TB cases having contacts with pulmonary/multi-drug resistance TB are currently target groups for LTBI screening and intervention treatment regardless of background TB epidemiology (WHO, 2018a). In this study, we found that acquisition of LTBI was associated with being older, male sex, non-religious Roman Catholic, and have been in contact with TB patients. We observed the high annual risk of infection (around 20%) in heavy alcohol users, former or current smoker, and have been in contact with TB patients over one year before enrollment and during follow up. Preventive interventions to control disease development from latent tuberculosis should be targeted for heavy alcohol users, former or current smoker, and subjects being contacts of TB patients for long period of time who are as the high risk of acquiring LTBI as HIV-infected subjects.

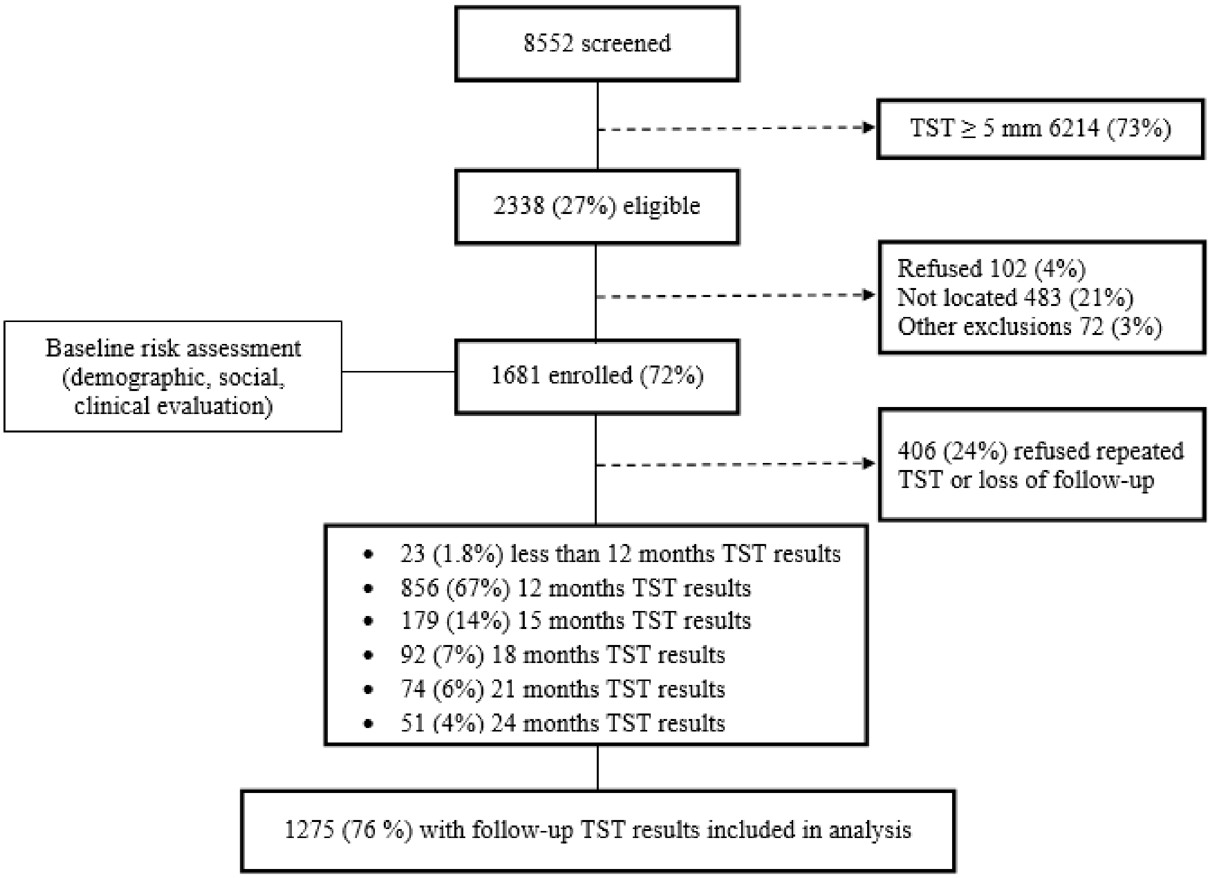

Figure 3. 1 Study profile for recruiting and following participants in Kampala, Uganda, 2014 - 2017

Table 3. 1 Characteristics of 1275 participants with available TST follow up

Characteristics	Frequency (%)
Age in years, median (IQR)	24 (20, 29)
Sex	
Female	747 (58.6)
Male	528 (41.4)
Monthly income, Ushs	
99,999 or less than	453 (35.6)
100,000 - 199,999	383 (30.1)
200,000 or more	435 (34.2)
Religion	
Roman Catholic	518 (40.7)
Others	755 (59.3)
Marital status	
Married	707 (55.5)
Never married	568 (44.5)
Education level	
None or Primary	406 (31.9)
Secondary/Post-secondary	866 (68.1)
BCG vaccination[¥]	
No/Unknown	99 (7.8)
Probably Yes	147 (11.5)
Yes	1029 (80.7)
Smoking	
Never smoked	1219 (96.1)
Former smoker	24 (1.9)
Current smoker	25 (2.0)
Alcohol use	
Non-users	989 (78.7)
Light users	192 (15.3)
Heavy users	75 (6.0)
Type of alcohol drunk*	
Beer/wine	243 (19.1)
Spirits/crude/waragi	103 (8.1)
Local brew	64 (5)
Non-users	989 (77.6)
HIV test result at baseline	
Negative	1205 (94.5)
Positive	61 (4.8)
Refused	9 (0.7)
No. of people at residence, median (IQR)	3 (2, 5)

No. of habitable room, median (IQR)	2 (1, 3)
Type of residence	
Free standing/semi-detached house	418 (33.3)
Muzigo	839 (66.7)

* Total exceed 1275 due to multiple responses

¥ Yes includes confirmation by immunization card, confirmation from verbal report and presence of BCG scar, or BCG scar only; Probably Yes includes confirmation by verbal report only

Table 3. 2 Cumulative incidence and incidence density of HIB infection and LTBI

	Baseline N (%)	Follow up N (%)	Estimates from sub-cohort with available TST/HIV tests at follow up				
			N†	n††	Simple cumulative incidence, % (95% CI)	Incidence Density per 100 person-year (95% CI)	Follow up days, median (IQR)
TST result over study period							
Positive	0 (0)	194 (11.5)	1275	194	15.2 (13.4, 17.3)	13.2 (11.6, 15.1)	379 (366, 431)
Negative	1681 (100)	1081 (64.3)					
Refused	0 (0)	406 (24.2)					
TST result over 12 months follow up							
Positive	0 (0)	143 (8.5)	1213	143	11.8 (10.1, 13.8)	11.7 (10.1, 13.7)	365 (365. 375)
Negative	1681 (100)	1070 (63.7)					
Refused	0 (0)	468 (27.8)					
HIV test result							
Yes	79 (4.7)	101 (6.0)	1185	22	1.9 (1.2, 2.8)	1.6 (1.1, 2.4)	379 (367, 431)
No	1557 (92.6)	1163 (69.2)					
Refused	45 (2.7)	417 (24.8)					

† No. of susceptible participants for developing HIV or LTBI

†† No. of incident HIV infection or LTBI

Table 3. 3 TST induration at follow up according to HIV test result at follow up

	Total N (%)	HIV test result at follow up, N (%)		
		Positive	Negative	Unknown
TST induration for participants with available TST result at the end of study (N=1275)				
0 mm	992 (77.8)	62 (74.7)	899 (78.7)	31 (62.0)
0.1 to 4.9 mm	42 (3.3)	3 (3.6)	39 (3.4)	-
5 to 9.9 mm	50 (3.9)	3 (3.6)	46 (4.0)	1 (2.0)
10 to 14.9 mm	124 (9.7)	11 (13.3)	98 (8.6)	15 (3.0)
≥ 15 mm	67 (5.3)	4 (4.8)	60 (5.3)	3 (6.0)
TST induration for participants with available TST result at 12 months follow up only (N=1213)				
0 mm	981 (80.9)	62 (79.5)	890 (81.5)	29 (67.4)
0.1 to 4.9 mm	42 (3.5)	3 (3.8)	39 (3.6)	-
5 to 9.9 mm	49 (4.0)	2 (2.6)	46 (4.2)	1 (2.3)
10 to 14.9 mm	87 (7.2)	8 (10.3)	69 (6.3)	10 (23.3)
≥ 15 mm	54 (4.5)	3 (3.8)	48 (4.4)	3 (7.0)

Table 3. 4 Annual risk of latent tuberculosis infection according to some characteristics among 1213 participants who had TST result at 12 months

Variables	Total	No. of incident LTBI	Annual Risk of Infection
Age in years			
17 - 21	384	26	6.8 (4.3, 9.3)
22 - 29	557	75	13.5 (10.7, 16.3)
30 - 60	272	42	15.4 (11.1, 19.7)
Sex			
Female	714	67	9.4 (7.3, 11.5)
Male	499	76	15.2 (12, 18.4)
Monthly income, Ushs			
99,999 or less than	434	37	8.5 (5.9, 11.1)
100,000 - 199,999	360	44	12.2 (8.8, 15.6)
200,000 or more	415	62	14.9 (11.5, 18.3)
Religion			
Roman Catholic	495	45	9.1 (6.6, 11.6)
Others	716	97	13.5 (11, 16)
Religion			
Roman Catholic	495	45	9.1 (6.6, 11.6)
Anglican	303	41	13.5 (9.7, 17.3)
Muslim	284	37	13 (9.1, 16.9)
Adventist	18	4	22.2 (3, 41.4)
Others	111	15	13.5 (7.1, 19.9)
BCG vaccination			
No	94	11	11.7 (5.2, 18.2)
Probably Yes	137	10	7.3 (2.9, 11.7)
Yes	982	122	12.4 (10.3, 14.5)
Smoking			
Never smoked	1163	132	11.3 (9.5, 13.1)
Former/Current smoker	44	10	22.7 (10.3, 35.1)
Alcohol use			
Non-users	938	102	10.9 (8.9, 12.9)
Light users	187	26	13.9 (8.9, 18.9)
Heavy users	71	14	19.7 (10.4, 29)
HIV test result at baseline			
Negative	1147	132	11.5 (9.7, 13.3)
Positive	57	11	19.3 (9.1, 29.5)
Ever known anyone with TB			

No	952	104	10.9 (8.9, 12.9)
Yes	246	39	15.9 (11.3, 20.5)
Have been in contact with TB patient			
No for both before and after enrollment	983	111	11.3 (9.3, 13.3)
No for before and Yes for after enrollment	117	14	12 (6.1, 17.9)
Yes for before and No for after enrollment	59	10	16.9 (7.3, 26.5)
Yes for both before and after enrollment	39	8	20.5 (7.8, 33.2)

Table 3. 5 Crude relative risk of developing LTBI according to participants' characteristics

Variables	Total	No. of incident LTBI (%)	Crude Relative Risk (95% CI)
Age in years			
17 - 21	398	36 (9)	Ref
22 - 29	585	98 (17)	**1.85 (1.29, 2.65)**
30 - 60	292	60 (21)	**2.27 (1.55, 3.34)**
Sex			
Female	747	95 (13)	Ref
Male	528	99 (19)	**1.47 (1.14, 1.91)**
Monthly income, Ushs			
99,999 or less than	453	54 (12)	Ref
100,000 - 199,999	383	61 (16)	1.34 (0.95, 1.88)
200,000 or more	435	79 (18)	**1.52 (1.11, 2.1)**
Religion			
Roman Catholic	518	62 (12)	Ref
Others	755	131 (17)	**1.45 (1.09, 1.92)**
Religion			
Roman Catholic	518	62 (12)	Ref
Anglican	321	56 (17)	**1.46 (1.04, 2.03)**
Muslim	300	52 (17)	**1.45 (1.03, 2.03)**
Adventist	19	5 (26)	**2.2 (1.00, 4.83)**
Others	115	18 (16)	**1.31 (0.81, 2.21)**
Marital status			
Married	707	114 (16)	Ref
Never married	568	80 (14)	0.87 (0.67, 1.14)
Education level			
None or Primary	406	60 (15)	Ref
Secondary	740	111 (15)	1.02 (0.76, 1.36)
Post-secondary	126	23 (18)	1.24 (0.8, 1.91)

BCG vaccination			
No/Unknown	99	16 (16)	Ref
Probably Yes	147	18 (12)	0.76 (0.41, 1.41)
Yes	1029	160 (16)	0.96 (0.6, 1.54)
Smoking			
Never smoked	1219	178 (15)	Ref
Former/Current smoker	49	14 (29)	**1.96 (1.23, 3.11)**
Alcohol use			
Non-users	989	143 (14)	Ref
Light users	192	30 (16)	1.08 (0.75, 1.55)
Heavy users	75	18 (24)	**1.66 (1.08, 2.55)**
HIV test results at baseline			
Negative	1205	179 (15)	Ref
Positive	61	15 (25)	**1.66 (1.05, 2.62)**
No. of people at residence			
3 people or more	737	116 (16)	Ref
Less than 3 people	529	78 (15)	0.94 (0.72, 1.22)
No. of habitable room			
2 rooms or more	751	113 (15)	Ref
Less than 2 rooms	512	79 (15)	1.03 (0.79, 1.34)
Type of residence			
Free standing/semi-detached house	418	59 (14)	Ref
Muzigo	839	133 (16)	1.12 (0.85, 1.49)

Table 3. 6 Crude relative risk of developing LTBI according to history of exposure to TB patient before and during follow up

Variables	Before enrollment	During follow up	Total	No. incident LTBI (%)	Crude RR (95% CI)
Ever known anyone with TB					
	No	-	1001	141 (14)	Ref
	Yes	-	267	51 (19)	**1.35 (1.01, 1.8)**
Ever lived in a home with TB patient					
	No	-	1154	173 (15)	Ref
	Yes	-	114	19 (17)	1.11 (0.72, 1.7)
Have been in contact with TB patient					
	No	No	1033	150 (14.5)	Ref
	No	Yes	121	18 (14.9)	1.02 (0.65, 1.61)
	Yes	No	61	12 (19.7)	1.35 (0.8, 2.3)
	Yes	Yes	43	12 (27.9)	**1.92 (1.16, 3.18)**
Live at the same house with TB patient					
	No	No	1179	179 (15.2)	Ref
	No	Yes	38	4 (10.5)	0.69 (0.27, 1.77)
	Yes	No	28	6 (21.4)	1.41 (0.69, 2.91)
	Yes	Yes	13	3 (23.1)	1.52 (0.56, 4.14)
Sleep in the same bedroom with TB patient					
	No	No	1225	183 (14.9)	Ref
	No	Yes	16	2 (12.5)	0.84 (0.23, 3.08)
	Yes	No	12	5 (41.7)	**2.79 (1.41, 5.52)**
	Yes	Yes	5	2 (40.0)	2.68 (0.91, 7.9)
Spent more than 4 hours at a time with TB patient					
	No	No	1135	170 (15.0)	Ref
	No	Yes	70	11 (15.7)	1.05 (0.6, 1.84)
	Yes	No	39	8 (20.5)	1.37 (0.73, 2.58)
	Yes	Yes	14	3 (21.4)	1.43 (0.52, 3.94)
Knew contact with TB receiving treatment					
	No	No	1026	157 (15.3)	Ref

	No	Yes	70	5 (7.1)	0.47 (0.2, 1.1)
	Yes	No	115	16 (13.9)	0.91 (0.56, 1.46)
	Yes	Yes	47	14 (29.8)	**1.95 (1.23, 3.09)**
Took care TB patient					
	No	No	1154	174 (15.1)	Ref
	No	Yes	34	5 (14.7)	0.98 (0.43, 2.22)
	Yes	No	56	10 (17.9)	1.18 (0.66, 2.11)
	Yes	Yes	14	3 (21.4)	1.42 (0.52, 3.91)
TB contact coughing while being with you					
	-	No	1124	166 (15)	Ref
	-	Yes	151	27 (18)	1.2 (0.83, 1.74)
Nursed or cared for any patient					
	-	No	1045	164 (16)	Ref
	-	Yes	230	29 (13)	0.8 (0.55, 1.15)

Table 3. 7 Univariate and multivariate analysis with modified Poisson regression to identify risk factors of incident LTBI

Variables	Total	No. of incident LTBI	Crude RR (95% CI)	Adjusted RR (95% CI)
Age in years				
17 - 21	398	36 (9)	Ref	Ref
22 - 29	585	98 (17)	1.85 (1.29, 2.65)	1.83 (1.28, 2.62)
30 - 60	292	60 (21)	2.27 (1.55, 3.34)	2.16 (1.47, 3.18)
Sex				
Female	747	95 (13)	Ref	Ref
Male	528	99 (19)	1.47 (1.14, 1.91)	1.46 (1.13, 1.88)
Monthly income, Ushs				
99,999 or less than	453	54 (12)	Ref	
100,000 - 199,999	383	61 (16)	1.34 (0.95, 1.88)	
200,000 or more	435	79 (18)	1.52 (1.11, 2.10)	
Religion				
Roman Catholic	518	62 (12)	Ref	Ref
Others	755	131 (17)	1.45 (1.09,1.92)	1.47 (1.11, 1.94)
Smoking				
Never smoked	1219	178 (15)	Ref	
Former/Current smoker	49	14 (29)	1.96 (1.23, 3.11)	
Alcohol use				
Non-users	989	143 (14)	Ref	
Light users	192	30 (16)	1.08 (0.75, 1.55)	
Heavy users	75	18 (24)	1.66 (1.08, 2.55)	
HIV test result at baseline				
Negative	1205	179 (15)	Ref	
Positive	61	15 (25)	**1.66 (1.05, 2.62)**	
Have been in contact with TB patient				
No for both before and after enrollment	1033	150 (15)	Ref	Ref
No for before and Yes for after enrollment	121	18 (15)	1.02 (0.65, 1.61)	0.88 (0.55, 1.41)
Yes for before and No for after enrollment	61	12 (20)	1.31 (0.77, 2.23)	1.27 (0.75, 2.15)
Yes for both before and after enrollment	43	12 (28)	1.88 (1.13, 3.11)	**1.81 (1.13, 2.9)**

Sleep in the same bedroom with TB patient			
No for both before and after enrollment	1225	183 (15)	Ref
No for before and Yes for after enrollment	16	2 (13)	0.84 (0.23, 3.08)
Yes for before and No for after enrollment	12	5 (42)	2.79 (1.41, 5.52)
Yes for both before and after enrollment	5	2 (40)	2.68 (0.91, 7.9)
Knew contact with TB receiving treatment			
No for both before and after enrollment	1026	157 (15)	Ref
No for before and Yes for after enrollment	70	5 (7)	0.47 (0.2, 1.1)
Yes for before and No for after enrollment	115	16 (14)	0.91 (0.56, 1.46)
Yes for both before and after enrollment	47	14 (30)	1.95 (1.23, 3.09)

Table 3. 8 Multivariate analysis using modified Poisson regression including interactions to explain sex differences in acquisition of LTBI

Variables	Total	No. of LTBI (%)	Adjusted RR (95% CI)
Religion			
Roman Catholic	518	62 (12)	Ref
Others	755	131 (17)	**1.47 (1.11, 1.94)**
Have been in contact with TB patient			
No for both before and after enrollment	1033	150 (15)	Ref
No for before and Yes for after enrollment	121	18 (15)	0.87 (0.54, 1.40)
Yes for before and No for after enrollment	61	12 (20)	1.18 (0.64, 2.18)
Yes for both before and after enrollment	43	12 (28)	1.67 (0.94, 2.97)
Age in years × Sex			
Age, 17 – 21 years old			
Female	236	22 (9)	Ref
Male	162	14 (9)	0.96 (0.5, 1.84)
Age, 22 – 29 years old			
Female	346	47 (14)	Ref
Male	239	51 (21)	**1.62 (1.13, 2.31)**
Age, 30 – 60 years old			
Female	165	26 (16)	Ref
Male	127	34 (27)	**1.65 (1.04, 2.61)**
Ever know anyone with TB × Sex			
Ever know anyone with TB, Yes			
Female	166	31 (19)	Ref
Male	101	20 (20)	1.07 (0.64, 1.78)
Ever know anyone with TB, No			
Female	577	64 (11)	Ref
Male	424	78 (18)	**1.64 (1.21, 2.23)**

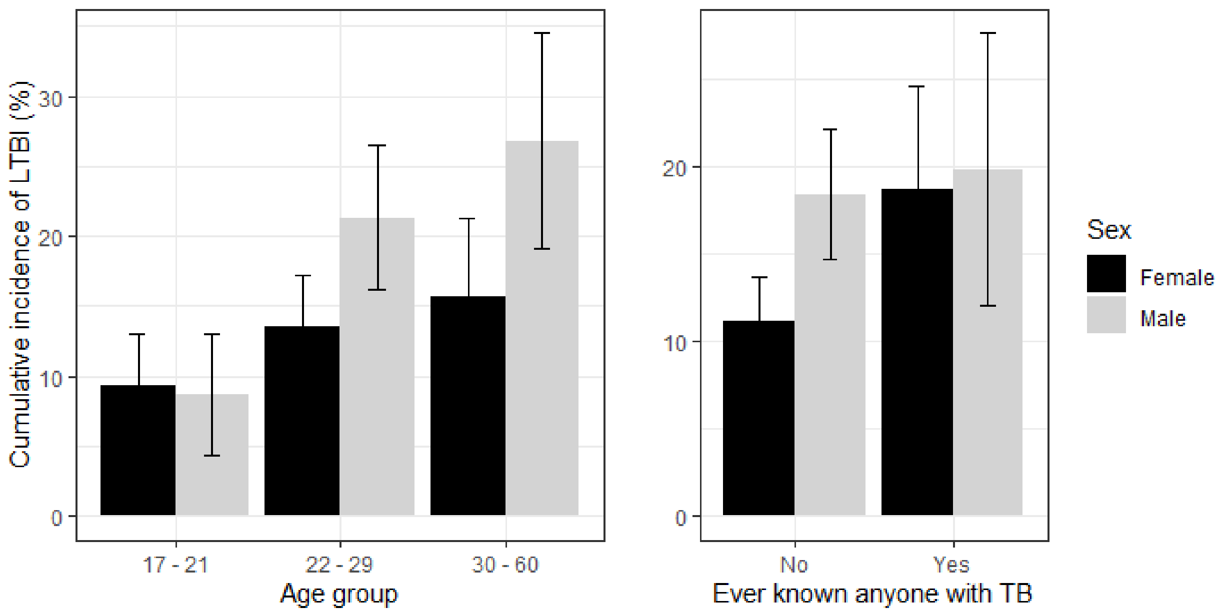

Figure 3. 2 Difference between male and female in cumulative incidence of LTBI across age group or ever known anyone with TB status

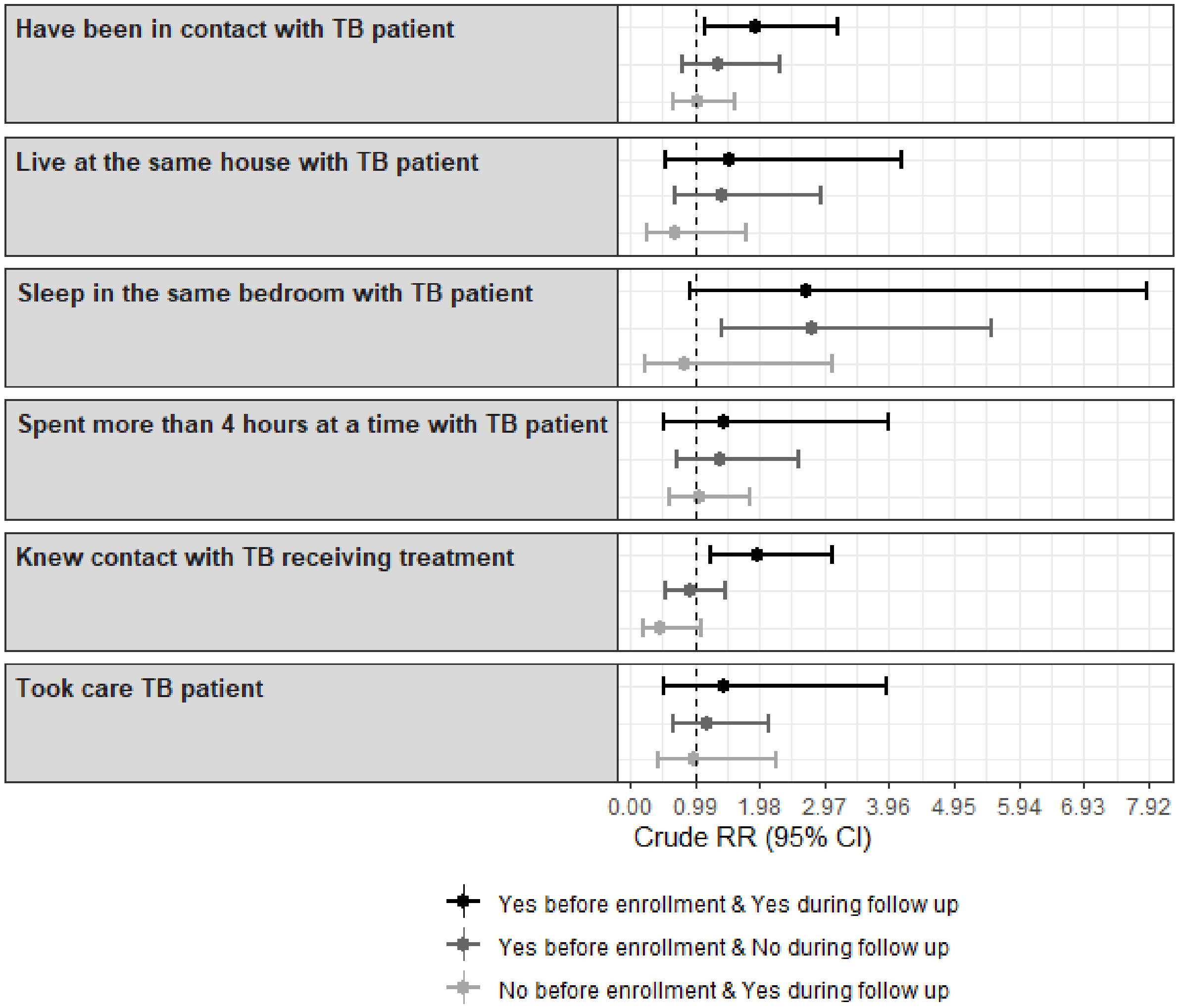

Figure 3. 3 Crude relative risk of developing LTBI based on history of exposing to TB patient before enrollment and during follow up

SUPPLEMENT

Table S3. 1 Baseline characteristics of study population according to available of TST follow up

Characteristics		Total	Availability of TST follow up		p-value
			Yes (n=1275)	No (n=406)	
Age in years, median (IQR)		24 (20, 29)	24 (20, 29)	24 (20, 29)	0.376
Sex					
	Female	1006 (59.8)	747 (58.6)	259 (63.8)	0.056
	Male	673 (40.0)	528 (41.4)	145 (35.7)	
	(Missing)	2 (0.1)	0 (0.0)	2 (0.5)	
Monthly income, Ushs					
	99,999 or less than	598 (35.6)	453 (35.5)	145 (35.7)	0.992
	100,000 - 199,999	504 (30.0)	383 (30.0)	121 (29.8)	
	200,000 or more	572 (34.0)	435 (34.1)	137 (33.7)	
	(Missing)	7 (0.4)	4 (0.3)	3 (0.7)	
Religion					
	Roman Catholic	675 (40.2)	518 (40.6)	157 (38.7)	0.552
	Others	1002 (59.6)	755 (59.2)	247 (60.8)	
	(Missing)	4 (0.2)	2 (0.2)	2 (0.5)	
Marital status					
	Married	920 (54.7)	707 (55.5)	213 (52.5)	0.367
	Never married	759 (45.2)	568 (44.5)	191 (47.0)	
	(Missing)	2 (0.1)	0 (0.0)	2 (0.5)	
Education level					
	None or Primary	526 (31.3)	406 (31.8)	120 (29.6)	0.474
	Secondary/Post-secondary	1148 (68.3)	866 (67.9)	282 (69.5)	
	(Missing)	7 (0.4)	3 (0.2)	4 (1.0)	
BCG vaccination					
	No/Unknown	134 (8.0)	99 (7.8)	35 (8.6)	0.770
	Probably yes	190 (11.3)	147 (11.5)	43 (10.6)	
	Yes	1357 (80.7)	1029 (80.7)	328 (80.8)	
Smoking					
	Never smoked	1604 (95.4)	1219 (95.6)	385 (94.8)	0.608
	Former smoker	33 (2.0)	24 (1.9)	9 (2.2)	
	Current smoker	36 (2.1)	25 (2.0)	11 (2.7)	
	(Missing)	8 (0.5)	7 (0.5)	1 (0.2)	
Alcohol use					

Non-users	1310 (77.9)	989 (77.6)	321 (79.1)	0.671
Light users	249 (14.8)	192 (15.1)	57 (14.0)	
Heavy users	95 (5.7)	75 (5.9)	20 (4.9)	
Type of alcohol drunk*				
Beer/wine	316 (17.1)	243 (19.1)	73 (18)	0.772
Spirits/crude/waragi	142 (7.7)	103 (8.1)	39 (9.6)	
Local brew	83 (4.5)	64 (5)	19 (4.7)	
Non-users	1310 (70.8)	989 (77.6)	321 (79.1)	
(Missing)	27 (1.6)	19 (1.5)	8 (2.0)	
HIV test results at baseline				
No	1557 (92.6)	1205 (94.5)	352 (86.7)	1.000
HIV infection	79 (4.7)	61 (4.8)	18 (4.4)	
(Missing)	45 (2.7)	9 (0.7)	36 (8.9)	
Have been contact with TB patient over the past one year before enrollment				
No	1534 (91.3)	1158 (90.8)	376 (92.6)	0.391
Yes	139 (8.3)	110 (8.6)	29 (7.1)	
(Missing)	8 (0.5)	7 (0.5)	1 (0.2)	
Have been in contact with TB patient during follow up				
No	1486 (88.4)	1108 (86.9)	378 (93.1)	0.001
Yes	195 (11.6)	167 (13.1)	28 (6.9)	

Table S3. 2 Change in TST induration from baseline TST to follow-up TST result

	Total N (%)	TST induration at follow up, N (%)	
		≥ 10 mm	< 10 mm
Change in TST induration for participants with available TST result at any follow up time (N=1275)			
≤0 mm	1001 (78.5)	-	1001 (92.4)
0.1 to 5.9 mm	47 (3.7)	-	47 (4.3)
6 to 9.9 mm	54 (4.2)	18 (9.4)	36 (3.3)
10 to 14.9 mm	121 (9.5)	121 (63.4)	-
≥ 15 mm	52 (4.1)	52 (27.2)	-
Change in TST induration for participants with available TST result at 12 months follow up only (N=1213)			
≤0 mm	990 (81.6)	-	990 (92.4)
0.1 to 5.9 mm	47 (3.9)	-	47 (4.4)
6 to 9.9 mm	48 (4.0)	13 (9.2)	35 (3.3)
10 to 14.9 mm	88 (7.3)	88 (62.4)	-
≥ 15 mm	40 (3.3)	40 (28.4)	-

Table S3. 3 Sensitivity analysis for cumulative incidence of LTBI at 12 months visit or at the end of study

	Original data	**Adjusted for booster**	**Adjusted for false-positive comparing to IGRA**	**Adjusted for false-positive comparing to IGRA and booster**
TST result at the end of study (n=1681)				
Positive	194 (11.5)	160 (9.7)	112 (6.7)	78 (4.7)
Negative	1081 (64.3)	1081 (65.6)	1163 (69.2)	1163 (70.6)
Refused	406 (24.2)	406 (24.7)	406 (24.2)	406 (24.7)
TST result at 12 months (n=1681)				
Positive	143 (8.5)	109 (6.6)	84 (5.0)	50 (3.0)
Negative	1070 (63.7)	1070 (65.0)	1129 (67.2)	1129 (68.5)
Refused	468 (27.8)	468 (28.4)	468 (27.8)	468 (28.4)
TST result at the end of study, excluding participants refused to retest (n=1275)				
Positive	194 (15.2)	168 (13.4)	112 (8.8)	86 (6.8)
Negative	1081 (84.8)	1081 (86.6)	1163 (91.2)	1163 (93.2)
TST result at 12 months, excluding participants refused to retest (n=1213)				
Positive	143 (11.8)	119 (10.0)	84 (6.9)	60 (5.0)
Negative	1070 (88.2)	1070 (90.0)	1129 (93.1)	1129 (95.0)

Assume 2% of the cohort had booster TST reaction
Of TST converters with increment ≥ 15 mm, 79% had positive QFT-GIT
Of TST converters with increment < 15 mm, 50% had positive QFT-GIT

CHAPTER 4

SOCIAL BEHAVIORS ASSOCIATED WITH INCIDENCE OF TUBERCULOSIS INFECTION [2]

[2] Quach HTT, Zalwango S, Kakaire R, Kiwanuka N, Sekandi NJ, Dobbin KK, Naeher L, Castellanos ME, Whalen CC. To be submitted to International Journal of Tuberculosis and Lung Disease.

ABSTRACT

Objectives: Our understanding of the effect of local determinants of TB transmission in high burden country was limited**.** This study was to examine social behaviors associated with TB transmission.

Method: We conducted a prospective community-based cohort study of adult without latent tuberculosis infection (LTBI) in Kampala, Uganda from 2014 to 2016. After one year of follow up, participants were retested with tuberculin skin test (TST) and HIV rapid test to evaluate new infection. Tests for independence (chi-square and Fisher's exact test) were used to identify sex-specific behaviors. Multivariate Poisson regression with robust error variance was used to identify risk factors for TB transmission.

Results: We enrolled 1681 participants. Of these, 406 (24%) were lost to follow up**.** Among 1275 with available follow up TST results, proportion of male was 58.6% and the median (IQR) of age was 24 (20 – 29). Men were more often to be smoker, heavy alcohol users, drink in type of local alcoholic drinks, and travel to work. Men also experienced a higher risk of getting LTBI than women. However, we were unable to link these sex-specific behaviors with higher risk of getting LTBI in men. Rather, sex plays a role as a confounder in the association between these social behaviors and acquisition of TB infection. Being older (aRR 1.03, 95% CI 1.01 – 1.04), being male (aRR 1.44, 95% CI 1.11 – 1.86), non-religious Roman Catholic (95% CI 1.49, 95% CI 1.13 – 1.97), and have been in contact with TB patients over past one year before enrollment (aRR 1.51, 95% CI 1.05 – 2.17) were risk factors for development of LTBI. Drug shop attendance reduced the risk of getting LTBI among participants with secondary or post-secondary education (aRR 0.40, 95% CI 0.25 – 0.65), but did not among participants with no formal education or primary level (aRR 1.02, 95% CI 0.59 – 1.77).

Conclusion: Although many social behaviors are sex-specific, they are not explainable to sex differences in incidence of LTBI**.** A further investigation on the association between drug shop attendance and acquisition of LTBI was needed.

INTRODUCTION

Over decades of efforts, global TB epidemic remarkably improved outcomes in regard to TB mobility and mortality by enhancing access to diagnosis and treatment. From 2011 to 2015, a 47% drop in TB mortality rates was achieved, compared to the 50% target set by Global Plan to stop TB (WHO, 2016). However, all efforts had little effect on TB disease incidence and we failed to drive down the TB epidemic. In 2019, tuberculosis was one of the ten leading cause of death with an estimated 10 million cases and 1.4 million deaths (WHO, 2018b). TB disease incidence is falling at about 2% per year. Between 2015 and 2019, the cumulative reduction was 9%. This was less than half way to the End TB Strategy milestone of 20% reduction between 2015 and 2020 (WHO, 2020b). In meanwhile, the global rate of decline in tuberculosis incidence was projected to increase to 4% - 5% by 2020 and then to 10% per year by 2025 to meet the WHO End TB Strategy targets.

Nearly one fourth of the world's population is infected with TB, representing a large reservoir of people at risk of progression to active TB disease (WHO, 2018b). To meet the End TB targets, interrupting tuberculosis transmission is central to achieving the reductions in incidence of tuberculosis disease. However, this critical component to drive down TB epidemic has been too often neglected. Although our understanding of tuberculosis has improved substantially over the intervening century of tuberculosis research, many gaps of TB transmission remain. To date, studies of latent tuberculosis infection (LTBI) have mainly focused on high risk population such as children, household contacts of TB cases, healthcare workers, and prisons (Chandrasekaran et al., 2018; Hanifa et al., 2009; Janagond et al., 2017; J. Young & O'connor, 2005), and very few community-based studies have conducted in urban population (Kizza et al., 2015; Ncayiyana et al., 2016). Most of studies measured the prevalence of LTBI which indicates the burden of TB and does not represent on-going TB transmission. To our knowledge, only one study conducted in China measured incidence of LTBI in general population which is an epidemiological index to measure the extent of TB transmission in the community. Also, both studies measuring prevalent and incident LTBI examined the limited number of factors. Gaps in local determinants of transmission underscore how little we know about transmission and how that ignorance may be undermining our efforts to end TB. In our study, we aimed to measure incidence of LTBI and identify social behaviors associated with TB transmission in an African city.

METHODS

Study population and measurements

We performed a prospective study within a cohort of adult African individuals without evidence of latent tuberculosis infection (LTBI). Between June 2014 to June 2016, a cohort of 1681 individuals was recruited from residents of Rubaga division of Kampala, Uganda. The inclusion criteria were: Tuberculin skin test (TST) below 5 mm at baseline, age between 17 and 60 years, and no signs or symptoms of active tuberculosis. A standard clinical evaluation was performed to assess risk of acquiring a new tuberculosis infection at baseline and quarterly visits. At one year, participants were retested with TST to detect new infection defined as TST conversion. We planned to recruit 2000 participants and follow them for one year. It is expected that 5% of them converted TST. However, we were not able to enroll 2000 participants in reality, and thus had to increase the follow up time to ensure power of study. Participants who were negative with TST at the end of one year, were asked to extend their follow-up time up to 2 years.

At baseline, demographic, social, and clinical characteristics were obtained through interviews performed by trained field workers using standardized questionnaires. During follow up, we interviewed participants quarterly to obtain information regarding to healthcare facility attendance and travelling outside Kampala.

TST was performed by placing 5 tuberculin units of purified protein derivative on the left forearm of each participant using the Mantoux method. Two field workers independently read the diameter of induration within 48 to 72 hours. The diameter of the skin test induration was measured using the "ball-point" technique with digital calipers to reduce digit preference bias. HIV testing was performed following the Uganda Ministry of Health National Testing algorithms. All participants were administered a Determine HIV-1/2 and a HIV 1/2 STAT-PAK; a Uni-gold HIV test was performed if there were discrepant results for the initial tests.

In HIV-seronegative subjects, a TST conversion was defined as having a second tuberculin skin test reading of 10 millimeters or greater with an increase in reaction of six millimeters or greater from the first to the second reading. In HIV-seropositive subjects, TST conversion was defined as having a second tuberculin skin test reading of five millimeters or greater with an increase in reaction of three millimeters or greater from the first to the second reading. If the above conditions were not met, subjects were classified as persistent skin test negative.

Analytic strategy

Baseline characteristics of the study population and the subset of subjects with available repeated TST results were summarized with proportions and measures of central tendency.

Incidence of TST conversion was estimated by two methods: simple cumulative incidence and incidence density. Cumulative incidence of TST conversion was estimated as proportion with 95% confidence intervals. To estimate cumulative incidence of TST over study period, we used TST results with the longest follow up time. To estimate annual risk of LTBI (cumulative incidence of TST conversion over 12 months follow up), we restricted to TST results within 12 months follow up only. In estimation of incidence density of TST conversion, we used the date of retesting TST or last date seen to obtain follow up time. The incidence of TST conversion was stratified by sex.

As history of seeking healthcare and travelling outside Kampala were collected every 3 month visits, we summarized them as ‘Yes’ if ‘Yes’ for at least one visit and ‘No’ for ‘No’ in all visits. Other variables were measured at baseline only. For descriptive analysis, social behavioral factors including smoking and drinking habits, history of exposure to high risk setting, healthcare facilities attendance, transportation usage, and history of travelling outside Kampala were stratified by sex and incident LTBI status and summarized as median and interquartile range (IQR) for continuous variables and frequencies with proportions for categorical variables. To test independence between sex or LTBI status and the variables, Chi-square test was used when cell frequency was 5 or more, and Fisher’s exact test was used when cell frequency was less than 5.

The Poisson regression model with robust error variance was used as it is a better approach for estimating relative risks for cohort studies with common binary outcome compared to using logistic regression (Zou, 2004). We performed univariate and multivariate analysis on a set of variables with p-value less than 0.2 from independence tests. The quasi-likelihood under the independence model criterion (QIC) was applied to compare models and determine the risk factors that showed the best model fit in multivariate model. Lower QIC value indicated a better model fit, but there was no test for statistical significance of the differences. To explore potential interactions, a global test for two-way interactions between factors included multivariate analysis and other factors was performed and found to be significant at the 10% level. Multivariate analysis with potential interaction terms was tested with statistically significant level at the 5%. R version 3.6.1 was used for all analyses.

RESULTS

Study population characteristics

Among 1275 participants, the median age was 24 years (IQR 20 – 29), 528 (41%) were males, 61 (5%) were HIV-infected, and 92% of participants were vaccinated with BCG. Roman Catholic religion accounted for 40%, most of participants (96%) had never smoked, 21% consumed alcohol. Nine percent of participants reported that they had been in contact with a TB patient over the past one year before enrollment (Table 4.1).

Sex differences in incidence of LTBI and social behaviors

Annual risk of TB infection was 15.2 (95% CI 12.3, 18.7) in male and 9.0 (95% CI 7.2, 11.7) in female. As a result, for over one-year period, male had higher risk of getting LTBI than female (risk ratio 1.68, 95% CI 1.24 – 2.29). This risk ratio was lower at 1.47 (95% CI 1.14, 1.91) when TST results over study period was used (Table 4.2).

Men were more likely to be smokers and alcohol users than women. Except for drinking on celebration occasion, men were often to drink outside road side shops, inside established bar, or in type of local alcoholic drink (Malwa/Waragi/Tonto) than women. The proportion of women working at home was approximately 8 times higher than that of men (34.7% vs. 4.5%, p-value <0.001) (Table 4.3). For seeking healthcare, women were more likely to attend health center, clinic, hospital than men. However, the proportion of attending drug shop in male was similar to that of female (22.5% in male vs. 23.0% in female, p-value=0.891) (Table 4.4).

Compared to men, women were more often to walk (42.2% vs. 18.4%, p-value <0.001), and were less likely to use bicycle/motorcycle (17.8% vs. 32.1%, p-value <0.001) or private car and lorry (0.9% vs. 7.9%, p-value <0.001). However, they were similar as regards to using taxi or bus (41.7% in male vs. 39.0% in female, p-value=0.344). Men were more often to travel outside Kampala than women (76.5% vs. 67.9%, p-value=0.001). The reasons for travelling outside Kampala were different by sex except for purpose of vocation or holiday. Men were more likely to travel to work (47.0% vs. 10.3%, p-value <0.001), but less likely to travel for visiting family or relatives (44.9% vs. 50.9%, p-value = 0.040) and attending funeral or burial (19.7% vs. 25.2%, p-value = 0.026). Men and women were similar in using taxi or bus as modes of transportation used to travel outside Kampala (66.7% in men vs. 64.9% in women, p-value = 0.559). However, men were often to choose motorcycle (11.7% vs. 7.2%, p-value = 0.008), and private vehicle or lorry (28.0% vs. 10.8%, p-value < 0.001) to travel outside Kampala than women. Men spent longer on a mode of transportation to travel outside Kampala than women (4.45 vs. 3.80 hours) (Table 4.5).

Multivariate analysis of social behaviors and acquisition of LTBI

In univariate analysis, being former/current smoker, being heavy alcohol users, drinking in type of local alcoholic drink (Malwa/Waragi/Tonto), and travelling outside Kampala to work increased the risk of acquiring LTBI, while attending drug shop lowered the risk. The associations between these risk factors (e.g. being former/current smoker, being heavy alcohol users, drinking in traditional settings and travelling outside Kampala) and incident LTBI were confounded by sex as the relative risks were reduced more than 10% for being former/current smokers or become insignificant for other factors after adjusted for sex in bivariate analysis (Table 4. 6 and Appendix Table C. 1). Also, sex played roles as exposure and effect modifier, which is discussed in chapter 3. After adjusted for age, sex, religion, and contacting with TB patients over past 12 months before enrollment in multivariate model, only attending drug shop was a factor associated with acquisition of LTBI (aRR 0.59, 95% CI 0.40 – 0.85).

Education level modified the effect of attending drug shop on acquisition of TB infection. Attending drug shop lowered the risk of LTBI among participants with secondary or post-secondary level (aRR 0.40, 95% CI 0.25 – 0.65), but did not among none or primary education (aRR 1.02, 95% CI 0.59 – 1.77). Alcohol usage modified the effect of travel outside Kampala to work on acquisition of LTBI. Travel outside Kampala to work was a risk factor of getting LTBI among alcohol users (aRR 2.00, 95% CI 2.00 – 3.44), but was not among non-users (aRR 0.99, 95% CI 0.68 – 1.45) (Table 4.7).

DISCUSSION

In our study, we aimed to identify the behaviors associated with acquisition of TB infection. We observed that men experienced a higher risk of getting TB infection than women. Also, men were more often to be smoker, heavy alcohol users, drink in type of local drink, and travel to work. However, we cannot link these behaviors with the higher risk of acquiring LTBI in men. Rather, sex was a confounder in the association between these behaviors and acquisition of TB infection. We found that being older, male sex, non-religious Roman Catholic, and have been in contact with TB patients over past one year before enrollment were risk factors for development of LTBI in general population. Besides these factors, we observed that travelling outside Kampala to work increased the risk of getting TB infection among alcohol users, but did not among non-alcohol users. Drug shop attendance could lower the risk of getting LTBI among participants with secondary or post-secondary education, but could not among participants with no formal education or primary education.

Our study examined drug shop attendance on development of TB infection in general population. We found that drug shop attendance reduced the risk of getting LTBI among participants with secondary or post-secondary level, but did not among participants with none or primary education. Participants with higher level of education more believed in modern medicine and had sufficient knowledge about TB (Mondal, Nazrul, Chowdhury, & Howard, 2014). Possibly, these participants attended drug shop for practices which prevent acquisition of LTBI (e.g. buying medical masks or treating themselves with prophylaxis therapy). This explanation is just our hypothesis. If this association is true, the different practices in this subgroup can reduce TB transmission by 60%. It is worthwhile to have an investigation to further explore the reasons behind this association.

Obviously, travelling or migration has been a pathway for disseminating infectious diseases throughout human history. In this study, we found that travelling to work was a risk factor of getting LTBI but this relationship was modified by alcohol use. Also, we examined other reasons for travelling outside Kampala such as visiting family or relatives, vocation or holiday, and burial or funeral and did not observed a higher risk of LTBI for these reasons. Travelling to work meets both of two criteria that are more likely to facilitate TB transmission than travelling for other reasons: trips with long duration and potential exposures to usual and unusual or unknown contacts who might have TB. Alcohol consumption facilitates TB infection by two pathways (Imtiaz et al., 2017). First, drinking alcohol impairs the immune system, which increases susceptibility to the infection. Second, drinking alcohol leads to presence in social environments that enhance the spread of TB infection. As a result, there might be a synergic effect of drinking alcohol and travelling to work on acquisition of LTBI.

In conclusion, age, sex, religion, and have been in contact with TB patients over past one year before enrollment was associated with acquisition of TB. There could be a synergic effect between alcohol consumption and travelling to work on increased risk of getting LTBI. Apart from these factors, drug shop attendance lowered the risk of getting TB infection among people with higher level of education. A further investigation on how drug shop attendance could lower the risk of getting in a subgroup was necessary to fulfil our knowledge about TB transmission and effective practices to interrupt transmission in high burden settings.

Table 4. 1 Characteristics of 1275 participants with available TST follow up

Characteristics	Frequency (%)
Age in years, median (IQR)	24 (20, 29)
Sex	
Female	747 (58.6)
Male	528 (41.4)
Monthly income, Ushs	
99,999 or less than	453 (35.6)
100,000 - 199,999	383 (30.1)
200,000 or more	435 (34.2)
Religion	
Roman Catholic	518 (40.7)
Others	755 (59.3)
Marital status	
Married	707 (55.5)
Never married	568 (44.5)
Education level	
None or Primary	406 (31.9)
Secondary/Post-secondary	866 (68.1)
BCG vaccination	
No/Unknown	99 (7.8)
Probably Yes	147 (11.5)
Yes	1029 (80.7)
Smoking	
Never smoked	1219 (96.1)
Former/current smoker	49 (3.9)
Alcohol use	
Non-users	989 (78.7)
Light users	192 (15.3)
Heavy users	75 (6.0)
HIV test at baseline	
Negative	1205 (94.5)
Positive	61 (4.8)
Refused	9 (0.7)
Have been in contact with TB patient	
No	1158 (91.3)
Yes	110 (8.7)
Spent more than 4 hours at a time with TB patient	
No	1209 (95.6)
Yes	56 (4.4)

Table 4. 2 Cumulative incidence and incidence density of HIV infection and LTBI

	Male				Female				Risk ratio	Rate ratio
	N†	n††	Simple cumulative incidence, % (95% CI)	Incidence Density per 100 person-year (95% CI)	N†	n††	Simple cumulative incidence, % (95% CI)	Incidence Density per 100 person-year (95% CI)		
TST result over study period (n=1275)	528	99	18.8 (15.6, 22.3)	16.1 (13.4, 19.2)	747	95	12.7 (10.5, 15.3)	11.1 (9.2, 13.4)	1.47 (1.14, 1.91)	1.45 (1.10, 1.92)
TST result over 12 months follow up (n=1213)	499	76	15.2 (12.3, 18.7)	15.2 (12.3, 18.6)	741	67	9.0 (7.2, 11.3)	9.3 (7.4, 11.7)	1.68 (1.24, 2.29)	1.62 (1.17, 2.26)

† Number of susceptible participants for developing HIV or LTBI

†† Number of incident HIV infection or LTBI cases

Table 4. 3 Personal habits and history of exposure to high risk setting stratified by gender and LTBI status in 1275 participants

Variables	Total N (%)	Gender		p-value	Incident LTBI		p-value
		Female	Male		Yes	No	
Smoking and drinking habits							
Smoking							
Never smoked	1219 (96.1)	731 (98.3)	488 (93.1)	<0.001	178 (92.7)	1041 (96.7)	0.013
Former/Current smoker	49 (3.9)	13 (1.7)	36 (6.9)		14 (7.3)	35 (3.3)	
Alcohol use							
Non-users	989 (78.7)	599 (81.2)	390 (75.3)	0.011	143 (74.9)	846 (79.4)	0.084
Light users	192 (15.3)	106 (14.4)	86 (16.6)		30 (15.7)	162 (15.2)	
Heavy users	75 (6.0)	33 (4.5)	42 (8.1)		18 (9.4)	57 (5.4)	
Mostly drink in drinking places outside road side shops							
No	1196 (95.1)	714 (97.0)	482 (92.5)	<0.001	181 (94.3)	1015 (95.3)	0.666
Yes	61 (4.9)	22 (3.0)	39 (7.5)		11 (5.7)	50 (4.7)	
Mostly drink inside established bar							
No	1148 (91.3)	687 (93.3)	461 (88.5)	0.004	174 (90.6)	974 (91.5)	0.813
Yes	109 (8.7)	49 (6.7)	60 (11.5)		18 (9.4)	91 (8.5)	
Mostly drink in Malwa/Waragi/Tonto drinking setting							
No	1231 (97.9)	727 (98.8)	504 (96.7)	0.021	184 (95.8)	1047 (98.3)	0.052
Yes	26 (2.1)	9 (1.2)	17 (3.3)		8 (4.2)	18 (1.7)	

Mostly drink on celebration occasion							
No	1178 (93.7)	689 (93.6)	489 (93.9)	0.954	183 (95.3)	995 (93.4)	0.407
Yes	79 (6.3)	47 (6.4)	32 (6.1)		9 (4.7)	70 (6.6)	
Workplace and history of incarceration							
Work at home							
No	966 (77.8)	475 (65.3)	491 (95.5)	<0.001	152 (80.4)	814 (77.4)	0.405
Yes	275 (22.2)	252 (34.7)	23 (4.5)		37 (19.6)	238 (22.6)	
Work in a mine							
No	1212 (97.7)	722 (99.3)	490 (95.3)	<0.001	188 (97.9)	1024 (97.6)	1.000
Yes	29 (2.3)	5 (0.7)	24 (4.7)		4 (2.1)	25 (2.4)	
Work in a healthcare facility							
No	1225 (98.0)	716 (97.7)	509 (98.5)	0.450	188 (98.4)	1037 (97.9)	0.857
Yes	25 (2.0)	17 (2.3)	8 (1.5)		3 (1.6)	22 (2.1)	
Ever incarcerated							
No	1157 (91.5)	725 (97.7)	432 (82.6)	<0.001	172 (88.7)	985 (92.0)	0.168
Yes	108 (8.5)	17 (2.3)	91 (17.4)		22 (11.3)	86 (8.0)	

Table 4. 4 Healthcare facilities attendance stratified by gender and incident LTBI status in 1275 participants

Variables	Total N (%)	Gender		p-value	Incident LTBI		p-value
		Female	Male		Yes	No	
Hospitalization							
No	1198 (94.0)	690 (92.4)	508 (96.2)	0.007	184 (94.8)	1014 (93.8)	0.691
Yes	77 (6.0)	57 (7.6)	20 (3.8)		10 (5.2)	67 (6.2)	
Attend any medical clinics/facilities							
No	398 (31.2)	195 (26.1)	203 (38.4)	<0.001	73 (37.6)	325 (30.1)	0.044
Yes	877 (68.8)	552 (73.9)	325 (61.6)		121 (62.4)	756 (69.9)	
Type of medical clinics/facilities attended							
Attend drug shop							
No	984 (77.2)	575 (77.0)	409 (77.5)	0.891	166 (85.6)	818 (75.7)	0.003
Yes	291 (22.8)	172 (23.0)	119 (22.5)		28 (14.4)	263 (24.3)	
Attend health center							
No	1094 (85.9)	622 (83.3)	472 (89.6)	0.002	172 (88.7)	922 (85.4)	0.272
Yes	180 (14.1)	125 (16.7)	55 (10.4)		22 (11.3)	158 (14.6)	
Attend clinic							
No	673 (52.8)	365 (48.9)	308 (58.3)	0.001	111 (57.2)	562 (52.0)	0.206
Yes	602 (47.2)	382 (51.1)	220 (41.7)		83 (42.8)	519 (48.0)	
Attend hospital							
No	1161 (91.1)	668 (89.4)	493 (93.4)	0.020	176 (90.7)	985 (91.1)	0.966
Yes	114 (8.9)	79 (10.6)	35 (6.6)		18 (9.3)	96 (8.9)	

Visit family or friend in hospital							
No	869 (68.2)	496 (66.4)	373 (70.6)	0.123	127 (65.5)	742 (68.6)	0.429
Yes	406 (31.8)	251 (33.6)	155 (29.4)		67 (34.5)	339 (31.4)	

Table 4. 5 Transportation use and travel history stratified by gender and LTBI status in 1275 participants

Variables	Total N (%)	Gender		p-value	Incident LTBI		p-value
		Female	Male		Yes	No	
Transportation use in daily life							
Model of transport used most							
Walking	409 (32.4)	313 (42.2)	96 (18.4)	<0.001	52 (26.9)	357 (33.4)	0.139
Bicycle/motorcycle	299 (23.7)	132 (17.8)	167 (32.1)		55 (28.5)	244 (22.8)	
Taxi/Bus	506 (40.1)	289 (39.0)	217 (41.7)		76 (39.4)	430 (40.2)	
Private car/Lorry	48 (3.8)	7 (0.9)	41 (7.9)		10 (5.2)	38 (3.6)	
Use taxi							
No	425 (33.8)	269 (36.3)	156 (30.1)	0.026	71 (36.8)	354 (33.2)	0.376
Yes	834 (66.2)	472 (63.7)	362 (69.9)		122 (63.2)	712 (66.8)	
Number of hours spent on taxi per day, mean (SD)	3.89 (4.95)	3.71 (4.79)	4.13 (5.15)	0.218	4.45 (6.17)	3.80 (4.71)	0.176
Travel outside Kampala							
Travel outside Kampala							
No	364 (28.5)	240 (32.1)	124 (23.5)	0.001	53 (27.3)	311 (28.8)	0.745
Yes	911 (71.5)	507 (67.9)	404 (76.5)		141 (72.7)	770 (71.2)	
Reasons to travel outside Kampala							
Travel to visit family/relatives							
No	658 (51.6)	367 (49.1)	291 (55.1)	0.040	105 (54.1)	553 (51.2)	0.494
Yes	617 (48.4)	380 (50.9)	237 (44.9)		89 (45.9)	528 (48.8)	
Travel for vocation/holiday							
No	1177 (92.3)	682 (91.3)	495 (93.8)	0.131	182 (93.8)	995 (92.0)	0.480
Yes	98 (7.7)	65 (8.7)	33 (6.2)		12 (6.2)	86 (8.0)	

Travel to work							
No	950 (74.5)	670 (89.7)	280 (53.0)	<0.001	131 (67.5)	819 (75.8)	0.020
Yes	325 (25.5)	77 (10.3)	248 (47.0)		63 (32.5)	262 (24.2)	
Travel for funeral/burial							
No	983 (77.1)	559 (74.8)	424 (80.3)	0.026	150 (77.3)	833 (77.1)	1.000
Yes	292 (22.9)	188 (25.2)	104 (19.7)		44 (22.7)	248 (22.9)	
Modes of transportation used to travel outside Kampala							
Use motorcycle to travel							
No	1159 (90.9)	693 (92.8)	466 (88.3)	0.008	174 (89.7)	985 (91.1)	0.616
Yes	116 (9.1)	54 (7.2)	62 (11.7)		20 (10.3)	96 (8.9)	
Use private vehicle/lorry to travel							
No	1046 (82.0)	666 (89.2)	380 (72.0)	<0.001	151 (77.8)	895 (82.8)	0.120
Yes	229 (18.0)	81 (10.8)	148 (28.0)		43 (22.2)	186 (17.2)	
Use taxi/bus to travel							
No	438 (34.4)	262 (35.1)	176 (33.3)	0.559	65 (33.5)	373 (34.5)	0.851
Yes	837 (65.6)	485 (64.9)	352 (66.7)		129 (66.5)	708 (65.5)	
Duration of time spent on transportation to travel outside Kampala							
Average hours in a mode of transport, Mean (SD)	4.09 (2.60)	3.80 (2.22)	4.45 (2.98)	<0.001	4.29 (3.37)	4.05 (2.44)	0.318

Table 4. 6 Univariate, Bivariate and multivariate analysis using modified Poisson regression to identify risk factors of incident LTBI (model without interaction)

Variables	Total	No. of incident LTBI (%)	Univariate analysis Crude RR (95% CI)	Bivariate analysis Adjusted RR (95% CI)	Multivariate analysis Adjusted RR (95% CI)
Age in years, median (IQR)			**1.03 (1.02, 1.04)**	**1.03 (1.01, 1.05)**	**1.03 (1.01, 1.04)**
Sex					
Female	747	95 (12.7)	1.00	1.00	1.00
Male	528	99 (18.8)	**1.47 (1.14, 1.91)**	**1.47 (1.14, 1.91)**	**1.44 (1.11, 1.86)**
Religion					
Roman Catholic	518	62 (12.0)	1.00	1.00	1.00
Others	755	131 (17.4)	**1.45 (1.09, 1.92)**	**1.46 (1.08, 1.98)**	**1.49 (1.13, 1.97)**
Smoking					
No	1219	178 (14.6)	1.00	1.00	
Yes	49	14 (28.6)	**1.96 (1.23, 3.11)**	**1.76 (1.01, 3.05)**	
Alcohol use					
Non-users	989	143 (14.5)	1.00	1.00	
Light users	192	30 (15.6)	1.08 (0.75, 1.55)	1.06 (0.72, 1.57)	
Heavy users	75	18 (24.0)	**1.66 (1.08, 2.55)**	1.57 (0.96, 2.57)	
Contact with TB patients over past 12 months before enrollment					
No	1158	168 (14.5)	1.00	1.00	1.00
Yes	110	25 (22.7)	**1.57 (1.08, 2.27)**	**1.61 (1.06, 2.45)**	**1.51 (1.05, 2.17)**
Mostly drink in Malwa/Waragi/Tonto drinking setting					
No	1231	184 (14.9)	1.00	1.00	
Yes	26	8 (30.8)	**2.06 (1.14, 3.72)**	1.89 (0.93, 3.86)	

Attend drug shop					
No	984	166 (16.9)	1.00	1.00	1.00
Yes	291	28 (9.6)	**0.57 (0.39, 0.83)**	**0.57 (0.38,0.85)**	**0.59 (0.40, 0.85)**
Model of transport used most					
Walking	409	52 (12.7)	1.00	1.00	
Bicycle/Motorcycle	299	55 (18.4)	**1.45 (1.02, 2.09)**	1.30 (0.88, 1.92)	
Taxi/Bus	506	76 (15.0)	1.18 (0.85, 1.64)	1.11 (0.77, 1.58)	
Private car/Lorry	48	10 (20.8)	1.64 (0.89, 3.01)	1.35 (0.67, 2.71)	
Number of hours spent on taxi per day, mean (SD)	1275	194 (15.2)	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)	
Travel to visit family/relatives					
No	658	105 (16.0)	1.00	1.00	
Yes	617	89 (14.4)	0.90 (0.7, 1.17)	0.92 (0.70, 1.23)	
Travel to work					
No	950	131 (13.8)	1.00	1.00	
Yes	325	63 (19.4)	**1.41 (1.07, 1.85)**	1.22 (0.87, 1.69)	
Use private vehicle/lorry to travel					
No	1046	151 (14.4)	1.00	1.00	
Yes	229	43 (18.8)	1.30 (0.96, 1.77)	1.18 (0.83, 1.67)	

Table 4. 7 Multivariate analysis using modified Poisson regression to identify risk factors for new LTBI (model with interactions)

Variables	Total	No. of LTBI (%)	Adjusted RR (95% CI)
Age in years, median (IQR)	1252	190	**1.03 (1.01, 1.04)**
Sex			
Female	736	95 (12.9)	1.00
Male	516	95 (18.4)	1.30 (0.97, 1.73)
Religion			
Roman Catholic	506	60 (11.9)	1.00
Others	746	130 (17.4)	**1.49 (1.12, 1.97)**
Contact with TB patients over past 12 months before enrollment			
No	1145	165 (14.4)	**1.00**
Yes	107	25 (23.4)	**1.51 (1.05, 2.17)**
Education level × Attend drug shop			
Education level, None or primary			
Attend drug shop, No	312	45 (14.4)	1.00
Attend drug shop, Yes	87	13 (14.9)	1.02 (0.59, 1.77)
Education level, Secondary/Post-secondary			
Attend drug shop, No	655	117 (17.9)	1.00
Attend drug shop, Yes	198	15 (7.6)	**0.40 (0.25, 0.65)**
Alcohol user × Travel outside Kampala to work			
Alcohol user, No			
Travel outside Kampala to work, No	749	106 (14.2)	1.00
Travel outside Kampala to work, Yes	237	37 (15.6)	0.99 (0.68, 1.45)
Alcohol user, Yes			
Travel outside Kampala to work, No	187	24 (12.8)	1.00
Travel outside Kampala to work, Yes	80	23 (29.1)	**2.00 (1.17, 3.44)**

CHAPTER 5

TUBERCULOSIS TRANSMISSION IN PUBLIC SETTINGS IN AN AFRICAN CITY: RESULTS FROM POPULATION-BASED PROSPECTIVE COHORT STUDY [3]

[3] Quach HTT, Kiwanuka N, Zalwango S, Kakaire R, Sekandi NJ, Dobbin KK, Naeher L, Castellanos ME, Whalen CC. To be submitted to Clinical Infectious Diseases.

ABSTRACT

Objectives: Although more than 80% of TB transmission occurred outside households of TB cases, there has been a lack of knowledge on where TB transmission occurred in the community. This study was to identify social settings associated to TB transmission.

Method: We conducted a prospective, community-based cohort study of adult individuals without latent tuberculosis infection (LTBI) in Kampala, Uganda from 2014 to 2016. After one year of follow up, participants were retested with TST and HIV rapid test to evaluate new infection. We measured the amount of time spent per day in different 12 settings during typical day and weekend at baseline and every 3 month visits. Wilcoxon or Kruskal-Wallis tests were used to examine discrepancy in the amount time spent by typical day or weekend, sex, and age groups. Mean or max amount of time spent among visits were fitted into modified Poisson regression models to identify settings associated with TB transmission.

Results: We enrolled 1681 participants. Of these, 406 (24%) were lost to follow up. Among 1275 with available follow up TST results, proportion of male was 58.6% and the median (IQR) of age was 24 (20 – 29). Participants spent most of their time at own home and workplace. The amount of time spent in settings was different by typical day/weekend, sex, and age groups. Spending time at worship center (aRR 1.14, 95% CI 1.07 – 1.21 for typical day) and schools (aRR 1.09, 95% CI 1.00 – 1.18 for typical day and aRR 1.16, 95% CI 1.02 – 1.31 for weekend) increased risk of getting LTBI, while staying at home especially during weekend (aRR 0.96, 95% CI 0.93 – 0.99) lowered the risk of getting LTBI.

Conclusion: Worship centers and schools were hot spots for TB transmission. The findings of this study can guide the infection control interventions for National TB Control Programs by finding TB cases and reducing TB transmission in these two places.

INTRODUCTION

Tuberculosis (TB) has existed for millennia and remains a major global health problem. In 2019, TB is one of the ten leading causes of death worldwide with 10 million incident cases and 1.4 million deaths (WHO, 2020b). Nearly one fourth of the world's population is infected with TB and at risk of progressing to tuberculosis disease (WHO, 2018b). Uganda is one of the 30 WHO-designated countries with a high burden of TB/HIV. In 2019, the estimated incidence rate for TB was 200 per 100,000 population and mortality rate was 35 per 100,000 population (WHO, 2020b). HIV has been an important driver of the epidemic. Although the prevalence of HIV infection was 5.7% among adults aged 15 to 49 years old in Uganda ("HIV and AIDS in Uganda," 2020), the prevalence of latent TB infection in this age group was high at 49% (Kizza et al., 2015). It is likely that there are other factors contributing to high rates of tuberculosis transmission in urban African settings.

Despite the huge global burden of tuberculosis disease, there are important gaps in understanding TB transmission: locations or settings where TB transmission occurs. Household contact investigations are the key components of tuberculosis control programs as the majority of transmission is thought to occur among close household contacts. However, recent studies suggest that the proportion of transmission that actually occurs in household in high burden countries was less than 20% (Martinez, Shen, et al., 2017). Given that a minority of transmission occurs among household contacts in high-burden countries, the majority of transmission presumably occurs in a variety of community-based settings. However, to date, there has been a few of studies using modified Wells and Riley equation to estimate TB transmission in social settings (e.g. public transportation, prison, religious hall, and etc.) (Andrews et al., 2014; Andrews et al., 2013; Hella et al., 2017; Wood et al., 2012). A modified Wells and Riley equation takes into account the rebreathed air fraction (estimated from indoor and outdoor CO2 levels), time at risk, the infectious dose (quanta of contagion), and the number of people occupying the confined space to estimate TB transmission in a specific location. There have been no studies designed to estimate risk of TB transmission in relation to social settings.

We therefore conducted a study to estimate risk of TB infection from a susceptible cohort. We identified potential settings associated to TB transmission in African city by measuring duration of time spent in different settings per day and then linking it with risk of TB transmission.

METHOD

Study population and measurements

We performed a prospective study within a cohort of adult African individuals without evidence of latent tuberculosis infection (LTBI). Between June 2014 to June 2016, a cohort of 1681 individuals was recruited from residents of Rubaga division of Kampala, Uganda. The inclusion criteria were: Tuberculin skin test (TST) below 5 mm at baseline, age between 17 and 60 years, and no signs or symptoms of active tuberculosis. A standard clinical evaluation was performed to assess risk of acquiring a new tuberculosis infection at baseline and quarterly visits. At one year, participants were retested with TST to detect new infection defined as TST conversion. We planned to recruit 2000 participants and follow them for one year. To estimate sample size of 2000 participants, we assumed that 5% of participants converted TST. However, we were not able to enroll 2000 participants in reality, and thus had to increase the follow up time to ensure power of study. Participants who were negative with TST at the end of one year, were asked to extend their follow-up time to 2 years.

Demographic, social, and clinical characteristics were obtained through interviews performed by trained field workers using standardized questionnaires. Participants had a visit for every 3 months and were asked how the amount of time spent in settings during typical day and weekend. Because the perception of time in Uganda is discontinuous and not measured by clocks or watches, we developed a pictorial survey that adapts a familiar local board game to measure amount of time spent in 16 settings including own home, friend's home, relative home, neighbor's home, workplace, school, worship center, club/association, women group, bar, market, trading center/kiosk/shop, hair saloon, gym/recreation, hospital/clinic, and public transport. The game included a board with a representative set of pictures from settings where residents of Kampala may spend their time. A participant was given 24 beads to represent 24 hours in the day and was asked to place beads on the board as the number of hours spend in each setting. This instrument was proved to be valid and reliable (Schwartz et al., 2019).

TST was performed by placing 5 tuberculin units of purified protein derivative on the left forearm of each participant using the Mantoux method. Two field workers independently read the diameter of induration within 48 to 72 hours. The diameter of the skin test induration was measured using the "ball-point" technique with digital calipers to reduce digit preference bias. HIV testing was performed following the Uganda Ministry of Health National Testing algorithms. All participants were administered a Determine HIV-1/2 and a HIV 1/2 STAT-PAK; a Uni-gold HIV test was performed if there were discrepant results for the initial tests.

In HIV-seronegative subjects, a TST conversion was defined as having a second tuberculin skin test reading of 10 millimeters or greater with an increase in reaction of six millimeters or greater from the first to the second reading. In HIV-seropositive subjects, a TST conversion was defined as having a second tuberculin skin test reading of five millimeters or greater with an increase in induration of three millimeters or greater from the first to the second reading. If the above conditions were not met, subjects were classified as persistent skin test negative.

Analytic strategy

Baseline characteristics of subset of subjects with available repeated TST results were summarized with proportions and measures of central tendency. We combined women group and club/association as social gathering; relative homes, friend's home, and neighbor's home as other homes; market and trading center/kiosk/shop as shopping sites.

Incidence of TST conversion was estimated by two methods: simple cumulative incidence and incidence density. Cumulative incidence of TST conversion was estimated as proportion with 95% confidence intervals. To estimate cumulative incidence of TST over study period, we used TST results with the longest follow up time. To estimate annual risk of LTBI (cumulative incidence of TST conversion over 12 months of follow up), we restricted to TST results within 12-month period. In estimation of incidence density, we used the date of retesting TST or last date seen to obtain duration of following up. Because the incidence of TST conversion was reported in chapter 3 and 4, the incidence was not presented in this chapter. To fit into univariate and multivariate models, TST conversion over study period was used.

We summarized how participants spent their time over their typical day and weekend in table 5.2 and figure 5.1. For each setting, we estimated the number of participants attending, and the number of visits that participants specified their attendance. We are more interested in the amount of time spent at a setting if a participant visited a setting than the mean duration of time spent in a day across participants. Therefore, we excluded visits without participant's attendance before estimating duration of time spent in each setting during typical day or weekend in table 5.2. The distribution of time spent in each setting over typical day or weekend was illustrated by histograms (figure 5.1). Duration of time spent in each setting during typical day or weekend was summarized as mean with standard deviation and median with interquartile range (table 5.2).

Because the amount of time spent in settings did not have a normal distribution, discrepancy in the amount of time spent over typical day and weekend was detected by Wilcoxon test and the tests were conducted on subgroup of participants attending the settings only.

We described the differences between men and women in the amount of time spent in 12 settings (figure 5.2). We want to know that when men and women spent their time in a setting in a day, whether men spent shorter or longer duration of time in a specific setting. Therefore, we excluded visits without participants' attendance. The Wilcoxon test was used to detect the discrepancy in the amount of time spent in a setting between men and women. Similarly, we stratified the amount of time spent by age category and then examined the discrepancy in the amount of time spent among age groups by Kruskal-Wallis test.

As an explanatory analysis explored potential settings where TB transmission might occur, we stratified the amount of time spent by TST conversion status. If participants did not attend a setting, the amount of time is zero and included in this analysis. Because the majority of participants did not attend some settings, the median with interquartile is not an effective way to summarize the amount of time spent in settings. We summarized the amount of time spent in a setting by mean with standard deviation though data is not normally distributed.

As we measured duration of time spent at every three months, we had multiple measurements for the amount of time spent in each setting. To fit into the model, we used the mean or max of duration of time spent across the visits as a summary. The Poisson regression model with robust error variance was used as it is a better approach for estimating relative risks for cohort studies with common binary outcome compared to using logistic regression (Zou, 2004). We performed univariate and multivariate models for each setting separately. In multivariate models, we adjusted for age, sex, religion, have been in contact with TB patients over past one year before enrollment, and drug shop attendance. To explore potential interactions, a global test for two-way interactions between the amount of time spent in a setting and other factors was performed and found to be significant at the 10% level. Multivariate analysis with potential interaction terms was tested with statistically significant level at the 5%. R version 3.6.1 was used for all analyses.

RESULTS

Study population characteristics

Of 1681 participants, 1275 participants (76%) had TST follow up. Except for history of contact with TB patient during follow up, characteristics of participants with available TST follow up were similar to characteristics of participants who were lost to follow up. Among 1275 participants, the median age was 24 years (IQR 20 – 29). The proportion of male was 41%. The prevalence of HIV-infection at baseline was 5%. Roman Catholic religion accounted for 40%. Most of participants were BCG vaccinated (92%) and have never smoked (96%). The proportion of participants consuming alcohol was 21% including 15% light users and 6% heavy users. The proportion of participants being in contact with a TB patient over the past one year before enrollment was 9% (Table 5.1).

The amount of time spent in different setting over typical day or weekend

The number of visits when participants specified their attendance in a setting, the number of participants attending, and the amount of time spent in a setting over typical day and weekend were described in figure 5.1 and table 5.2. A total of 6439 visits occurred to interview 1275 participants about how they spent their time in typical day and weekend. Of 6439 visits, spending at own home was listed most with 6384 visits for typical day and 6371 visits for weekend, following by workplace with 4793 visits for typical day and 3210 visits for weekend. Participants were more often to attend social settings during weekend than typical day. For typical day, settings listed in more than 1000 visits were public transport (1700 visits) and shopping sites (1175 visits). For weekend, setting listed in more than 1000 visits were worship center (2161 visits), public transport (1411 visits), other homes (1253 visits), and shopping sites (1038 visits).

All participants reported their attendance in their own home over typical day and weekend, following by workplace with 1212 participants for typical day and 1099 participants for weekend. During typical day, the settings with more than a quarter of participants attending were public transport (866 participants), shopping sites (659 participants), and other homes (528 participants). For weekend, settings with more than a quarter of participants attending were worship center (995 participants), public transport (812 participants), other homes (789 participants), and shopping sites (626 participants) (figure 5.1 and table 5.2).

The mean and median amount of time spent were estimated among participants reporting their attendance in a setting. The setting with longest duration of time spent was own home with median 12 hours during typical day and 15 hours during weekend, following by workplace with median 11 hours during typical day and 10 hours during weekend and school with median 8 hours during typical day and 6.0 during weekend. Otherwise, participants spent a median of 4 hours or less in other settings in their typical day and weekend (figure 5.1 and table 5.2). Except for social gathering and public transportation, the amount of time spent in settings in typical day was different from that of weekend. Compared to weekend, participants spent more time at workplace (median 11.2 vs. 10.0 hours, p-value < 0.001), school (median 8.8 vs. 7.3 hours, p-value = 0.001), and hair saloon (mean 3.2 vs 2.0 hours, p-value = 0.013) during typical day. In contrast, participants spent more time at own home (mean 15.8 vs. 13.8 hours, p-value < 0.001), other homes (mean 3.6 vs. 2.9 hours, p < 0.001), and bar (mean 4.2 vs. 3.2, p-value < 0.001 during weekend than typical day.

We stratified the duration of time spent in settings by sex and age groups. If the amount of time spent is zero, it was excluded from this analysis. During typical day, compared to men, women spent more time at own home and worship center, and spent less time at workplace and shopping sites instead. During weekend, compared to men, women spent more time at own home, worship center, hair saloon, and public transport, and spent less time at other homes and shopping sites instead. In terms of age groups, participants aged 30 to 60 years had the lowest amount of time spent at home, but highest amount of time spent at bar than others age groups in both typical day and weekend. Participants aged 17 to 21 years old had the highest amount of time spent at school than other age groups in both typical day and weekend. Across the age groups, the amount of time spent at shopping sites increased as age increased.

We stratified the duration of time spent by LTBI status. During typical day, participants with the development of LTBI spent more time at worship center than participants without the development of LTBI (mean 0.3 vs. 0.1 hours). During weekend, participants acquiring LTBI spent more time at other homes (mean 0.9 vs. 0.7 hours), but spent less time at their own homes (mean 15.0 vs. 15.7 hours), compared to participants who did not acquiring LTBI.

We adjusted for age, sex, religion, having contact with TB patients over past one year before enrollment, and attending drug shop in multivariate models. Spending time at worship center (aRR 1.14, 95% CI 1.07 – 1.21 for typical day) and school (aRR 1.09, 95% CI 1.00 – 1.18 for typical day and aRR 1.16, 95% CI 1.02 – 1.31 for weekend) increased the risk of acquiring LTBI. Spending time at own home over typical day (RR 0.97, 95% CI 0.93 – 1.00) and weekend (RR 0.96, 95% CI 0.93 – 1.00) lowered the risk of acquiring LTBI in univariate analysis. After adjusted for other factors, spending time at own home was not statistically significant association with TB transmission. As a sensitivity analysis, we used max amount of time spent as a summary.

Spending time at worship center and school during typical day were still risk factors for development of LTBI, while spending at their own home during weekend was a protective factor against acquisition of LTBI (aRR 0.96, 95% CI 0.93 – 0.99).

DISCUSSION

To our knowledge, there have been no studies measuring incidence of latent tuberculosis infection in general population: a direct outcome of TB transmission in the community and then linked this outcome with duration of time spent in different settings. Over decades, we conducted household contact investigation as households have the high yield of new TB cases. However, conducting active case finding in household of TB cases was not sufficient to control TB because most of tuberculosis infections (more than 80%) were estimated to be outside of one's own household in high burden countries. There has been a lack of studies on settings or locations where TB transmission occurred in high burden countries. Our study provides insight into where TB transmission can occur by using optimal estimation for TB transmission – incidence of TB infection. In this study, we found that participants spent most of their time at own home and workplace. The amount of time spent in settings was different by typical day or weekend day, sex, and age groups. In our models, we take into account these differences. Spending time at worship centers and schools increased risk of getting LTBI, while staying at home especially during weekend lowered the risk of getting LTBI.

Schools are characterized by high social contact rates, crowding and high population density. Also, schools are one of setting types contributed the majority of indoor contacts in the community (Wood et al., 2012). These make school be an ideal environment for TB transmission in both rural or urban settings. In our study, spending time at school during typical day and weekend was found as a risk factor for acquisition of LTBI in both models using mean and max of exposure. A study using models derived from Wells – Riley equation found that schools were a high-risk environment for transmission among young adults (Andrews et al., 2014; Patterson et al., 2017). In another study conducted in Tanzania, their models derived from Wells-Riley equation found that annual risk of TB transmission in school is small at around 4% (Taylor et al., 2016). The reason to explain this lower risk was that schools in Tanzania had open windows and good ventilation. Obviously, environment profile of indoor settings varied by countries and relied on cultural construction. With local knowledge of the school environment in Kampala Uganda, schools could be places for TB transmission.

In our study, we found that spending time at worship centers during typical day was found as a risk factor for acquisition of TB infection in both models using mean and max of exposure. However, we did not found a statistical significant association between spending time at worship center during weekend and acquisition of LTBI. The reason for this could be that number of participants attending church increased substantially from typical day to weekend. As a result, the size effect was diluted or reduced. In contrast to school, worship centers are places for mixing between age groups and sex and likely drive TB transmission from men to women and from adults to young children. It is reported that 19% of casual contact occurred in worship center (Dodd et al., 2015), which suggests that worship centers are important areas for TB transmission and can play an crucial role in TB control program.

Participants spent most of their time at their own home and workplace. Most of close contact (73%) occurred at own home in South Africa, while workplace contained 5% of close contacts and 15% of casual contacts. Obviously, own homes and workplaces would be important areas for TB transmission if TB cases are present in these areas. In our study, we found that staying at home during could reduce the transmission, which is obviously true in the application to

COVID-19 pandemic. However, it is reported that 41% of TB transmission among adults occurred in workplaces, which is contrast to our study result – no association between spending time at workplaces and acquisition of LTBI (Andrews et al., 2014). An explanation for this could be that workplaces could include various types of setting such as office building, flea market, and etc. This is limitation of our study that we did not collect type of settings for workplaces.

In conclusion, staying at home can protect participants against TB infection, while spending time at worship centers and schools increase the risk of acquiring TB infection. The findings of this study can guide the targeted infection control interventions for National TB Control Programs. Schools are places mainly for young adults while worship centers are general mixing between age groups or between sex. Therefore, TB Control Programs targeting at schools can be appropriate for population with the huge burden of TB infection contributing mainly from young adults, while the programs targeting at worship centers are appropriate to reduce TB transmission in overall population.

Table 5. 1 Characteristics of 1275 participants with available TST follow up

Characteristics	Frequency (%)
Age in years, median (IQR)	24 (20, 29)
Sex	
Female	747 (58.6)
Male	528 (41.4)
Monthly income, Ushs	
99,999 or less than	453 (35.6)
100,000 - 199,999	383 (30.1)
200,000 or more	435 (34.2)
Religion	
Roman Catholic	518 (40.7)
Others	755 (59.3)
Marital status	
Married	707 (55.5)
Never married	568 (44.5)
Education level	
None or Primary	406 (31.9)
Secondary/Post-secondary	866 (68.1)
BCG vaccination	
No/Unknown	99 (7.8)
Probably Yes	147 (11.5)
Yes	1029 (80.7)
Smoking	
Never smoked	1219 (96.1)
Former/current smoker	49 (3.9)
Alcohol use	
Non-users	989 (78.7)
Light users	192 (15.3)
Heavy users	75 (6.0)
HIV test at baseline	
Negative	1205 (94.5)
Positive	61 (4.8)
Refused	9 (0.7)
Have been in contact with TB patients over past one year before enrollment (n=1268)	
No	1158 (91.3)
Yes	110 (8.7)
Drug shop attendance (n=1274)	
No	1094 (85.9)
Yes	180 (14.1)

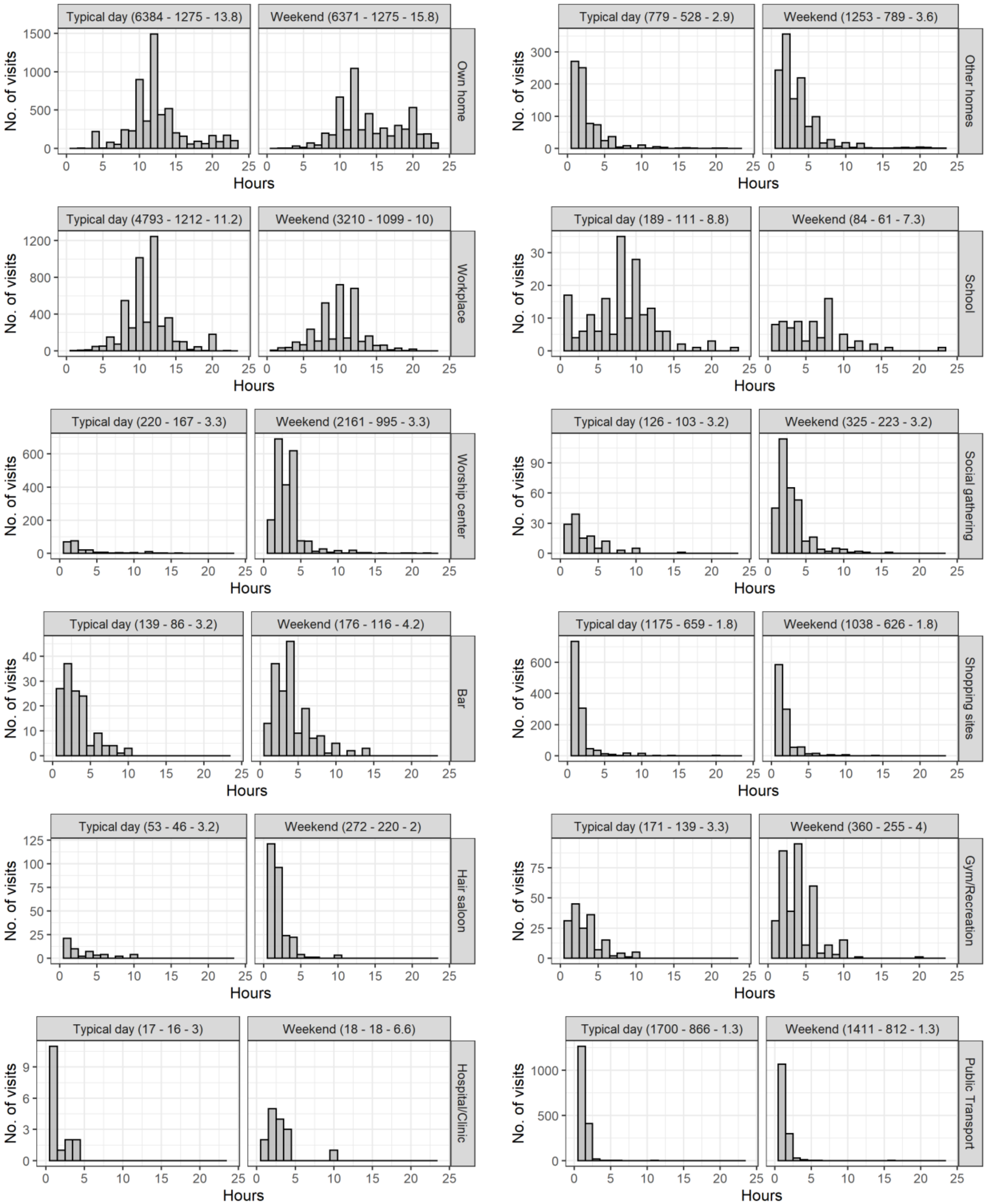

Figure 5. 1 Distribution of time spent at 12 different settings over their typical day and weekend in 1275 participants. Total number of visits is 6439. In panels with x1 – x2 –x3, x1 is the number of visits, and x2 is the number of participants attending, x3 is mean of duration of time spent.

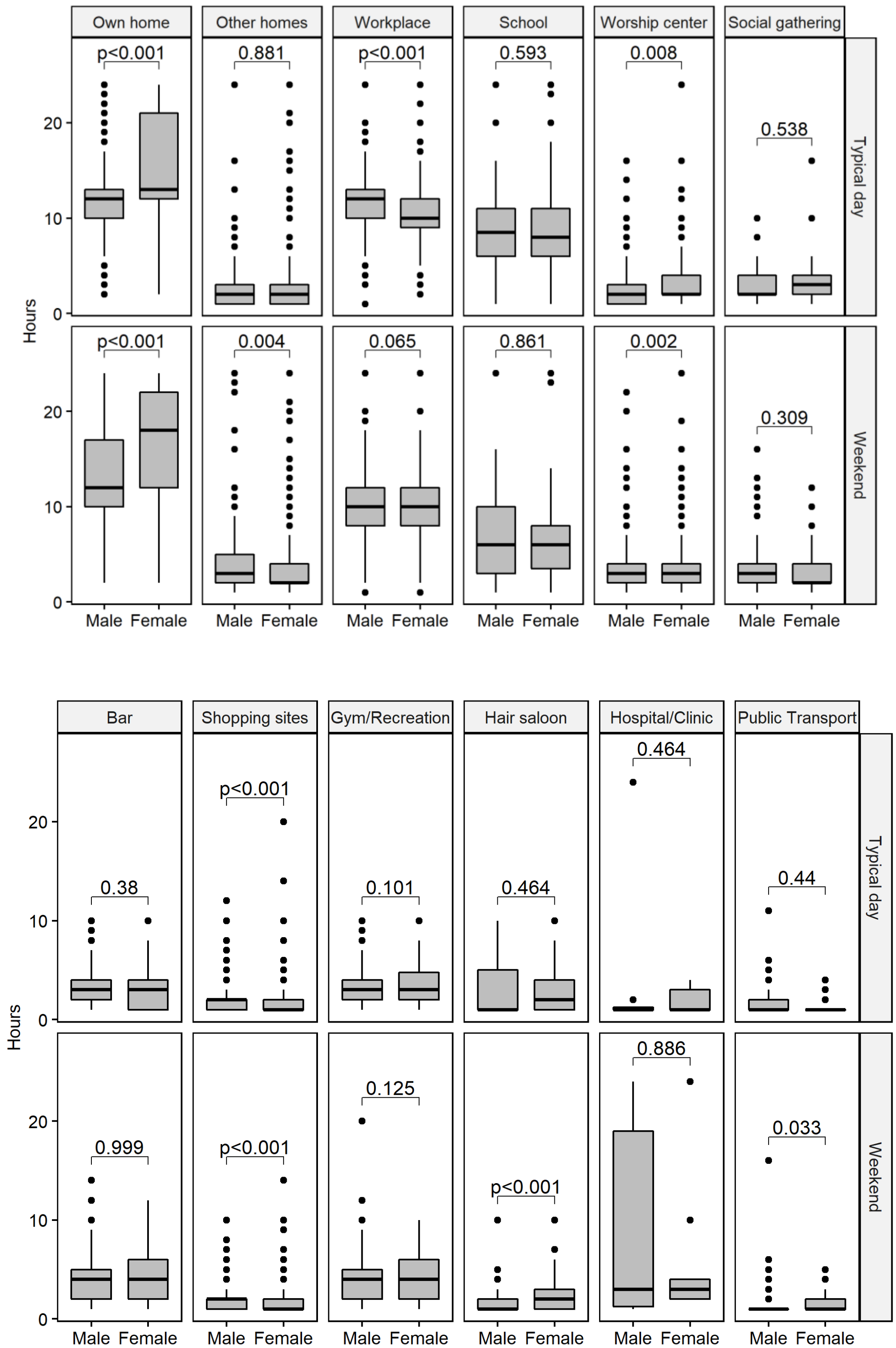

Figure 5. 2 Differences in duration of time spent between male and female over typical day and weekend

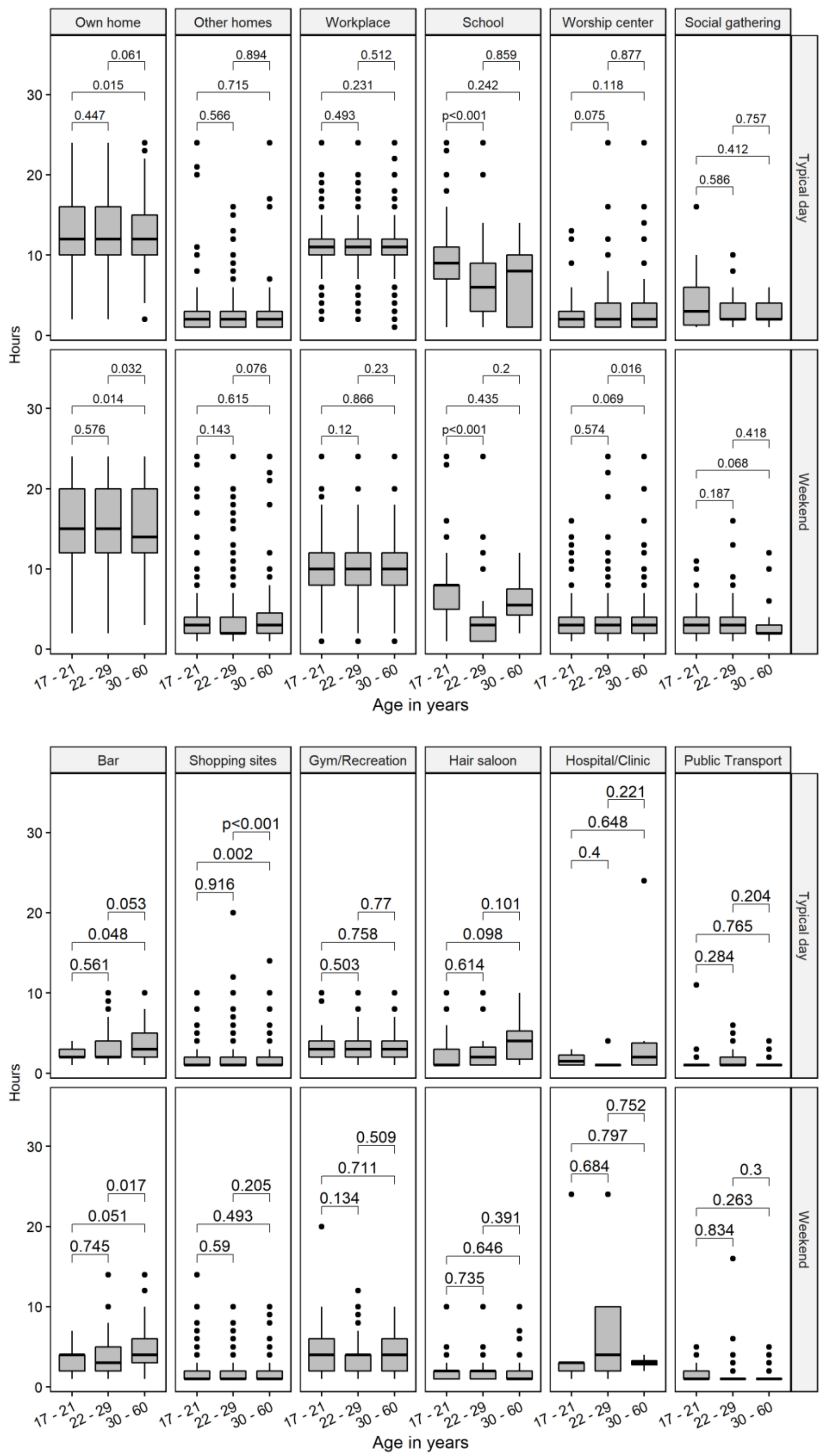

Figure 5. 3 Differences in duration of time spent between age groups over typical day and weekend

Table 5. 2 Compare duration of time spent over typical day and weekend among 1275 participants when they spent time at a setting

Settings	Typical day recall				Weekend recall				p-value*
	N†	n††	Total Mean (SD) ¥	Median (IQR) ¥	N†	n†	Total Mean (SD) ¥	Median (IQR) ¥	
Own home	6384	1275	13.8 (5.3)	12.0 (10.0, 16.0)	6371	1275	15.8 (5.4)	15.0 (12.0, 20.0)	<0.001
Other homes	779	528	2.9 (3.3)	2.0 (1.0, 3.0)	1253	789	3.6 (3.3)	3.0 (2.0, 4.0)	<0.001
Workplace	4793	1212	11.2 (3.1)	11.0 (10.0, 12.0)	3210	1099	10.0 (3.2)	10.0 (8.0, 12.0)	<0.001
School	189	111	8.8 (5.2)	8.0 (6.0, 11.0)	84	61	7.3 (6.1)	6.0 (3.0, 8.0)	0.001
Worship center	220	167	3.3 (3.7)	2.0 (1.0, 4.0)	2161	995	3.3 (2.0)	3.0 (2.0, 4.0)	<0.001
Social gathering	126	103	3.2 (2.5)	2.0 (2.0, 4.0)	325	223	3.2 (2.2)	3.0 (2.0, 4.0)	0.461
Bar	139	86	3.2 (2.1)	3.0 (2.0, 4.0)	176	116	4.2 (2.6)	4.0 (2.0, 6.0)	<0.001
Shopping sites	1175	659	1.8 (1.7)	1.0 (1.0, 2.0)	1038	626	1.8 (1.4)	1.0 (1.0, 2.0)	0.003
Hair Saloon	53	46	3.2 (2.7)	2.0 (1.0, 4.0)	272	220	2.0 (1.4)	2.0 (1.0, 2.0)	0.013
Gym/Recreation	171	139	3.3 (2.1)	3.0 (2.0, 4.0)	360	255	4.0 (2.4)	4.0 (2.0, 6.0)	<0.001
Hospital/Clinic	17	16	3.0 (5.5)	1.0 (1.0, 3.0)	18	18	6.6 (8.3)	3.0 (2.0, 4.0)	0.008
Public Transport	1700	866	1.3 (0.6)	1.0 (1.0, 2.0)	1411	812	1.3 (0.7)	1.0 (1.0, 1.0)	0.641

† Number of visits when participant specified their attendance

†† Number of participants attending

¥ the estimation excluded zeros which indicates that participants did not attend a setting

*p-value from Wilcoxon test and on the subgroup spending their time in the setting only

Table 5. 3 Duration of time spent in 12 settings among 1275 participants stratified by incident LTBI status. When participants did not attend a setting, the amount of time spent was zero and included to estimate mean.

Settings	Typical day recall				Weekend recall			
	Total Mean (SD)	Incident LTBI		p-value*	Total Mean (SD)	Incident LTBI		p-value*
		Yes Mean (SD) (n=194)	No Mean (SD) (n=1081)			Yes Mean (SD) (n=194)	No Mean (SD) (n=1081)	
Own home	13.7 (3.6)	13.2 (3.5)	13.8 (3.6)	0.146	15.6 (3.5)	15.0 (3.6)	15.7 (3.4)	0.036
Other homes	0.4 (0.7)	0.3 (0.5)	0.4 (0.8)	0.666	0.7 (1.1)	0.9 (1.2)	0.7 (1.0)	0.053
Workplace	8.4 (3.9)	8.7 (4.2)	8.3 (3.9)	0.337	5.0 (3.6)	5.3 (3.8)	4.9 (3.6)	0.726
School	0.3 (1.3)	0.4 (1.5)	0.3 (1.2)	0.243	0.1 (0.7)	0.2 (0.9)	0.1 (0.6)	0.310
Worship center	0.1 (0.6)	0.3 (1.2)	0.1 (0.5)	0.013	1.1 (1.3)	1.1 (1.7)	1.1 (1.1)	0.006
Social gathering	0.1 (0.3)	0.1 (0.2)	0.1 (0.3)	0.825	0.1 (0.5)	0.2 (0.5)	0.1 (0.4)	0.424
Bar	0.1 (0.4)	0.1 (0.6)	0.1 (0.4)	0.219	0.1 (0.5)	0.1 (0.6)	0.1 (0.5)	0.397
Shopping sites	0.3 (0.5)	0.3 (0.4)	0.3 (0.5)	0.413	0.3 (0.4)	0.3 (0.5)	0.3 (0.4)	0.838
Hair Saloon	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	0.214	0.1 (0.2)	0.1 (0.3)	0.1 (0.2)	0.202
Gym/Recreation	0.1 (0.3)	0.1 (0.4)	0.1 (0.3)	0.623	0.2 (0.6)	0.2 (0.7)	0.2 (0.6)	0.787
Hospital/Clinic	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.757	0.0 (0.3)	0.0 (0.4)	0.0 (0.2)	0.628
Public Transport	0.3 (0.4)	0.3 (0.3)	0.3 (0.4)	0.982	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.202

*p-value from Wilcoxon test

Table 5. 4 Univariate and multivariate modified Poisson regression to identify settings that TB transmission could occur during typical day

Variables	Models with mean exposure across visits as summary		Models with max exposure across visits as summary	
	Crude RR (95% CI)	Adjusted RR (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
Own home	**0.97 (0.93, 1)**	0.99 (0.95, 1.04)	**0.97 (0.94, 0.99)**	0.98 (0.95, 1.01)
Other homes	0.91 (0.75, 1.10)	0.91 (0.75, 1.10)	0.96 (0.91, 1.01)	096 (0.91, 1.01)
Workplace	1.02 (0.98, 1.06)	1 (0.96, 1.04)	0.99 (0.96, 1.02)	0.98 (0.95, 1.01)
School	1.05 (0.97, 1.14)	**1.09 (1, 1.18)**	1.02 (0.98, 1.05)	**1.03 (1, 1.06)**
Worship center	**1.19 (1.12, 1.27)**	**1.14 (1.07, 1.21)**	**1.05 (1.01, 1.1)**	**1.04 (1, 1.09)**
Social gathering	0.81 (0.48, 1.36)	0.76 (0.45, 1.28)	0.94 (0.83, 1.05)	0.92 (0.82, 1.04)
Bar	1.19 (0.98, 1.46)	0.98 (0.76, 1.26)	1.05 (0.94, 1.16)	0.97 (0.87, 1.08)
Shopping sites	0.88 (0.68, 1.15)	0.85 (0.66, 1.10)	0.96 (0.88, 1.04)	0.95 (0.87, 1.03)
Hair saloon	0.78 (0.32, 1.94)	0.84 (0.37, 1.91)	0.87 (0.67, 1.13)	0.89 (0.7, 1.13)
Gym/Recreation	1.16 (0.82, 1.64)	1.02 (0.72, 1.45)	1 (0.9, 1.1)	0.96 (0.87, 1.07)
Hospital/Clinic	0.23 (0.01, 8.82)	0.26 (0.01, 10.33)	0.73 (0.38, 1.42)	0.75 (0.37, 1.53)
Public Transport	0.94 (0.66, 1.34)	0.9 (0.63, 1.29)	0.93 (0.79, 1.08)	0.9 (0.77, 1.05)

Adjusted for age, sex, religion, having contact with TB patients over past 1 year before enrollment, attending drug stores

Table 5. 5 Univariate and multivariate modified Poisson regression to identify settings that TB transmission could occur during weekend

Variables	Models with mean exposure across visits as summary		Models with max exposure across visits as summary	
	Crude RR (95% CI)	Adjusted RR (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
Own home	**0.96 (0.93, 1)**	0.99 (0.95, 1.03)	**0.94 (0.92, 0.97)**	**0.96 (0.93, 0.99)**
Other homes	**1.11 (1.01, 1.22)**	1.10 (0.99, 1.22)	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)
Workplace	1.01 (0.98, 1.05)	0.99 (0.95, 1.03)	1 (0.97, 1.02)	0.98 (0.96, 1.01)
School	**1.13 (0.99, 1.3)**	**1.16 (1.02, 1.31)**	1.03 (0.98, 1.07)	1.03 (0.99, 1.07)
Worship center	0.98 (0.84, 1.14)	1 (0.88, 1.12)	0.95 (0.88, 1.02)	0.97 (0.9, 1.03)
Social gathering	1.12 (0.95, 1.32)	1.06 (0.89, 1.27)	1.00 (0.93, 1.08)	0.98 (0.91, 1.05)
Bar	1.1 (0.91, 1.33)	0.93 (0.75, 1.17)	1.02 (0.95, 1.1)	0.97 (0.89, 1.06)
Shopping sites	1.14 (0.88, 1.47)	1.10 (0.86, 1.40)	1.01 (0.93, 1.10)	1.01 (0.93, 1.09)
Hair saloon	0.76 (0.3, 1.93)	0.93 (0.42, 2.04)	0.88 (0.74, 1.03)	0.93 (0.79, 1.09)
Gym/Recreation	1.02 (0.8, 1.29)	0.96 (0.75, 1.22)	0.98 (0.92, 1.04)	0.97 (0.91, 1.03)
Hospital/Clinic	1.11 (0.74, 1.69)	1.07 (0.69, 1.67)	1.02 (0.94, 1.11)	1.01 (0.93, 1.11)
Public Transport	1.2 (0.83, 1.71)	1.16 (0.82, 1.64)	1.02 (0.91, 1.15)	1.02 (0.92, 1.14)

Adjusted for age, sex, religion, having contact with TB patients over past 1 year before enrollment, attending drug stores

CHAPTER 6

SYNTHESIS OF RESULTS, PUBLIC HEALTH IMPLICATIONS AND CONCLUSION

Scientific knowledge on the subject

Tuberculosis incidence rate was falling, but fail to reach the 2020 milestone of a 20% reduction between 2015 and 2020 (WHO, 2020b). Actually, the cumulative reduction from 2015 to 2019 was 9%, which was less than half way to the milestone (WHO, 2020b). The global rate of decline in tuberculosis incidence was projected to increase to 10% per year by 2025, while this rate is just 2.3% between 2018 and 2019. Obviously, our current tools to halt TB transmission having around for decades were not enough to drive down TB epidemics and meet End TB targets. WHO emphasized that to achieve the target, it requires expanding the scope and research for TB prevention. A critical component of what is necessary for success has been too often neglected: an explicit focus on halting transmission. There have been gaps in understanding TB transmission including local determinants of transmission and where TB transmission occurred in the community. These gaps may be undermining our efforts to end TB. Incidence of LTBI is a key epidemiological indicator of the extent of TB transmission in a community. Therefore, we conducted a study to measure incidence of TB infection, examine risk factors for TB transmission, and identify settings or locations where TB transmission occurred. Compared to other studies, our study had multiple strengths that are conducting on general population vs. high risk population, estimating incidence of TB infection vs. prevalence of TB infection, examining a myriad of potential risk factors vs. a few of risk factors, identifying locations or settings for TB transmission by using incidence of TB infection as outcome vs. modelling with some assumptions and using prevalence of TB infection. The main disadvantages of our study was 24% of loss of follow up, which could cause selection bias, affecting the accuracy of incidence of LTBI and measurement of exposure.

What this study adds to the field

The annual risk of TB infection in an African city was high (11.8%). Annual risk of LTBI in HIV-infected individuals was 1.93%. Former/current smoker (22.7%), heavy alcohol users (19.7%), and individuals being in contact with TB patients over one year before enrollment and during follow up (20.5) were as high risk of acquiring LTBI as HIV-infected individuals. Although confidence intervals for annual risk of infections in these special populations including HIV-infected participants were wide due to small sample sizes, this suggests that preventive therapy to control TB disease development from LTBI should be targeted on these special populations, the same as we did for HIV-infection population. The current WHO guideline does not recommend prophylaxis treatment on people who engage in the harmful use of alcohol, smokers, and extra household contacts of TB case (WHO, 2020c).

The prevalence of HIV infection at baseline was 4.7%. The incidence of HIV infection was low at 1.9% for average of 379 days of follow up. However, prevalence of TB infection in the general population in Uganda was estimated to be 49% (Kizza et al., 2015). Uganda is one of the 30 WHO-designated countries with a high burden of TB/HIV as the overall TB incidence rate was estimated 204 per 100,000 population, of which 40% were co-infected with HIV (WHO, 2018b). Obviously, HIV infection could be explained for as much as 40% of TB incidence rate in Uganda, but cannot explain for the high prevalence and high incidence of LTBI in general population. Of 143 LTBI at the end of 12-month period, only 11 (7.7%) were HIV-infected. Of overall annual risk of LTBI of 11.8%, only 1.2% are from HIV-infected participants and the remainder of 10.6% are from uninfected HIV. It is likely that other factors drive TB epidemics in Uganda.

Of 1275 participants, the proportion of participants who have been in contact with a TB patient was 15% for either one year before enrollment or during follow up and 3% for both periods. Obviously, a small proportion of population (3%) was always in contact with TB cases year by year. A high proportion of population (18%) was in contact with their known TB cases though prevalence of TB cases was approximately 1% in general population (J. Sekandi et al., 2014). We do not know how high the proportion of population being in recent contact of TB cases is when unaware TB contacts were not considered. However, we can estimate the lower limit for this proportion. Because the incidence of LTBI among participants who reported that they have not been in contact with TB cases in one year before enrollment and during follow up was 14.5%, at least 14.5% of these participants were in contact with unaware TB cases. As a results, at least 29.4% of population have been in contact with TB cases.

Being older was positively associated with acquisition of LTBI. Because all participants were negative with TST at enrollment, the higher risk of getting LTBI among older people could not be explained by the cumulative risk over their lifetime which is thought to be the reason in numerous cross-sectional studies (Gao et al., 2015; Kizza et al., 2015). Findings from other studies has shown that prevalence of LTBI was not different between age groups who were household contacts of TB cases (Kakaire et al., 2020). It is found that increasing numbers of social contacts occurred throughout childhood, adolescence, and young adulthood (Wood et al., 2012). Therefore, we suggest that the reasons to explain the higher risk of LTBI among older people were more social contacts and more mobility as age increased. We found that the group aged 17 to 21 years old had the highest duration of time spent at school (median 8 hours) and spending time at school also increased the risk of getting LTBI. As a result, schools are places for TB transmission among adolescent and young adulthood. A TB control program targeted at school should be appropriate to reduce the TB in adolescent and young adulthood. When peoples were above school-age, they spent a large proportion of the day in workplace instead of school. Workplaces therefore have the high probability of being places where TB transmission occurs. In our study, we did not find the significant association between incidence of LTBI and duration of time spent at workplace because workplace could include a variety of setting types. Our study did not collect the information to classify the workplaces. How participants spent their time during typical day is different from during weekend. Besides own home and workplace, people were more likely to attend social settings or other homes over weekend than during typical day. This suggests that TB transmission was more often to occur in social settings or other homes during weekend than during typical day. In our study, we found that besides school, worship centers were congregate settings associated with TB transmission. Worship centers have the mixing between age groups and sex and therefore are more likely to drive TB transmission from men to women and from adults to young children. The TB control program targeted in worship center can reduce the TB transmission in all components of the population. Because TB cases were not restricted their mobility, worship centers and schools in Kampala Uganda should be constructed and improved by the way that have a good ventilation. Social gathering during weekend should be encouraged to be held outdoor or indoor settings with good ventilation or staying at home especially during weekend could reduce the risk of acquiring TB infection. In addition to worship centers as TB hot spots for TB transmission, religious affiliations could affect the risk of getting LTBI. Differences in risk of getting LTBI between religions could be attributable to differences in religious environment and practices. The further research is needed to explore the reasons behind.

Annual risk of LTBI was 9.0% (95% CI 7.2 – 11.3) among women and 15.2 (95% CI 12.3 – 18.7) among men. As a result, men had 1.6 (95% CI 1.24 – 2.29) times higher risk of getting LTBI than women. Rather than the biological differences between men and women, the reason for this could be that men had more social activities and therefore have more opportunities to expose to TB cases than women. Based on our analysis results, we have multiple evidences to support the reason for higher risk of acquiring LTB among men. Firstly, the interaction between sex and ever known any TB cases. Men and women had the same risk of getting LTBI if they reported that they have ever known any TB cases, which indicated that men were as susceptible as women to TB infection. The risk of getting LTBI was different by sex when they reported that they have never known any TB cases, which suggests that men were more likely to be in social contact of TB case than women. Secondly, the risk of getting LTBI was not different by sex among group aged 17 to 21 years old, but was different among older groups. As peoples are at school age, the number of their social contacts was lower than older groups and mainly come from school, which is not likely to differentiate between men and women. Thirdly, compared to women, men were less likely to work at home (4.5% vs. 34.7%) and were likely to travel to work (47.0% vs. 10.3%). Last but not least, men spent less time at own home during typical day and weekend than women, so men spent more time outside their own home and had more extra household contacts. We found that spending time at own home during weekend could reduce the risk of getting LTBI.

Drug shop attendance could lower the risk of getting LTBI among participants with secondary or post-secondary education, but could not among people with none or primary education. Possibly, participants with secondary or post-secondary attended drug shop for practices which could prevent TB infection. However, this is just our hypothesis. A further research is needed to explore the methods to prevent infection, which might exist in a subgroup of the population.

Policy implications

The findings of this study were meaningful to authority and the public by different ways. For the public, they should be informed of the following findings: (1) heavy alcohol users, smokers, HIV-infected persons, and have been in contact with TB patients for successive years are at high risk of getting TB infection with 20% per year or 1 in 5 getting infection per year; (2) TB transmission more likely occurs in worship centers and schools; (3) 18% of population who know that they are in contact of TB cases. Even though peoples think they have not been in contact with TB case, they are more likely to be in contact network of unknown TB case and are at risk of getting infection with 10% per year or 1 in 10 getting infection per year. Therefore, the public could take actions accordingly. For example, screening with TST test and treating TB infection if they are infected, wearing masks in high risk settings or crowded areas, and preferring outdoor activities to reduce the transmission. They should be aware of persons with coughing and avoid being close proximity to both known TB cases or suspected TB cases with coughing. For local authority or government, they need to be informed of the following results: (1) Annual risk of TB infection is high at 12%. Therefore, both human and financial resources should be budgeted for TB control program; (2) Heavy alcohol users, smokers, and have been in contact with TB patients for successive years are as high risk of getting TB infection as HIV-infected person with 20% per year or 1 in 5 getting infection per year. The prophylaxis treatment for latent tuberculosis infection should be given to not only HIV-infected person but also smokers, heavy alcohol users, and persons who have been in contact with TB patients for multiple successive years; (3) TB transmission more likely occurs in worship centers and schools. They should improve building code in worship centers or schools to increase ventilation. Schools should be targeted places to reduce TB burden among adolescent and young adults while worship center should be targeted places for TB control program to reduce TB burden in all age group.

Conclusion

At least 29% of adults have been in contact with TB patients. As a result, tuberculosis is spread at high rate in urban African setting. Around 12% of a susceptible population will get infected annually. Some subgroups of the population were as high risk of getting LTBI as HIV-infected group, including smokers, heavy alcohol users, and being in contact with TB patient year by year. Therefore, prophylaxis treatment should be considered on these subgroups. Among participants who got infected over 12-month period, only 8% were HIV-infected. In meanwhile, HIV-infected accounted for 40% of TB cases in Uganda. Men and women were different in social behaviors and the amount of time spent in settings. Being older, men, non-religious Roman Catholic were risk factors for acquisition of TB infection, while attending drug shop and staying at own home were protective factors against acquisition of TB infection. Worship centers and schools were community-based settings where TB transmission occurred. The higher risk of getting LTBI among men and older people was explained by the more social activities rather than biological differences. Religious affiliation and churches could play an important role in TB control program. A further research was needed to understand why drug shop attendance could lower risk of LTBI among people with higher level of education. There may be local practices which were used by this group only and were effective to prevent TB transmission.

REFERENCE

Adams, S., Ehrlich, R., Baatjies, R., van Zyl-Smit, R. N., Said-Hartley, Q., Dawson, R., & Dheda, K. (2015). Incidence of occupational latent tuberculosis infection in South African healthcare workers. *European Respiratory Journal, 45*(5), 1364-1373.

Adetifa, I. M., Muhammad, A. K., Jeffries, D., Donkor, S., Borgdorff, M. W., Corrah, T., & D'Alessandro, U. (2015). A tuberculin skin test survey and the annual risk of Mycobacterium tuberculosis infection in Gambian school children. *PLoS One, 10*(10), e0139354.

Andrews, J. R., Hatherill, M., Mahomed, H., Hanekom, W. A., Campo, M., Hawn, T. R., . . . Scriba, T. J. (2015). The dynamics of QuantiFERON-TB gold in-tube conversion and reversion in a cohort of South African adolescents. *American Journal of Respiratory and Critical Care Medicine, 191*(5), 584-591.

Andrews, J. R., Morrow, C., Walensky, R. P., & Wood, R. (2014). Integrating social contact and environmental data in evaluating tuberculosis transmission in a South African township. *The Journal of infectious diseases, 210*(4), 597-603.

Andrews, J. R., Morrow, C., & Wood, R. (2013). Modeling the role of public transportation in sustaining tuberculosis transmission in South Africa. *American Journal of Epidemiology, 177*(6), 556-561.

Awofeso, N. (2010). Prisons as social determinants of hepatitis C virus and tuberculosis infections. *Public Health Reports, 125*(4_suppl), 25-33.

Balkhy, H. H., El Beltagy, K., El-Saed, A., Aljasir, B., Althaqafi, A., Alothman, A. F., . . . Al-Jahdali, H. (2017). Prevalence of latent Mycobacterium tuberculosis infection (LTBI) in Saudi Arabia; population based survey. *International Journal of Infectious Diseases, 60*, 11-16.

Blanco-Guillot, F., Castañeda-Cediel, M. L., Cruz-Hervert, P., Ferreyra-Reyes, L., Delgado-Sanchez, G., Ferreira-Guerrero, E., . . . Torres-Gonzalez, P. (2018). Genotyping and spatial analysis of pulmonary tuberculosis and diabetes cases in the state of Veracruz, Mexico. *PLoS One*, *13*(3), e0193911.

Borgdorff, M. W. (2002). Annual risk of tuberculous infection: time for an update? *Bulletin of the World Health Organization, 80*, 501-502.

Brooks-Pollock, E., Becerra, M. C., Goldstein, E., Cohen, T., & Murray, M. B. (2011). Epidemiologic inference from the distribution of tuberculosis cases in households in Lima, Peru. *Journal of Infectious Diseases, 203*(11), 1582-1589.

Carbone, A. d. S. S., Paião, D. S. G., Sgarbi, R. V. E., Lemos, E. F., Cazanti, R. F., Ota, M. M., . . . Simionatto, S. (2015). Active and latent tuberculosis in Brazilian correctional facilities: a cross-sectional study. *BMC Infectious Diseases*, *15*(1), 24.

Castellanos, M., Kirimunda, S., Martinez, L., Quach, T., Woldu, H., Kakaire, R., . . . Whalen, C. (2018). Performance of the QuantiFERON®-TB Gold In-Tube assay in tuberculin skin test converters: a prospective cohort study. *The international journal of tuberculosis and lung disease*, *22*(9), 1000-1006.

Cauthen, G., Pio, A., & Ten Dam, H. (2002). Annual risk of tuberculous infection. *Bulletin of the World Health Organization, 80*, 503-511.

Cdc., A. (1990). Tuberculosis Among Foreign-Born Persons Entering the United States--Recommendations of the Advisory Committee for Elimination of Tuberculosis. *MMWR.*, *39*(RR-18), 1-21.

Chamie, G., Wandera, B., Marquez, C., Kato-Maeda, M., Kamya, M. R., Havlir, D. V., & Charlebois, E. D. (2015). Identifying locations of recent TB transmission in rural Uganda: a multidisciplinary approach. *Tropical Medicine & International Health*, *20*(4), 537-545.

Chandrasekaran, P., Mave, V., Thiruvengadam, K., Gupte, N., Shivakumar, S. V. B. Y., Hanna, L. E., . . . Paradkar, M. (2018). Tuberculin skin test and QuantiFERON-Gold In Tube assay for diagnosis of latent TB infection among household contacts of pulmonary TB patients in high TB burden setting. *PLoS One, 13*(8), e0199360.

Churchyard, G., Kim, P., Shah, N. S., Rustomjee, R., Gandhi, N., Mathema, B., . . . Cardenas, V. (2017). What we know about tuberculosis transmission: an overview. *The Journal of infectious diseases*, *216*(suppl_6), S629-S635.

Cobelens, F. G., Egwaga, S. M., Ginkel van, T., Muwinge, H., Matee, M. I., & Borgdorff, M. W. (2006). Tuberculin skin testing in patients with HIV infection: limited benefit of reduced cutoff values. *Clinical Infectious Diseases, 43*(5), 634-639.

Colditz, G. A., Berkey, C. S., Mosteller, F., Brewer, T. F., Wilson, M. E., Burdick, E., & Fineberg, H. V. (1995). The efficacy of bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. *Pediatrics*, *96*(1), 29-35.

Cook, V., Kuramoto, L., Noertjojo, K., Elwood, R., & Fitzgerald, J. (2006). BCG vaccination and the prevalence of latent tuberculosis infection in an aboriginal population. *The international journal of tuberculosis and lung disease, 10*(12), 1347-1353.

Dodd, P. J., Looker, C., Plumb, I. D., Bond, V., Schaap, A., Shanaube, K., . . . Corbett, E. L. (2015). Age-and sex-specific social contact patterns and incidence of Mycobacterium tuberculosis infection. *American Journal of Epidemiology, 183*(2), 156-166.

Doocy, S. C., Todd, C. S., Llainez, Y. B., Ahmadzai, A., & Burnham, G. M. (2008). Population-based tuberculin skin testing and prevalence of tuberculosis infection in Afghanistan. *World Health Population, 10*(1), 44-53.

Drain, P. K., Bajema, K. L., Dowdy, D., Dheda, K., Naidoo, K., Schumacher, S. G., . . . Sherman, D. R. (2018). Incipient and subclinical tuberculosis: a clinical review of early stages and progression of infection. *Clinical Microbiology Reviews, 31*(4), e00021-00018.

Edelson, P. J., & Phypers, M. (2011). TB transmission on public transportation: a review of published studies and recommendations for contact tracing. *Travel Medicine and Infectious Disease, 9*(1), 27-31.

Fox, G. J., Barry, S. E., Britton, W. J., & Marks, G. B. (2013). Contact investigation for tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal, 41*(1), 140-156.

Gao, L., Bai, L., Liu, J., Lu, W., Wang, X., Li, X., . . . Xin, H. (2016). Annual risk of tuberculosis infection in rural China: a population-based prospective study. *European Respiratory Journal, 48*(1), 168-178.

Gao, L., Lu, W., Bai, L., Wang, X., Xu, J., Catanzaro, A., . . . Du, J. (2015). Latent tuberculosis infection in rural China: baseline results of a population-based, multicentre, prospective cohort study. *The Lancet Infectious Diseases, 15*(3), 310-319.

Gardy, J. L., Johnston, J. C., Sui, S. J. H., Cook, V. J., Shah, L., Brodkin, E., . . . Holt, R. (2011). Whole-genome sequencing and social-network analysis of a tuberculosis outbreak. *New England Journal of Medicine, 364*(8), 730-739.

Glaziou, P., Sismanidis, C., Zignol, M., & Floyd, K. (2020). Methods used by WHO to estimate the global burden of TB disease. *Global TB Programme, WHO, Geneva*.

Grabowski, M. K., Serwadda, D. M., Gray, R. H., Nakigozi, G., Kigozi, G., Kagaayi, J., . . . Lutalo, T. (2017). HIV prevention efforts and incidence of HIV in Uganda. *New England Journal of Medicine, 377*(22), 2154-2166.

Guwatudde, D., Nakakeeto, M., Jones-Lopez, E., Maganda, A., Chiunda, A., Mugerwa, R., . . . Whalen, C. C. (2003). Tuberculosis in household contacts of infectious cases in Kampala, Uganda. *American Journal of Epidemiology, 158*(9), 887-898.

Hanifa, Y., Grant, A., Lewis, J., Corbett, E., Fielding, K., & Churchyard, G. (2009). Prevalence of latent tuberculosis infection among gold miners in South Africa. *The international journal of tuberculosis and lung disease, 13*(1), 39-46.

Hella, J., Morrow, C., Mhimbira, F., Ginsberg, S., Chitnis, N., Gagneux, S., . . . Fenner, L. (2017). Tuberculosis transmission in public locations in Tanzania: A novel approach to studying airborne disease transmission. *Journal of Infection, 75*(3), 191-197.

HIV and AIDS in Uganda. (2020). Retrieved from https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/uganda

Horna-Campos, O., Bedoya-Lama, A., Romero-Sandoval, N., & Martin-Mateo, M. (2010). Risk of tuberculosis in public transport sector workers, Lima, Peru. *The international journal of tuberculosis and lung disease, 14*(6), 714-719.

Horna-Campos, O. J., Consiglio, E., Sánchez-Pérez, H. J., Navarro, A., Caylà, J. A., & Martín-Mateo, M. (2011). Pulmonary tuberculosis infection among workers in the informal public transport sector in Lima, Peru. *Occupational and environmental medicine, 68*(2), 163-165.

Horne, D. J., Campo, M., Ortiz, J. R., Oren, E., Arentz, M., Crothers, K., & Narita, M. (2012). Association between smoking and latent tuberculosis in the US population: an analysis of the National Health and Nutrition Examination Survey. *PLoS One, 7*(11), e49050.

Ijaz, K., Yang, Z., Matthews, H. S., Bates, J. H., & Cave, M. D. (2002). Mycobacterium tuberculosis transmission between cluster members with similar fingerprint patterns. *Emerging Infectious Diseases, 8*(11), 1257.

Imtiaz, S., Shield, K. D., Roerecke, M., Samokhvalov, A. V., Lönnroth, K., & Rehm, J. (2017). Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. *European Respiratory Journal, 50*(1).

Janagond, A. B., Ganesan, V., Kumar, G. V., Ramesh, A., Anand, P., & Mariappan, M. (2017). Screening of health-care workers for latent tuberculosis infection in a Tertiary Care Hospital. *International Journal of Mycobacteriology, 6*(3), 253.

Joshi, R., Reingold, A. L., Menzies, D., & Pai, M. (2006). Tuberculosis among health-care workers in low-and middle-income countries: a systematic review. *PLoS medicine, 3*(12), e494.

Kakaire, R., Kiwanuka, N., Zalwango, S., Sekandi, J. N., Quach, T. H. T., Castellanos, M. E., . . . Whalen, C. C. (2020). Excess Risk of Tuberculosis Infection Among Extra-household Contacts of Tuberculosis Cases in an African City. *Clinical Infectious Diseases*.

Kasamba, I., Nash, S., Seeley, J., & Weiss, H. A. (2019). HIV incidence among women at high risk of HIV infection attending a dedicated clinic in Kampala, Uganda: 2008-2017. *Sex Transm Dis*. doi:10.1097/olq.0000000000000978

Kaufmann, S. H. (2002). Protection against tuberculosis: cytokines, T cells, and macrophages. *Annals of the Rheumatic Diseases, 61*(suppl 2), ii54-ii58.

Kim, S., Hong, Y., Lew, W., Yang, S., & Lee, E. (1995). Incidence of pulmonary tuberculosis among diabetics. *Tubercle and lung disease, 76*(6), 529-533.

King, E., Trabue, C., Yin, D., Yao, Z. Q., & Moorman, J. P. (2007). Hepatitis C: the complications of immune dysfunction. *Expert Review of Clinical Immunology, 3*(2), 145-157.

Kizza, F. N., List, J., Nkwata, A. K., Okwera, A., Ezeamama, A. E., Whalen, C. C., & Sekandi, J. N. (2015). Prevalence of latent tuberculosis infection and associated risk factors in an urban African setting. *BMC Infectious Diseases, 15*(1), 165.

Legesse, M., Ameni, G., Mamo, G., Medhin, G., Bjune, G., & Abebe, F. (2011). Community-based cross-sectional survey of latent tuberculosis infection in Afar pastoralists, Ethiopia, using QuantiFERON-TB Gold In-Tube and tuberculin skin test. *BMC Infectious Diseases, 11*(1), 89.

Lin, H.-H., Ezzati, M., & Murray, M. (2007). Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. *PLoS medicine, 4*(1), e20.

Lin, Y.-J., Lin, H.-C., Yang, Y.-F., Chen, C.-Y., Ling, M.-P., Chen, S.-C., . . . Liao, C.-M. (2019). Association between ambient air pollution and elevated risk of tuberculosis development. *Infection and Drug Resistance, 12*, 3835.

Lin, Y.-T., Wu, P.-H., Lin, C.-Y., Lin, M.-Y., Chuang, H.-Y., Huang, J.-F., . . . Chuang, W.-L. (2014). Cirrhosis as a risk factor for tuberculosis infection—a nationwide longitudinal study in Taiwan. *American Journal of Epidemiology, 180*(1), 103-110.

Luo, T., Yang, C., Peng, Y., Lu, L., Sun, G., Wu, J., . . . Mei, J. (2014). Whole-genome sequencing to detect recent transmission of Mycobacterium tuberculosis in settings with a high burden of tuberculosis. *Tuberculosis, 94*(4), 434-440.

Mack, U., Migliori, G., Sester, M., Rieder, H., Ehlers, S., Goletti, D., . . . Kampmann, B. (2009). LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. *European Respiratory Journal*, *33*(5), 956-973.

MacPherson, D. W., Gushulak, B. D., & Macdonald, L. (2007). Health and foreign policy: influences of migration and population mobility. *Bulletin of the World Health Organization*, *85*, 200-206.

Malacarne, J., Rios, D. P. G., Silva, C. M. F. P. d., Braga, J. U., Camacho, L. A. B., & Basta, P. C. (2016). Prevalence and factors associated with latent tuberculosis infection in an indigenous population in the Brazilian Amazon. *Revista da Sociedade Brasileira de Medicina Tropical*, *49*(4), 456-464.

Mancuso, J. D., Diffenderfer, J. M., Ghassemieh, B. J., Horne, D. J., & Kao, T.-C. (2016). The prevalence of latent tuberculosis infection in the United States. *American Journal of Respiratory and Critical Care Medicine, 194*(4), 501-509.

Mangili, A., & Gendreau, M. A. (2005). Transmission of infectious diseases during commercial air travel. *The Lancet*, *365*(9463), 989-996.

Martinez, L., Shen, Y., Mupere, E., Kizza, A., Hill, P. C., & Whalen, C. C. (2017). Transmission of Mycobacterium tuberculosis in households and the community: a systematic review and meta-analysis. *American Journal of Epidemiology, 185*(12), 1327-1339.

Martinez, L., Zhu, L., Castellanos, M. E., Liu, Q., Chen, C., Hallowell, B. D., & Whalen, C. C. (2017). Glycemic control and the prevalence of tuberculosis infection: a population-based observational study. *Clinical Infectious Diseases, 65*(12), 2060-2068.

Matsunaga, K., Klein, T. W., Friedman, H., & Yamamoto, Y. (2002). In vitro therapeutic effect of epigallocatechin gallate on nicotine-induced impairment of resistance to Legionella pneumophila infection of established MH-S alveolar macrophages. *The Journal of infectious diseases, 185*(2), 229-236.

Middelkoop, K., Mathema, B., Myer, L., Shashkina, E., Whitelaw, A., Kaplan, G., . . . Bekker, L.-G. (2014). Transmission of tuberculosis in a South African community with a high prevalence of HIV infection. *The Journal of infectious diseases, 211*(1), 53-61.

Miller, B. P., Zalwango, S., Galiwango, R., Kakaire, R., Sekandi, J., Steinbaum, L., . . . Kiwanuka, N. (2021). Association between tuberculosis in men and social network structure in Kampala, Uganda. *BMC Infectious Diseases, In press*.

Mondal, M., Nazrul, H. M., Chowdhury, M., & Howard, J. (2014). Socio-demographic factors affecting knowledge level of Tuberculosis patients in Rajshahi City, Bangladesh. *African Health Sciences, 14*(4), 855-865.

Moore, M., Valway, S. E., Ihle, W., & Onorato, I. M. (1999). A train passenger with pulmonary tuberculosis: evidence of limited transmission during travel. *Clinical Infectious Diseases, 28*(1), 52-56.

Morrison, J., Pai, M., & Hopewell, P. C. (2008). Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. *The Lancet Infectious Diseases, 8*(6), 359-368.

Musoke Mudido, P., Guwatudde, D., Nakakeeto, M., Bukenya, G., Nsamba, D., Johnson, J., . . . Whalen, C. (1999). The effect of bacille Calmette-Guerin vaccination at birth on tuberculin skin test reactivity in Ugandan children. *The international journal of tuberculosis and lung disease, 3*(10), 891-895.

Ncayiyana, J. R., Bassett, J., West, N., Westreich, D., Musenge, E., Emch, M., . . . Sanne, I. (2016). Prevalence of latent tuberculosis infection and predictive factors in an urban informal settlement in Johannesburg, South Africa: a cross-sectional study. *BMC Infectious Diseases, 16*(1), 661.

Negrato, C. A., & Gomes, M. B. (2013). Historical facts of screening and diagnosing diabetes in pregnancy. *Diabetology & metabolic syndrome, 5*(1), 22.

Olmos, P., Donoso, J., Rojas, N., Landeros, P., Schurmann, R., Retamal, G., . . . Martinez, C. (1989). Tuberculosis and diabetes mellitus: a longitudinal-retrospective study in a teaching hospital. *Rev Med Chil, 117*(9), 979-983.

Pablos-Mendez, A., Blustein, J., & Knirsch, C. A. (1997). The role of diabetes mellitus in the higher prevalence of tuberculosis among Hispanics. *American Journal of Public Health, 87*(4), 574-579.

Patterson, B., Morrow, C. D., Kohls, D., Deignan, C., Ginsburg, S., & Wood, R. (2017). Mapping sites of high TB transmission risk: Integrating the shared air and social behaviour of TB cases and adolescents in a South African township. *Science of the Total Environment, 583*, 97-103.

Paz-Soldan, V. A., Reiner Jr, R. C., Morrison, A. C., Stoddard, S. T., Kitron, U., Scott, T. W., . . . Astete, H. (2014). Strengths and weaknesses of Global Positioning System (GPS) dataloggers and semi-structured interviews for capturing fine-scale human mobility: findings from Iquitos, Peru. *PLoS Neglected Tropical Diseases, 8*(6), e2888.

Perri, B. R., Proops, D., Moonan, P. K., Munsiff, S. S., Kreiswirth, B. N., Kurepina, N., . . . Ahuja, S. D. (2011). Mycobacterium tuberculosis cluster with developing drug resistance, New York, New York, USA, 2003–2009. *Emerging Infectious Diseases, 17*(3), 372.

Rao, V., Gopi, P., Yadav, R., Subramani, R., Bhat, J., Anvikar, A., . . . Bhondeley, M. (2008). Annual risk of tuberculosis infection among tribal population of central India. *Tropical Medicine & International Health, 13*(11), 1372-1377.

Reis, N., Lopes, C., Teles, S. A., Matos, M., Carneiro, M., Marinho, T., . . . Martins, R. (2011). Hepatitis C virus infection in patients with tuberculosis in Central Brazil. *The international journal of tuberculosis and lung disease, 15*(10), 1397-1402.

Romeo, J., Wärnberg, J., Nova, E., Díaz, L. E., Gómez-Martinez, S., & Marcos, A. (2007). Moderate alcohol consumption and the immune system: a review. *British Journal of Nutrition, 98*(S1), S111-S115.

Rudnick, S. N., & Milton, D. K. (2003). Risk of indoor airborne infection transmission estimated from carbon dioxide concentration. *Indoor Air, 13*(3), 237-245. doi:10.1034/j.1600-0668.2003.00189.x

Sacchi, F. P., Praça, R. M., Tatara, M. B., Simonsen, V., Ferrazoli, L., Croda, M. G., . . . Croda, J. (2015). Prisons as reservoir for community transmission of tuberculosis, Brazil. *Emerging Infectious Diseases, 21*(3), 452.

Saito, K., Meyer, K., Warner, R., Basu, A., Ray, R. B., & Ray, R. (2006). Hepatitis C virus core protein inhibits tumor necrosis factor alpha-mediated apoptosis by a protective effect involving cellular FLICE inhibitory protein. *Journal of Virology, 80*(9), 4372-4379.

Schwartz, L. M., Mutanga, J., Kakaire, R., Davis-Olwell, P., Handel, A., Sekandi, J., . . . Whalen, C. C. (2019). Validation of a Pictorial Survey Tool to Measure Time Use in an African Urban Setting. *Sociological Methods & Research*, 0049124119826150.

Sekandi, J., List, J., Luzze, H., Yin, X., Dobbin, K., Corso, P., . . . Whalen, C. (2014). Yield of undetected tuberculosis and human immunodeficiency virus coinfection from active case finding in urban Uganda. *The international journal of tuberculosis and lung disease, 18*(1), 13-19.

Sekandi, J. N., Zalwango, S., Nkwata, A. K., Martinez, L., Kakaire, R., Mutanga, J. N., . . . Kiwanuka, N. (2018). Low Prevalence of Tuberculin Skin Test Boosting among Community Residents in Uganda. *Am J Trop Med Hyg, 98*(2), 379-381.

Shang, S., Ordway, D., Henao-Tamayo, M., Bai, X., Oberley-Deegan, R., Shanley, C., . . . Ackart, D. (2011). Cigarette smoke increases susceptibility to tuberculosis—evidence from in vivo and in vitro models. *Journal of Infectious Diseases, 203*(9), 1240-1248.

Stevenson, C. R., Forouhi, N. G., Roglic, G., Williams, B. G., Lauer, J. A., Dye, C., & Unwin, N. (2007). Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. *BMC Public Health, 7*(1), 234.

Swai, A., McLarty, D., & Mugusi, F. (1990). Tuberculosis in diabetic patients in Tanzania. *Tropical doctor, 20*(4), 147-150.

Taylor, J., Yates, T., Mthethwa, M., Tanser, F., Abubakar, I., & Altamirano, H. (2016). Measuring ventilation and modelling M. tuberculosis transmission in indoor congregate settings, rural KwaZulu-Natal. *The international journal of tuberculosis and lung disease, 20*(9), 1155-1161.

Van Crevel, R., Ottenhoff, T. H., & Van Der Meer, J. W. (2002). Innate immunity to Mycobacterium tuberculosis. *Clinical Microbiology Reviews*, *15*(2), 294-309.

Verver, S., Warren, R. M., Munch, Z., Richardson, M., van der Spuy, G. D., Borgdorff, M. W., . . . van Helden, P. D. (2004). Proportion of tuberculosis transmission that takes place in households in a high-incidence area. *The Lancet*, *363*(9404), 212-214.

Wang, W., Mathema, B., Hu, Y., Zhao, Q., Jiang, W., & Xu, B. (2014). Role of casual contacts in the recent transmission of tuberculosis in settings with high disease burden. *Clinical Microbiology and Infection*, *20*(11), 1140-1145.

Whalen, C. C. (2016). The Replacement Principle of Tuberculosis. Why Prevention Matters. In: American Thoracic Society.

Whalen, C. C., Zalwango, S., Chiunda, A., Malone, L., Eisenach, K., Joloba, M., . . . Mugerwa, R. (2011). Secondary attack rate of tuberculosis in urban households in Kampala, Uganda. *PLoS One*, *6*(2), e16137.

WHO. (2005). *Addressing poverty in TB control: options for national TB control programmes*: World Health Organization.

WHO. (2016). Global tuberculosis report 2016. In: WHO Geneva.

WHO. (2018a). *Latent tuberculosis infection: updated and consolidated guidelines for programmatic management* (9241550236). Retrieved from

WHO. (2018b). tuberculosis report 2018. *Geneva, Switzerland: World Health Organization*.

WHO. (2020a). Tuberculosis Fact Sheet. Retrieved from http://www.who.int/mediacentre/factsheets/fs104/en/

WHO. (2020b). tuberculosis report 2020. *Geneva, Switzerland: World Health Organization*.

WHO. (2020c). WHO consolidated guidelines on tuberculosis.

WHO. (2021). TB and migration. Retrieved from https://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis/areas-of-work/vulnerable-populations-risk-factors-and-social-determinants/tb-and-migration

Wilkinson, D., Pillay, M., Crump, J., Lombard, C., Davies, G. R., & Sturm, A. W. (1997). Molecular epidemiology and transmission dynamics of Mycobacterium tuberculosis in rural Africa. *Tropical Medicine & International Health, 2*(8), 747-753.

Williams, N. E., Thomas, T. A., Dunbar, M., Eagle, N., & Dobra, A. (2015). Measures of human mobility using mobile phone records enhanced with GIS data. *PLoS One, 10*(7), e0133630.

Woldu, H. G., Zalwango, S., Martinez, L., Castellanos, M. E., Kakaire, R., Sekandi, J. N., . . . Whalen, C. C. (2021). Defining an intermediate category of tuberculin skin test: A mixture model analysis of two high-risk populations from Kampala, Uganda. *PLoS One, 16*(1), e0245328.

Wood, R., Liang, H., Wu, H., Middelkoop, K., Oni, T., Rangaka, M. X., . . . Lawn, S. D. (2010). Changing prevalence of tuberculosis infection with increasing age in high-burden townships in South Africa. *The international journal of tuberculosis and lung disease, 14*(4), 406-412.

Wood, R., Racow, K., Bekker, L.-G., Morrow, C., Middelkoop, K., Mark, D., & Lawn, S. D. (2012). Indoor social networks in a South African township: potential contribution of location to tuberculosis transmission. *PLoS One, 7*(6), e39246.

Young, D. B., Perkins, M. D., Duncan, K., & Barry, C. E. (2008). Confronting the scientific obstacles to global control of tuberculosis. *The Journal of clinical investigation, 118*(4), 1255-1265.

Young, J., & O'connor, M. E. (2005). Risk factors associated with latent tuberculosis infection in Mexican American children. *Pediatrics, 115*(6), e647-e653.

Yuen, C. M., Amanullah, F., Dharmadhikari, A., Nardell, E. A., Seddon, J. A., Vasilyeva, I., . . . Becerra, M. C. (2015). Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment. *The Lancet, 386*(10010), 2334-2343.

Yusuf, H. R., Braden, C. R., Greenberg, A. J., Weltman, A. C., Onorato, I. M., & Valway, S. E. (1997). Tuberculosis transmission among five school bus drivers and students in two New York counties. *Pediatrics, 100*(3), E9.

Zhang, H., Xin, H., Li, X., Li, H., Li, M., Lu, W., . . . Jin, Q. (2017). A dose-response relationship of smoking with tuberculosis infection: A cross-sectional study among 21008 rural residents in China. *PLoS One*, *12*(4), e0175183.

Zou, G. (2004). A modified poisson regression approach to prospective studies with binary data. *American Journal of Epidemiology, 159*(7), 702-706.

APPENDICES

A QUESTIONNAIRES

Baseline TB Risk Assessment Form

41552

MAKERERE UNIVERSITY-UNIVERSITY OF GEORGIA RESEARCH COLLABORATION
COMMUNITY HEALTH AND SOCIAL NETWORKS OF TUBERCULOSIS
LONGITUDINAL BASELINE TB RISK ASSESSMENT FORM_ENGLISH Version_2

Network IDNO ☐☐☐☐☐ Interview Date ☐☐ / ☐☐ / ☐☐☐☐ (Day / Month / Year)

Now I would like to ask you questions that relate to how you may have interacted with diffent people.

1. Have you ever known anyone with TB disease?

☐ Yes ☐ No ☐ Uncertain

2. Have you ever lived in a home with someone who had TB disease?

☐ Yes ☐ No ☐ Uncertain

3a. In the past one year, have you been in contact with person(s) whom you knew had TB?

☐ Yes ☐ No ☐ Uncertain

If "YES" complete qns 3b-3d

3b. Did you live in the same household as this TB patient?

☐ Yes ☐ No ☐ Not applicable

3c. Did you sleep in the same bedroom as this TB patient?

☐ Yes ☐ No ☐ Not applicable

3d. Did you spend more than 4 hours at a time with this patient?

☐ Yes ☐ No ☐ Not applicable

[IF YES to EITHER questions 1 or 3a ask question 4 or else code 99 for Not applicable]

4a. To your knowledge did the person take treatment for TB?

☐ Yes ☐ Not applicable
☐ No ☐ Uncertain

4b. Did you help to take care of this patient?

☐ Yes ☐ Not applicable
☐ No ☐ Uncertain

Now I would like to ask you questionsabout your personal habits.

PERSONAL HABITS:

5. How would you describe your smoking habit?

☐☐
01 = Current smoker
02 = Former smoker (eg. quit) *Skip to 7a*
03 = Never smoked *Skip to Qn 8a*

6a. If currently smoking, for how long have you smoked?

☐☐ ☐ Days ☐ Months ☐ Years 99= Not applicable

6b. How many sticks do you smoke per day?:

☐☐ 99= Not applicable

7a. If former smoker, how many years did you smoke?

☐☐ Years 99= Not applicable *Skip to Qn 14*

8a. Do you drink alcohol ? ☐ Yes ☐ No

8b. If "Yes", what type of alcohol do you drink?

Tick all that Applies.

☐ Beer/Wine
☐ Spirits/crude/waragi
☐ Local brew
☐ Refused to answer
☐ Other Specify ☐

99= Not applicable

Int Initials: ☐☐	Comp Date	☐☐ / ☐☐ / ☐☐☐☐
Rev Initials: ☐☐	Rev Date	☐☐ / ☐☐ / ☐☐☐☐
DMO Initials: ☐☐	DMO Date	☐☐ / ☐☐ / ☐☐☐☐
CD Initials: ☐☐	CD Date	☐☐ / ☐☐ / ☐☐☐☐
		Day / Month / Year

Longitudinal Risk Assessment form page 1 of 3
Version 2 Date: Sept 10th, 2014

41552

TB RISK ASSESSMENT FORM_ENGLISH- Version2

Network IDNO ☐☐☐☐☐

Interview Date ☐☐ / ☐☐ / ☐☐☐☐ (Day / Month / Year)

9. When you drink, what type of setting do you use most times while drinking? [Prompt]
   - ☐ In drinking places outside road side shops
   - ☐ Inside an established bar
   - ☐ In a Malwa drinking setting
   - ☐ In Waragi/Tonto drinking setting
   - ☐ On celebration occasions
   - ☐ Other Specify ______

10. Have you ever tried to reduce your drinking habits or quit altogether? ☐ Yes ☐ No ☐ Uncertain

11. Has your family member, friend or healthcare provider told you that you should cut back on your drinking? ☐ Yes ☐ No ☐ Uncertain

12. Has your drinking ever interfered with your family life or work? ☐ Yes ☐ No ☐ Uncertain

13. Do you drink or crave a drink , as soon as you wake up from sleep? ☐☐ 01 = Yes 02 = No

14. Have you ever been incacerated? ☐ Yes ☐ No *If "NO" skip to Qn 17*

14b. Year of incarceration ☐☐☐☐

15. If "YES" ASK: For how long were you incacerated? ☐☐ ☐ Days ☐ Months ☐ Years

16 In which facility were you incacerated? ______

17. Do you work from home or outside the home? ☐ Work at home ☐ Work outside home

18. Have you worked in a mine /stone quarry/sand extraction ☐ Yes ☐ No *If "NO" Skip to Qn 19*

18a. If "Yes" for how long have you worked in this industry? ☐☐ ☐ Days ☐ Months ☐ Years

19. Do you work in a healthcare setting where you may have contact with patients? ☐ Yes ☐ No *If "NO" Skip to Qn 20*

19a. If "Yes" in which setting do you work?
   - ☐ Private hospital ☐ drug shop
   - ☐ Clinic ☐ Other ______
   - ☐ Pharmacy ☐ Public hospital

19b. For how long have you worked in this profession? ☐☐ ☐ Days ☐ Months ☐ Years

19c. What is/was your role at the hospital/clinic/office?
   - ☐ Doctor/Physician/clinician ☐ Laboratory technician
   - ☐ Nurse ☐ Admnistrator
   - ☐ Ancillary personnel ☐ Pharmacist

20. Over the last 30 days, how often did you ride in a Taxi? ☐☐
   - 01 = Daily
   - 02 = Less than one day/week
   - 03 = 1-3 days/week
   - 04 = 4-6 days per week
   - 05 = Every day
   - 99= Not applicable

21. Over the last 30 days, when you ride a taxi, how long is your usual trip? ☐☐
   - 01 = Less than one hr/trip
   - 02 = 1-3 hrs/trip
   - 03 = 4-6 hrs/trip
   - 04 = Over 6 hrs/trip
   - 99= Not applicable

Int Initials:	☐☐	Comp Date	☐☐ / ☐☐ / ☐☐☐☐
Rev Initials:	☐☐	Rev Date	☐☐ / ☐☐ / ☐☐☐☐
DMO Initials:	☐☐	DMO Date	☐☐ / ☐☐ / ☐☐☐☐
CD Initials:	☐☐	CD Date	☐☐ / ☐☐ / ☐☐☐☐
			Day / Month / Year

Longitudinal Risk Assessment form page 2 of 3)
Version 2 Date: September 10th, 2014

41552

RISK ASSESSMENT FORM_ENGLISH-ver2

Network IDNO ☐☐☐☐☐ Interview Date ☐☐ / ☐☐ / ☐☐☐☐ (Day / Month / Year)

22. Which form of transport do you use most often?

☐☐
01 = Bi/motorcycle/Bodaboda
02 = Taxi
03 = Private car
04 = Bus
05 = Private car (hire)
06 = Lorry/truck
88 = Others: ____________

23 .Have you ever been diagnosed with any of the following medical condition(s)? Prompt

a) Diabetes: ☐☐
b) Cancer (Hodgkins disease, head & neck cancer): ☐☐
c) Kidney disease: ☐☐
d) Depression: ☐☐
f) Asthma: ☐☐
g) Others(specify): ☐☐ ____________

01 = Yes
02 = No
77 = Uncertain
88= Other

24a. Do you take medication for your condition?:

☐ Yes ☐ No ☐ Not applicable

24b. If Yes, List medications: (refer to prescriptions, medicine bottle/packets)

____

25. Have ever been told you have HIV?

☐ Yes ☐ No ☐ No response

26. Have ever been told you have AIDS?

☐ Yes ☐ No ☐ No response

27. If "YES" how long have you known your HIV status?

☐☐ ☐ Days ☐ Months ☐ Years

Code 99 for Not Applicable

28. Are you currently taking HIV medication?

☐ Yes ☐ No ☐ Not applicable

If "YES" list meds in 24b above

29a. Do you attend any medical clinic regularly?:

☐ Yes ☐ No ☐ Not applicable

29b. If "Yes", what kind of clinic?:

☐ Taso Clinic
☐ HIV Clinic
☐ Diabetic Clinic
☐ High BP clinic
☐ Chest Clinic
☐ Cardiac Clinic
☐ Urology/Renal Clinic
☐ STD Clinic
☐ Antenatal Clinic
☐ Neurology Clinic
☐ Other (Specify) ____________

30. Have you been admitted to the hospital during the past 3 months? ☐ Yes ☐ No ☐ Don't remember

31a. Have you nursed or cared for any patient during the past 3 months?

☐ Yes ☐ No ☐ Don't remember

31b. If 'Yes' for what reason were you admitted?

____

HOUSING DWELLING

32. How many people live at your primary residence?

☐☐

33. How many habitable rooms are in your primary residence? ☐☐

34. What is the type of your primary residence?

☐ Muzigo: Walls not reaching celing/roof
☐ Muzigo: Walls reaching the ceiling/roof
☐ Free standing house
☐ Semi detached
☐ Other (specify) ____________

Int Initials: ☐☐	Comp Date	☐☐ / ☐☐ / ☐☐☐☐	
Rev Initials: ☐☐	Rev Date	☐☐ / ☐☐ / ☐☐☐☐	
DMO Initials: ☐☐	DMO Date	☐☐ / ☐☐ / ☐☐☐☐	
CD Initials: ☐☐	CD Date	☐☐ / ☐☐ / ☐☐☐☐	
		Day / Month / Year	

Longitudinal Risk Assessment form page 3 of 3)
Version 2 Date: September 10th, 2014

Quarterly TB Risk Assessment Form

29684

MAKERERE UNIVERSITY-UNIVERSITY OF GEORGIA RESEARCH COLLABORATION
COMMUNITY HEALTH AND SOCIAL NETWORKS OF TUBERCULOSIS
LONGITUDINAL STUDY QUARTERLY FOLLOW UP RISK ASSESSMENT-ENGLISH

Network IDNO ☐☐☐☐☐

Interview Date ☐☐ / ☐☐ / 2 0 ☐☐
dd mm yyyy

Visit Type
☐ Baseline ☐ 9 Months FUP
☐ 3 Months FUP ☐ 12 Months FUP
☐ 6 Months FUP ☐ Unscheduled

1. In the past 3 months, have you been in contact with person(s) whom you knew had TB?
☐ Yes ☐ No ☐ Don't Know

If "No", "don't know" Skip to Qn 8

2. Did you live in the same house as this person with
☐ Yes ☐ No

3. Did you sleep in the same bedroom as this person withTB?
☐ Yes ☐ No

4. Did you spend more than 4 hours at a time with this person with TB?
☐ Yes ☐ No

5. Was this person coughing while you were with them?
☐ Yes ☐ No ☐ Don't remember

6. To your knowledge was this TB patient taking medication for TB?
☐ Yes ☐ No ☐ Don't remember

7. Did you help to take care for this person with TB?
☐ Yes ☐ No ☐ Don't Remember

8. Over the past 3 months, have you been hospitalized for any reason?
☐ Yes ☐ No

9. Where were you hospitalized?
☐ Not Applicable

10. Over the past 3 months, have you visited a medical clinic/facility for any reason?
☐ Yes ☐ No

11. How many times did you visit the clinic?
☐☐

12.Which clinics did you visit/attend?
☐ Not Applicable

13. Over the past 3 months, have you visited any family member or friend in the hospital?
☐ Yes ☐ No ☐ Don't remember

14. Over the past 3 months, how many times did you visit family or friend in the hospital?
☐☐

15. Over the past 3 months, have you nursed or cared for any patient?
☐ Yes ☐ No ☐ Don't remember

16. Over the past 3 months, have you have you travelled outside of Kampala for more than one day?
☐ Yes ☐ Don't remember END HERE ☐ No END HERE

Int Initials:	☐☐	Comp Date:	☐☐ / ☐☐ / 2 0 ☐☐
Rev Initials:	☐☐	Rev Date:	☐☐ / ☐☐ / 2 0 ☐☐
DMO Initials:	☐☐	DMO Date:	☐☐ / ☐☐ / 2 0 ☐☐
CD Initials:	☐☐	CD Date:	☐☐ / ☐☐ / 2 0 ☐☐
			Day Month Year

Quarterly Assessment page 1 of 2)
Version 1 Date: August 10 2014

MWESO Game Form

MAKERERE UNIVERSITY-UNIVERSITY OF GEORGIA RESEARCH COLLABORATION
COMMUNITY HEALTH AND SOCIAL NETWORKS OF TUBERCULOSIS
LONGITUDINAL ASSESSMENT MODULE _ENGLISH Version2

1932

After each "MWESO" game count the number of beads placed in each location and record the number below

Network IDNO ☐☐☐☐☐

Interview date ☐☐ / ☐☐ / ☐☐☐☐
dd mm yyyy

Visit Type
☐ Baseline
☐ 3 Months FUP
☐ 6 Months FUP
☐ 9 Months FUP
☐ 12 Months FUP
☐ UnScheduled

MWESO GAME CODING SECTION (For both English & Luganda)

24 HOUR RECALL

How the participant spent his/her day YESTERDAY) :

OWN Home	☐☐	☐☐	Gym/Recreation	☐☐	Market place
RELATIVE Home	☐☐	☐☐	Club/association	☐☐	Saloon
FREIND'S Home	☐☐	☐☐	Hospital/Clinic	☐☐	Women group
Work place	☐☐	☐☐	Taxi/bus (Public transport)	☐☐	Bar
School	☐☐	☐☐	Neighbor's home	☐☐	Tradingcenter/Kiosk /shop
Worship center	☐☐	☐☐	Others(specify):		

WEEKEND RECALL

How the participant spent his/her SATURDAY OR SUNDAY):

OWN Home	☐☐	☐☐	Gym/Recreation	☐☐	Market place
RELATIVE Home	☐☐	☐☐	Club/association	☐☐	Saloon
FREIND'S Home	☐☐	☐☐	Hospital/Clinic	☐☐	Women group
Work place	☐☐	☐☐	Taxi/bus (Public transport)	☐☐	Bar
School	☐☐	☐☐	Neighbor's home	☐☐	Tradingcenter/Kiosk /shop
Worship center	☐☐	☐☐	Others(specify):		

SEVEN DAY RECALL

How the participant spends his/her Typical day

OWN Home	☐☐	☐☐	Gym/Recreation	☐☐	Market place
RELATIVE Home	☐☐	☐☐	Club/association	☐☐	Saloon
FREIND'S Home	☐☐	☐☐	Hospital/Clinic	☐☐	Women group
Work place	☐☐	☐☐	Taxi/bus (Public transport)	☐☐	Bar
School	☐☐	☐☐	Others(specify):	☐☐	Tradingcenter/Kiosk /shop
Worship center	☐☐				
Neighbor's home	☐☐				

Int Initials:	☐☐	Comp Date	☐☐ /	☐☐ /	☐☐☐☐
Rev Initials:	☐☐	Rev Date	☐☐ /	☐☐ /	☐☐☐☐
DMO Initials:	☐☐	DMO Date	☐☐ /	☐☐ /	☐☐☐☐
CD Initials:	☐☐	CD Date	☐☐ /	☐☐ /	☐☐☐☐
			Day	Month	Year

Questionnaire page 1 of 1)
September 10th 2014

Tuberculin Skin Test Result Form

13049

MAKERERE UNIVERSITY- UNIVERSITY OF GEORGIA RESEARCH COLLABORATION
COMMUNITY HEALTH AND SOCIAL NETWORKS OF TUBERCULOSIS
COMBINED TST RESULT FORM FOR STUDIES-Version 2

Network ID ☐☐☐☐☐

Interview Date ☐☐ / ☐☐ / ☐☐☐☐ (Day / Month / Year)

INSTRUCTION: For all TST administered, record date of placement and should be read between 48 - 72hrs. Also endeavor to read PPD within the stipulated time frame. However Readings after 72 hours should still be documented appropriately.

1. Respondent Category
- ☐ Community survey Participant
- ☐ Longitudinal Participant
- ☐ Social Network Participant → (go to 1b)
- ☐ Other [Specify] ________

1b. If Social Network Participant Specify below
- ☐ Contact of a TB case
- ☐ Contact of a Control
- ☐ Control participant
- ☐ Other [Specify] ________

2. Visit Type
- ☐ Social Network First visit TST result
- ☐ Social Network Repeat visit TST result
- ☐ Community survey visit TST result
- ☐ Longitudinal end of study visit TST result
- ☐ Other visit TST result [Specify visit] ________

PPD PLACEMENT MODULE

3. Was PPD given?
- ☐ Not Given [Ask Qn 4]
- ☐ Refused PPD [End here]
- ☐ Yes Given [Ask Qn 5]

4. If "NOT given," Give reason
- ☐ Previous PPD Positive
- ☐ Previously diagnosed with TB
- ☐ Previous culture positive result
- ☐ Previous Quantiferon positive result

If PPD was given,

5. Date PPD placed: ☐☐ / ☐☐ / ☐☐☐☐ (Day / Month / Year)

6. Initials of PPD injector ☐☐

7. Date PPD read: ☐☐ / ☐☐ / ☐☐☐☐ (Day / Month / Year) ☐ PPD Not read

6.Give reason ________

8a. 1st TST result ☐☐.☐ mm

9a. 1st READER INITIALS ☐☐

8b. 2nd TST result Reading: ☐☐.☐ mm

9b. 2nd READER INITIALS ☐☐

Int Initials:	☐☐	Comp Date	☐☐ /	☐☐ /	☐☐☐☐
Rev Initials:	☐☐	Rev Date	☐☐ /	☐☐ /	☐☐☐☐
DMO Initials:	☐☐	DMO Date	☐☐ /	☐☐ /	☐☐☐☐
CD Initials:	☐☐	CD Date	☐☐ /	☐☐ /	☐☐☐☐
			Day	Month	Year

Combined TST result Form (page 1 of 1)
Version 2 Date: November 12th, 2014

B APPENDIX FOR CHAPTER 3

Table B1. History of TB exposure over one year before enrollment and during follow up in 1275 participants

Characteristics	Total N (%)	Incident TB infection Yes	No	p-value
History of exposure to TB contact over past one year before enrollment				
Ever known anyone with TB				
No	1001 (78.9)	140 (74.1)	861 (79.8)	0.092
Yes	267 (21.1)	49 (25.9)	218 (20.2)	
Ever lived in a home with TB patient				
No	1154 (91.0)	170 (89.9)	984 (91.2)	0.678
Yes	114 (9.0)	19 (10.1)	95 (8.8)	
Have been in contact with TB patient				
No	1158 (91.3)	164 (86.8)	994 (92.1)	0.023
Yes	110 (8.7)	25 (13.2)	85 (7.9)	
Live at the same home with TB patient				
No	1226 (96.8)	180 (95.2)	1046 (97.0)	0.288
Yes	41 (3.2)	9 (4.8)	32 (3.0)	
Sleep in the same bedroom with TB patient				
No	1250 (98.7)	182 (96.3)	1068 (99.1)	0.007
Yes	17 (1.3)	7 (3.7)	10 (0.9)	
Spent more than 4 hours at a time with TB patient				
No	1209 (95.6)	177 (93.7)	1032 (95.9)	0.230
Yes	56 (4.4)	12 (6.3)	44 (4.1)	
Knew contact with TB receiving treatment				
No	1035 (86.2)	146 (83.9)	889 (86.6)	0.412
Yes	166 (13.8)	28 (16.1)	138 (13.4)	
Take care TB patient				

No	1125 (93.8)	161 (92.0)	964 (94.1)	0.359
Yes	74 (6.2)	14 (8.0)	60 (5.9)	
History of exposure to TB contact during follow up				
Have been in contact with TB patient				
No	1108 (86.9)	160 (84.2)	948 (87.4)	0.282
Yes	167 (13.1)	30 (15.8)	137 (12.6)	
Live at the same house with TB patient				
No	1223 (95.9)	184 (96.8)	1039 (95.8)	0.619
Yes	52 (4.1)	6 (3.2)	46 (4.2)	
Sleep in the same bedroom with TB patient				
No	1253 (98.3)	187 (98.4)	1066 (98.2)	1.000
Yes	22 (1.7)	3 (1.6)	19 (1.8)	
Spent more than 4 hours at a time with TB patient				
No	1189 (93.3)	176 (92.6)	1013 (93.4)	0.830
Yes	86 (6.7)	14 (7.4)	72 (6.6)	
TB contact coughing while being with you				
No	1124 (88.2)	164 (86.3)	960 (88.5)	0.466
Yes	151 (11.8)	26 (13.7)	125 (11.5)	
Knew contact with TB receiving treatment				
No	1156 (90.7)	171 (90.0)	985 (90.8)	0.836
Yes	119 (9.3)	19 (10.0)	100 (9.2)	
Take care TB patient				
No	1225 (96.1)	183 (96.3)	1042 (96.0)	1.000
Yes	50 (3.9)	7 (3.7)	43 (4.0)	
Nursed or cared for any patient				
No	1045 (82.0)	161 (84.7)	884 (81.5)	0.329
Yes	230 (18.0)	29 (15.3)	201 (18.5)	

Table B2. Estimates of relative risk according to exposure to TB patient before enrollment and during follow up

Variables	Total	No. incident LTBI (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
History of exposure to TB patient over the past one year before enrollment				
Ever known anyone with TB				
No	1001	141 (14)	Ref	Ref
Yes	267	51 (19)	**1.35 (1.01, 1.8)**	1.28 (0.96, 1.72)
Ever lived in a home with TB patient				
No	1154	173 (15)	Ref	Ref
Yes	114	19 (17)	1.11 (0.72, 1.7)	1.1 (0.72, 1.67)
Have been in contact with TB patient				
No	1158	167 (14)	Ref	Ref
Yes	110	25 (23)	**1.57 (1.08, 2.27)**	**1.53 (1.07, 2.21)**
Live at the same house with TB patient				
No	1226	183 (15)	Ref	Ref
Yes	41	9 (22)	1.59 (0.91, 2.78)	1.52 (0.85, 2.69)
Sleep in the same bedroom with TB patient				
No	1250	185 (15)	Ref	Ref
Yes	17	7 (41)	**2.77 (1.54, 4.96)**	**2.57 (1.39, 4.76)**
Spent more than 4 hours at a time with TB patient				
No	1209	180 (15)	Ref	Ref
Yes	56	12 (21)	1.43 (0.85, 2.41)	1.44 (0.87, 2.39)
Knew contact with TB receiving treatment				
No	1096	161 (15)	Ref	Ref
Yes	166	30 (18)	1.22 (0.86. 1.74)	1.18 (0.83, 1.68)
Took care TB patient				
No	1189	178 (15)	Ref	Ref
Yes	74	14 (19)	1.26 (0.77, 2.05)	1.27 (0.78, 2.06)

History of exposure to TB patient during follow up				
Have been in contact with TB patient				
No	1108	162 (15)	Ref	Ref
Yes	167	31 (19)	1.26 (0.89, 1.79)	1.13 (0.8, 1.61)
Live at the same house with TB patient				
No	1223	186 (15)	Ref	Ref
Yes	52	7 (13)	0.88 (0.44, 1.78)	0.79 (0.39, 1.58)
Sleep in the same bedroom with TB patient				
No	1253	189 (15)	Ref	Ref
Yes	22	4 (18)	1.26 (0.52, 3.07)	1.06 (0.42, 2.69)
Spent more than 4 hours at a time with TB patient				
No	1189	178 (15)	Ref	Ref
Yes	86	15 (17)	1.16 (0.72, 1.87)	1.01 (0.63, 1.63)
TB contact coughing while being with you				
No	1124	166 (15)	Ref	Ref
Yes	151	27 (18)	1.2 (0.83, 1.74)	1.08 (0.74, 1.57)
Knew contact with TB receiving treatment				
No	1156	174 (15)	Ref	Ref
Yes	119	19 (16)	1.05 (0.68, 1.63)	0.92 (0.6, 1.43)
Took care TB patient				
No	1225	185 (15)	Ref	Ref
Yes	50	8 (16)	1.05 (0.55, 2.02)	0.94 (0.49, 1.79)
Nursed or cared for any patient				
No	1045	164 (16)	Ref	Ref
Yes	230	29 (13)	0.8 (0.55, 1.15)	0.8 (0.56, 1.16)

C APPENDIX FOR CHAPTER 4

Table C. 1 Social behaviors stratified by both sex and incident LTBI

Variables	Male				Female			
	Total	Incident LTBI		p-value	Total	Incident LTBI		p-value
		Yes	No			Yes	No	
Smoking and drinking habits								
Smoking								
Never smoked	488	85 (17.4)	403 (82.6)	0.032	731	93 (12.7)	638 (87.3)	1.000
Former/Current smoker	36	12 (33.3)	24 (66.7)		13	2 (15.4)	11 (84.6)	
Alcohol use								
Non-users	390	66 (16.9)	324 (83.1)	0.257	599	77 (12.9)	522 (87.1)	0.085
Light users	86	20 (23.3)	66 (76.7)		106	10 (9.4)	96 (90.6)	
Heavy users	42	10 (23.8)	32 (76.2)		33	8 (24.2)	25 (75.8)	
Mostly drink in drinking places outside road side shops								
No	482	88 (18.3)	394 (81.7)	0.596	714	93 (13.0)	621 (87.0)	0.826
Yes	39	9 (23.1)	30 (76.9)		22	2 (9.1)	20 (90.9)	
Mostly drink inside established bar								
No	461	85 (18.4)	376 (81.6)	0.908	687	89 (13.0)	598 (87.0)	1.000
Yes	60	12 (20.0)	48 (80.0)		49	6 (12.2)	43 (87.8)	
Mostly drink in Malwa/Waragi/Tonto drinking setting								
No	504	92 (18.3)	412 (81.7)	0.398	727	92 (12.7)	635 (87.3)	0.181
Yes	17	5 (29.4)	12 (70.6)		9	3 (33.3)	6 (66.7)	
Mostly drink on celebration occasion								
No	489	94 (19.2)	395 (80.8)	0.249	689	89 (12.9)	600 (87.1)	1.000
Yes	32	3 (9.4)	29 (90.6)		47	6 (12.8)	41 (87.2)	
Healthcare facility attendance								
Hospitalization								

No	508	96 (18.9)	412 (81.1)	0.884	690	88 (12.8)	602 (87.2)	1.000
Yes	20	3 (15.0)	17 (85.0)		57	7 (12.3)	50 (87.7)	
Attend medical clinic/facility for any reasons								
No	203	46 (22.7)	157 (77.3)	0.088	195	27 (13.8)	168 (86.2)	0.671
Yes	325	53 (16.3)	272 (83.7)		552	68 (12.3)	484 (87.7)	
Attend drug shop								
No	409	83 (20.3)	326 (79.7)	0.121	575	83 (14.4)	492 (85.6)	0.014
Yes	119	16 (13.4)	103 (86.6)		172	12 (7.0)	160 (93.0)	
Attend health center								
No	472	91 (19.3)	381 (80.7)	0.504	622	81 (13.0)	541 (87.0)	0.681
Yes	55	8 (14.5)	47 (85.5)		125	14 (11.2)	111 (88.8)	
Attend clinic								
No	308	61 (19.8)	247 (80.2)	0.534	365	50 (13.7)	315 (86.3)	0.498
Yes	220	38 (17.3)	182 (82.7)		382	45 (11.8)	337 (88.2)	
Attend hospital								
No	493	93 (18.9)	400 (81.1)	0.978	668	83 (12.4)	585 (87.6)	0.604
Yes	35	6 (17.1)	29 (82.9)		79	12 (15.2)	67 (84.8)	
Visit family or friend in hospital								
No	373	64 (17.2)	309 (82.8)	0.183	496	63 (12.7)	433 (87.3)	1.000
Yes	155	35 (22.6)	120 (77.4)		251	32 (12.7)	219 (87.3)	
Workplace and history of incarceration								
Work at home								
No	491	90 (18.3)	401 (81.7)	0.510	475	62 (13.1)	413 (86.9)	0.864
Yes	23	6 (26.1)	17 (73.9)		252	31 (12.3)	221 (87.7)	
Work in a mine								
No	490	94 (19.2)	396 (80.8)	0.968	722	94 (13.0)	628 (87.0)	0.845
Yes	24	4 (16.7)	20 (83.3)		5		5 (100.0)	
Work in a healthcare facility								
No	509	95 (18.7)	414 (81.3)	1.000	716	93 (13.0)	623 (87.0)	1.000
Yes	8	1 (12.5)	7 (87.5)		17	2 (11.8)	15 (88.2)	
Ever incarcerated								
No	432	80 (18.5)	352 (81.5)	0.707	725	92 (12.7)	633 (87.3)	0.812

Yes	91	19 (20.9)	72 (79.1)		17	3 (17.6)	14 (82.4)	
Transportation use in daily life								
Use taxi								
No	156	38 (24.4)	118 (75.6)	0.051	269	33 (12.3)	236 (87.7)	0.822
Yes	362	60 (16.6)	302 (83.4)		472	62 (13.1)	410 (86.9)	
Number of hours spent on taxi per day, mean (SD)	4.13	3.96 (5.10)	4.17 (5.17)	0.774	3.71	4.93 (7.06)	3.52 (4.33)	0.031
Model of transport used most								
Walking	96	18 (18.8)	78 (81.2)	0.615	313	34 (10.9)	279 (89.1)	0.321
Bi/Motorcycle/Bodaboda	167	34 (20.4)	133 (79.6)		132	21 (15.9)	111 (84.1)	
Taxi/Bus	217	36 (16.6)	181 (83.4)		289	40 (13.8)	249 (86.2)	
Private car/Lorry	41	10 (24.4)	31 (75.6)		7		7 (100.0)	
Travel outside Kampala								
Travel outside Kampala								
No	124	23 (18.5)	101 (81.5)	1.000	240	30 (12.5)	210 (87.5)	0.996
Yes	404	76 (18.8)	328 (81.2)		507	65 (12.8)	442 (87.2)	
Reason to travel outside Kampala								
Travel to visit family/relatives								
No	291	58 (19.9)	233 (80.1)	0.510	367	47 (12.8)	320 (87.2)	1.000
Yes	237	41 (17.3)	196 (82.7)		380	48 (12.6)	332 (87.4)	
Travel for vocation/holiday								
No	495	92 (18.6)	403 (81.4)	0.886	682	90 (13.2)	592 (86.8)	0.281
Yes	33	7 (21.2)	26 (78.8)		65	5 (7.7)	60 (92.3)	
Travel to work								
No	280	47 (16.8)	233 (83.2)	0.264	670	84 (12.5)	586 (87.5)	0.798
Yes	248	52 (21.0)	196 (79.0)		77	11 (14.3)	66 (85.7)	
Travel for funeral/burial								
No	424	79 (18.6)	345 (81.4)	1.000	559	71 (12.7)	488 (87.3)	1.000
Yes	104	20 (19.2)	84 (80.8)		188	24 (12.8)	164 (87.2)	
Use mortocycle/bodaboda to travel								
No	466	85 (18.2)	381 (81.8)	0.516	693	89 (12.8)	604 (87.2)	0.876
Yes	62	14 (22.6)	48 (77.4)		54	6 (11.1)	48 (88.9)	
Use private vehicle/lorry to travel								

No	380	69 (18.2)	311 (81.8)	0.664	666	82 (12.3)	584 (87.7)	0.437
Yes	148	30 (20.3)	118 (79.7)		81	13 (16.0)	68 (84.0)	
Use taxi/bus to travel								
No	176	29 (16.5)	147 (83.5)	0.408	262	36 (13.7)	226 (86.3)	0.616
Yes	352	70 (19.9)	282 (80.1)		485	59 (12.2)	426 (87.8)	
Average hours in a mode of transport, mean (SD)	4.45	4.83 (4.23)	4.37 (2.61)	0.225	3.80	3.67 (1.81)	3.82 (2.27)	0.618