SPATIOTEMPORAL PATTERNS OF TUBERCULOSIS IN URBAN SUB-SAHARAN AFRICA: IMPLICATIONS FOR DISEASE CONTROL

by

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Abstract

Background

Tuberculosis (TB) is a leading cause of morbidity and mortality globally. Scale-up of evidence-based interventions has had limited impact at the population level. Targeting interventions based on geographic and movement patterns may improve TB control.

Objectives

We use the spatiotemporal epidemiology of TB to identify populations at high risk for experiencing barriers to care and acquiring TB disease and consider the possible impact of geographically targeted interventions in urban sub-Saharan Africa.

Methods

We conducted a facility and community-based case-control study in Kampala, Uganda. We describe heterogeneity of zone-level TB notifications and assessed the potential impact of using programmatic data to target active case finding in areas with high TB burden. We then characterize geographic mobility patterns using latent class analysis and assess the association of mobility with TB disease using conditional logistic regression. Finally, we assessed the association between distance from home to health care facility on treatment outcomes among TB patients using multivariable Poisson regression.

Results

In our study area, 5 geographic zones constituting 22% of the population accounted for 62% (95% CI 47-75%) of facility-based TB notifications and 42%

(95% CI 35-51%) of undiagnosed TB in the community. A two class model of geographic mobility was largely driven by frequency (≥9 times per month [84% mobile vs. 2% non-mobile] and duration (≥6 hours [78% vs 17%]) of travel >3 km from residence; there was no association between mobility and TB case status (adjusted odds ratio 0.85 [95% CI 0.44-1.6]). TB patients residing ≥2 km from their treatment health facility were less likely to be lost to follow-up (adjusted risk ratio [aRR] 0.57 [95%CI 0.41-0.79]) but more likely to die prior to completing treatment (aRR 1.42 (95%CI 0.99-2.03)].

Conclusions

Geographic targeting of active case finding interventions may be an efficient way to identify undiagnosed cases. Defining mobility is complex and further research is needed to understand mobility patterns and their association with health outcomes. Geographic barriers to care play a role in TB treatment outcomes. Spatiotemporal patterns are critical components to understanding the local context of TB and designing targeted interventions to reduce the TB epidemic.

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Chapter 1: Background and Study Context

Overview

Tuberculosis (TB) is a major contributor to morbidity and mortality globally. Despite substantial international and local investment in the scale-up of evidence-based interventions, global progress in reducing TB incidence has been slow (1). TB control interventions targeted at specific high-risk populations have shown promise; however, challenges remain in identifying and reaching those populations. Building off the current evidence of spatial heterogeneity of TB burden globally, this research aims to investigate individual spatiotemporal (i.e., location and movement) patterns as potential risk factors for TB and to develop spatially targeted interventions for improving TB control in high-risk populations in urban sub-Saharan Africa.

Epidemiology of Tuberculosis

There were an estimated 10 million cases of TB resulting in 1.5 million deaths in 2018, making TB the leading cause of mortality due to a single pathogen worldwide (1). The burden of TB is geographically heterogeneous; among 202 countries reporting data to the World Health Organization (WHO), TB rates range from <5 per 100,000 population to upwards of 500 per 100,000 population (1). The majority of new TB cases are found in African (24%) and South-East Asian countries (44%) (1).

The heterogeneity of TB disease is driven by risk factors that contribute to an individuals' likelihood of developing TB disease. Risk factors for TB include those that biologically increase an individuals' chance of disease by hindering the immune system response as well as factors that increase an individuals' likelihood of being exposed to

TB. Globally, HIV is one of the most important individual drivers of the TB epidemic (1), particularly in sub-Saharan Africa where approximately a third of TB patients are infected with HIV (2,3). People living with HIV may be more than 20 times as likely to develop active TB upon exposure compared to those without HIV (4). Treatment with antiretroviral therapy (ART) reduces but does not eliminate this risk (5). Areas with high HIV notifications are associated with increased TB burden (6), and TB death rates are largely driven by HIV (3). In some settings (particularly in southern and eastern Africa), HIV is the primary driver of TB risk, such that scale-up of ART leads to a population-level reduction in TB (7). Other individual risk factors that can increase risk of TB include diabetes (8–10), smoking (8,11), alcohol use (8,12), undernutrition (13), and exposure to indoor air pollution (14).

In addition to individual factors that may limit an individual's ability to control TB infection, the structural context contributes to TB risk; these factors range from distal factors such as government expenditures to more proximal factors such as individual living conditions (15). Structural determinants that increase risk for TB include urbanization, crowding, housing conditions, and demographic and economic trends (16). The structural context in which an individual lives is inextricably linked to social determinants that increase an individual's risk for TB (17,18). Most notably, TB has long been known to be a disease of poverty (19), with effects stretching from national health expenditures (20) to individual unemployment (6). Additionally, overcrowding (21,22), poor housing conditions (23), and homelessness (24) can lead to conditions for TB transmission. These social determinants are often associated with individual additional

risk factors for TB (25) that act on a biological level and must be addressed in order to have a population-level impact on TB burden (26).

Basis of TB Control

TB is an caused by transmission of the *Mycobacterium tuberculosis* bacteria (27). Upon infection, an individual's immune system may control the bacteria, resulting in an asymptomatic infection (latent tuberculosis infection [LTBI]); LTBI may reactivate and develop into active disease if an individual later becomes immunocompromised (28). Other individuals will immediately develop active TB disease. Only individuals with active TB are infectious (29) and while it is likely that coughing it the primary mechanism for transmitting TB (27), there is growing evidence of transmission of subclinical (active but asymptomatic) TB (30). Many TB control activities focus on understanding and preventing further transmission of TB (31); other strategies focus on preventing TB infection from reactivation of LTBI (32,33). In order to have an impact on TB, control efforts must both treat the existing cases as well as prevent future transmission, an approach called "turning off the tap" (34). Methods to halting transmission include improved case detection through active case finding and ensuring timely and adequate treatment of existing TB cases (34).

Active Case Finding

In most settings, TB is identified through passive detection in which individuals with symptoms seek care from a health facility or other health provider and are

subsequently diagnosed with TB in a clinical setting (35). This system puts the onus on the patient, and frequently leads to delays in diagnosis (36) or cases going undetected; globally it is estimated that 30% of cases are never diagnosed and notified to public health authorities (1). Not only does this meant the patient does not get the care they need (37), but because most transmission occurs prior to initiation of treatment (38), delays in diagnosis contribute to increased disease spread (39).

Active case finding is an intervention that aims to detect and diagnose individuals with TB by actively seeking them out rather than waiting for them to seek care on their own (35). Active case finding can detect cases earlier in their disease course, so they may be less infectious and have had less opportunity for further transmission (40,41). Although resource intensive, active case finding can greatly increase the number of TB cases being diagnosed (42) and can be cost-effective (43). In order to be effective, it is critical that active case finding interventions take the local epidemiology into account (35,44). Active case finding approaches can be targeted to high-risk groups or population-based (45).

Targeted active case can efficiently identify cases in known high-risk populations, such as people living with HIV (46), household contacts of TB cases (47), health care workers (48), and people living in prisons (49). For example, active case finding among people seeking care at HIV clinics has found TB prevalence of 8%, far higher than population-based testing (50). Recent contacts of TB cases are also at increased risk for TB (51). The WHO recommends household contact investigations due to their high yield (52,53), although in high-burden settings the majority of transmission occurs outside of the household so the effect on transmission may be limited (54). Institutional

transmission of TB is common in settings like prisons (55) and health care settings (56), making them ideal targets for case finding and halting transmission.

Community or population-based active case finding tends to be lower yield compared to targeted interventions (50) but can reach people who do not fall into known high-risk categories and would otherwise be missed (57). While there is evidence that mass screening activities can lead to sustained reductions in TB incidence (34,58), the implementation of broad community-based case finding interventions has had mixed results (59–63). Challenges in implementation include access to the target population, choice of screening and diagnostic tests, and linkages to the health care system (57). For example, the ZAMSTAR trial conducted in Zambia and South Africa found no effect of its enhanced case finding intervention, but only reached 6% of the population in its door to door testing efforts. Lack of sensitive diagnostics may also limit the yield of active case finding among people with mild or asymptomatic disease (62). Active case finding in Brazil led to increased case detection but no improvement in treatment initiation or outcomes (60); other studies have shown that patients identified by active case finding are less likely to complete treatment than those detected by passive case finding (64,65), thereby limiting the impact of active case finding on TB at the population level.

Treatment completion

Treatment for uncomplicated pulmonary TB currently requires six months of combination antibiotic therapy; the treatment course can be longer for those with extrapulmonary TB or drug resistance (66). Treatment can quickly reduce the

infectiousness of a TB patient but if an adequate course of treatment is not completed the patient is at increased risk for treatment failure or relapse. Therefore, treatment is critical not just for the patient's well-being but also to prevent ongoing transmission; early analyses suggested that treating infectious TB cases would be the most effective and cost-effective way to reduce TB transmission and mortality (67).

However, only 85% of diagnosed TB cases completed treatment in 2017 (1). Using a patient cascade approach, it is estimated that less than 50% of all TB cases complete treatment due to health system losses (37). Barriers to treatment adherence include health system limitations as well as individual patient knowledge, perceptions, and stigma (68). In individual patients, risk factors for poor treatment outcomes include HIV co-infection, older age, and alcoholism (69).

The primary strategy to improve treatment outcomes globally has been implementation of directly observed therapy (DOT), in which a healthcare provider or treatment supporter observes the patient taking their treatment (70). DOT, an important component of the WHO's TB control DOTS strategy (71), has not been shown to be consistently effective compared to self-administered therapy (72); improvements in treatment adherence and outcomes are dependent on successful implementation of DOT (73). Other interventions to improve treatment adherence and completion include material incentives and enablers (74), patient counselling and education (75), and appointment reminder systems (76). These interventions have shown improvement in treatment outcomes in some settings but overall results in improving treatment outcomes have been mixed (77).

End TB strategy and progress

In 2015, the WHO launched the End TB strategy, a follow-up to previous global TB control strategies that focuses on ending the TB epidemic (78). The strategy is founded on three pillars: 1. Integrated, patient-centered TB care and prevention; 2. Bold policies and supportive systems; and 3. Intensified research and innovation (79). The End TB strategy set ambitious targets of reducing the number of TB deaths by 95% and the TB incidence rate by 90% by 2035 (compared to 2015). More recently, there has been increased political support for the End TB strategy, including the first ever high-level United Nations (UN) meeting on TB held in September 2018. In this meeting, all UN member states reaffirmed their commitment to the End TB Strategy (1). Among other goals, they promised to find and treat 40 million TB cases by 2020; however, participants felt that the meeting fell short and were skeptical of the actual commitment to these goals (80). Others have expressed the need to improve access to prevention and treatment in order to reach the End TB goals and that more action is needed (81)

Indeed, we are not on target to achieve the End TB goals. The annual reduction in incidence rate over the past five years has been less than 2%, far below that required to reduce TB incidence by 90% by 2035 (1). While interventions including active case finding and treatment of active TB cases have been shown to be effective, the broad application of these interventions has not had the population level impact that early models had suggested (82). A large “delivery gap” persists for TB and other health care issues in developing countries such that the interventions known to work are not reaching the people that need it most (83). This is in part due to a broad “one-size-fits-all” approach to implementation of TB control interventions that fails to account for local

needs and contexts (84). This approach does not work in the reality that there is substantial heterogeneity of TB; even in areas of high burden the relative rarity of TB makes population-based interventions challenging (85). Therefore, in order to prioritize the efficiency of interventions, there is increasing interest in intensive and tailored small-scale interventions that can have a large impact (86). The most successful and effective interventions match implementation to the local context of the epidemic (87,88). This research aims to use in-depth understanding of the local context of TB in urban Uganda to identify approaches for improving the efficiency of TB control interventions in this setting.

Study location and context

This research was conducted in Uganda, a WHO high-priority country (1). Uganda has an estimated TB prevalence of 253 per 100,000 population and 24% of diagnosed TB cases in Uganda are co-infected with HIV (89). There is substantial heterogeneity in the geographic distribution of both TB and HIV in Uganda, although they are closely correlated (90) and the prevalence of both diseases is higher in urban areas compared to rural areas (89,91). While there have been few in-depth studies of the local burden of TB, one study in a region of Kampala (the capital city) estimated a TB incidence more than three times higher than that estimated by the prevalence survey (92), suggesting the burden of TB in urban settings may be underestimated. In additional to traditional risk factors for TB, including HIV, smoking and alcohol use, and

poverty and overcrowding (93), fishing communities are a key population for TB in Uganda due to their living conditions and limited access to health care (94).

The Uganda National TB and Leprosy Program (NTLP) oversees the provision of TB diagnosis and treatment services (95). These services are provided for free at public health facilities although patients often initially seek care in the private sector, which can lead to delays in diagnosis (96). Case detection and treatment completion remain challenges in Uganda. The NTLP primarily relies on passive diagnosis of TB cases which limits their ability to detect TB; only 39% of symptomatic TB patients have ever sought care for their symptoms, and 46% of TB cases go completely undetected (89). Although the national guidelines recommend that community-based DOT be provided and managed by a designated subcounty health worker, this is not widely enforced or monitored. Qualitative research suggests that facilitators of treatment success include a patient-centered approach to care and the use of village health teams; barriers to treatment success include lack of trained staff, funding shortages, and poor implementation of directly observed therapy (97).

This research was conducted as part of the STOMP-TB study in three parishes in central Kampala, Uganda. This is a densely populated area (approximately 50,000 people in less than 2.5 km^2), including some slums, that had an estimated prevalence of more than 300 TB cases per 100,000 population prior to the initiation of this study. Given the known geographic heterogeneity of TB burden in this area, this research aims to use the spatiotemporal epidemiology of TB in this population in urban Uganda to inform efficient interventions that could improve case detection and access to health care.

Spatial Epidemiology and TB control

The distribution of TB burden is not random or homogenous; spatial heterogeneity is demonstrated by varying national (1) and sub-national TB rates (98). In many countries, including Uganda, urban areas have higher burden of TB compared to rural ones, due to increased risk of exposure, infection, and disease associated with urban residence (99,100). Even within high-burden urban settings, there is often clustering of TB (100,101), particularly in the most densely populated (21,102) or extremely poor areas (21,103,104). Spatial clusters are often composed of individuals with similar risk factors, such as migrants (105,106), those with lower income or socioeconomic status (104,107–110), and people who use illicit drugs (108). While some of this clustering may be due to local transmission (107,108,111), clustering can also be driven these shared risk factors in the population (18). In programmatic settings, the molecular data required to identify local transmission is usually unavailable; therefore, interventions based on spatial data must use routine data to identify and prioritize areas for intervention. Spatially targeted interventions in high-burden urban settings can increase case notifications and diagnose cases earlier in their disease course, thereby reducing transmission (112,113). These geographically targeted interventions can also have a population-level effect on TB burden while focusing limited resources on the population that needs them the most (114). In aim 1, I considered the potential impacts of geographically targeted active case finding based on routinely collected TB notification rates, using a subsequent active case finding activity to assess whether TB notifications can predict the locations of undiagnosed TB in the community.

While the majority of geographically-prioritized interventions focus on TB burden based on location of residence, there is substantial evidence that in high-burden settings, most transmission is occurring outside of the household and may not be attributable to close contacts (54,115–119). Therefore, it is important to consider places outside of the immediate vicinity of the household where individuals spend time as potential locations for TB transmission (120). One approach to this is the assessment of geographic mobility, a special application of spatial epidemiology which considers not only locations but also movement patterns including distance and duration of travel (121). Geographic mobility may increase an individual's exposure to TB by influencing the frequency or duration of contact with TB cases (116,122). For example, transmission of TB has been documented during travel (123–125) including on public transportation (126). In aim 2, I investigated patterns of geographic mobility among people seeking care for TB symptoms; I also assessed the relationship between mobility and both TB disease as well as care seeking behavior.

In addition to potential risk for transmission or disease, location may affect TB epidemiology if it represents barriers to quality health care (127). People living in areas with high poverty rates, often correlated with TB burden, frequently experience limitations in their access to healthcare (102). For example, individuals who face a difficult journey between home and health facility, whether due to physical distance, travel time, or transport cost and availability, may face barriers to TB diagnosis and treatment (102,128). This may also be reflected in the choice of facility; the total cost to the patient may actually be lower if care is sought at a nearby private facility compared to a public facility that provides TB diagnosis and treatment for free but is further away

(83,96). There is evidence that geographic barriers may play a role in delays and loss to follow-up during the TB diagnostic process (129–131); in aim 3, I took that research a step further and investigated whether geographic barriers play a role in TB treatment outcomes.

The spatiotemporal epidemiology of TB is increasingly of both programmatic and research interest as spatial methods become more readily available. Primarily, spatial scan and autocorrelation techniques are used to identify areas at high risk for TB; these analyses are often limited by the use of TB notification data, which may not represent the true underlying burden of TB in the population (98,132–135). In aim 1, I built on this existing research by using community-based active case finding as an empiric measure of the TB in the population, thereby allowing assessment of the impact of a geographically targeted active case finding intervention in this setting. Additionally, while spatial assessments of TB risk in high-burden settings increasingly consider locations outside of the home as potential transmission locations, often these investigations are specific to the study setting and not broadly generalizable (136). In aim 2, I considered geographic mobility as an individual behavior characteristic, not tied to specific locations but representing movement that may affect an individual's risk for TB or care seeking behavior. The development of a definition of this mobility may be more widely applicable to identifying high-risk populations other high-burden settings that could be targeted for early case finding interventions. Finally, identifying populations for case finding interventions will have limited effect on the TB epidemic if those cases are not enrolled in care and cured; in aim 3, I considered the effect of location as a barrier to completing TB treatment.

At the local level, understanding these patterns can help inform geographically focused TB control interventions that efficiently target resources to the most high-need populations and reduce TB burden in these settings. From a research perspective, the development of methods to identify these high-risk populations that can be applied to other similar settings is critical. This research presents a combination of detailed understanding of the local context with methods that may be used in other high-burden settings to identify populations for active case finding and treatment adherence interventions, with the goal of reducing transmission and “turning off the tap” on TB transmission (34).

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Chapter 2: Using spatial heterogeneity of facility-based TB notification rates to identify areas with high burden of undiagnosed TB in Kampala, Uganda

Abstract

Background: Routine tuberculosis (TB) notifications are geographically heterogeneous, but their utility in predicting the location of undiagnosed TB cases is unclear.

Methods: We used routinely collected data to identify geographic areas with high TB notification rates and evaluated the extent to which these areas correlated with the location of undiagnosed cases during a subsequent community-wide active case finding intervention in Kampala, Uganda. We first enrolled all adults who lived within 35 contiguous zones and were diagnosed through routine care at four local TB Diagnosis and Treatment Units. We calculated average monthly TB notification rates in each zone and defined geographic areas of "high risk" as zones that constituted the 20% of the population with highest notification rates. We compared the observed proportion of TB notifications among residents of these "high-risk" zones to the expected proportion using simulated estimates based on population size and random variation alone. We then evaluated the extent to which these "high-risk" zones identified areas with high burdens of undiagnosed TB during a subsequent community-based active case finding campaign.

Results: We enrolled 45 adults diagnosed with TB through routine practices and who lived within the study area (estimated population of 49,527). Eighteen zones reported no TB cases in the 9-month period; among the remaining zones, monthly TB notification rates ranged from 3.9 to 39.4 per 100,000 population. The five zones with the highest notification rates constituted 62% (95%CI 47-75%) of TB cases and 22% of the population – significantly higher than would be expected if population size and random chance were the only determinants of zone-to-zone variation (48%, 95% simulation

interval 40-59%). These five “high-risk” zones accounted for 42% (95%CI 34-51%) of the 128 cases detected during the subsequent community-based case finding intervention, which was significantly higher than the 22% expected by chance ($p<0.001$) but lower than the 62% of cases notified from those zones during the pre-intervention period ($p=0.02$).

Conclusions: There is substantial heterogeneity in routine TB notification rates at the zone level. Using facility-based TB notification rates to prioritize high-yield areas for active case finding could double the yield of case finding interventions.

Introduction

More than 10 million people were diagnosed with tuberculosis (TB) in 2018. This burden is not distributed equally; the majority of TB cases are found in 30 countries designated as high burden by the World Health Organization (1). Even within high-burden countries, TB is geographically heterogeneous, often concentrated in densely-populated, low-income areas (2). This small-scale geographic heterogeneity, as seen among city neighborhoods, may reflect local transmission (3–5) and is often associated with neighborhood characteristics such as crowding or poverty (6,7). Models have suggested that interventions targeted at hotspots could have a large impact on overall incidence (8,9). However, in order to be actionable, hotspots would need to be identifiable based on routine data and reasonably stable over the time between hotspot identification and subsequent intervention. Understanding whether these criteria are met could inform local-level prioritization of interventions, as is critical for TB control at the global level (10).

In most high-burden settings, routine TB diagnosis depends on symptomatic presentation by patients, which places the burden on the patient to recognize their symptoms as warranting medical attention and to subsequently seek care. Such symptom-driven diagnosis often fails to detect TB in people with milder symptoms, groups with limited access to care, or areas with limited clinical resources (11,12). A recent prevalence survey in Uganda estimated that these current practices fail to detect 46% of TB cases (13). Active case finding, in which resources are leveraged at the community level to identify TB cases and link them to care, is therefore essential to detect undiagnosed TB in communities (14,15) and further reduce the burden of TB

(16). However, active case finding is resource intensive, and studies of broad community-wide active case finding have had mixed results (17–21). Targeted approaches to active case-finding, by focusing on people at higher-than-average risk for TB such as recent contacts of TB cases or persons living with HIV, are therefore important (22,23). Geographic targeting is an approach to TB case finding that may be feasible but has not been widely implemented, largely because of uncertainty regarding whether cases identified through routine systems can predict the locations of undiagnosed prevalent cases in the community.

A better understanding of local geographic heterogeneity in routinely identified TB cases and the correlation of that heterogeneity with the location of undiagnosed prevalent cases may therefore be useful in directing active case finding interventions to high-risk areas. We used routinely collected TB diagnosis data to identify small-scale geographic areas with high notification rates in Kampala, Uganda. We then evaluated the degree to which these areas contain a higher proportion of undiagnosed prevalent TB, using a subsequent community-wide active case finding intervention.

Methods

Study Overview and Population

This was a community-based study conducted in Kisugu, Wabigalo, and Bukasa parishes in Kampala, Uganda (an area of 2.2 km^2 with an estimated population of 49,527) from May 2018 through December 2019. The study site consists of 37 contiguous zones; zones are the smallest standard administrative area unit used by the

Uganda Bureau of Statistics, with a median size of 0.05km^2 within the study area. Prior to initiation of the study, a door-to-door census was conducted by the study team to estimate the population of each zone. Zones with a population of less than 500 were merged with neighboring zones with similar characteristics such that all areas for analysis had a population of at least 500 in order to ensure that each unit of analysis would contain at least two TB cases assuming spatial homogeneity and an anticipated TB prevalence of 400 cases per 100,000 population. Two zones for which the census could not be completed were excluded, resulting in 33 areas for analysis.

Case definition

A TB case was defined as any individual with a positive sputum smear or GeneXpert result, sputum culture positive for *Mycobacterium tuberculosis*, or documented initiation of TB treatment based on clinical judgment of pulmonary tuberculosis. The GeneXpert ("Xpert") system (Cepheid, Inc., Sunnyvale, CA, USA) was the primary test used for the study. Sputum samples were tested using Xpert MTB/RIF cartridges at the beginning of the study; the Xpert Ultra cartridge was implemented in February 2019. Sputum smears were used based on clinician request and were rare. Sputum culture was generally only performed for research purposes after TB diagnosis by other means; thus, TB diagnosis based only on culture was very uncommon. In this analysis, we included only individuals who were age 15 years or older and residing within the study area; zone of residence was self-reported and verified using landmarks and Google Maps. We conducted a sensitivity analysis using a case definition that only included microbiologically confirmed (Xpert, smear, or culture) cases.

Case Detection and Enrollment

The study prospectively enrolled TB patients in two phases: a facility-based phase (May 2018-January 2019) and a community-based phase (February-December 2019). In the facility-based phase, we enrolled all consenting adult TB cases who lived in the study area and were passively identified through routine TB diagnostic services at four outpatient TB Diagnosis and Treatment Units located within the study area. Clinicians at the facilities were responsible for making TB diagnoses based on clinical judgment and the results of any laboratory tests (for example, sputum smears); diagnosed cases were then referred for study enrollment.

In the community-based phase, we attempted to identify all prevalent TB cases in the community through a combination of passive and active case finding activities. Passive case detection continued at the four health facilities as described above. We also conducted door-to-door sputum collection and testing throughout the study area; this included participants who were at a residence other than their own at the time of testing as long as their residence was within the study area. Ten venue-based screening events were held at churches, markets, and other community locations in order to reach those who were not available during door-to-door testing. Contact investigation was also completed for all identified cases. If residents could be contacted but were not available at the time of screening, follow-up home appointments were scheduled. The goal of the community-based phase was to obtain a sputum specimen from every adult residing in the study area regardless of their TB symptomology.

Facility-based TB Rates

Average monthly TB notification rates (per 100,000 population) for the facility-based study phase were calculated by zone as: (number of TB cases residing in that zone)/(estimated population of the zone * facility-based phase duration, in months). We then ranked zones according to their average monthly TB notification rates and defined a "high-risk" group of zones by starting with the zone reporting the highest TB notification rate and including additional zones with the next-highest rates until the "high-risk" category accounted for at least 20% of the population. The 20% cutoff was an *a priori* threshold corresponding to the likely size of any targeted case-finding intervention that could be undertaken in the study area; sensitivity analyses were conducted using cutoffs of 10%, 15%, 25%, and 30% of the population. We calculated the proportion of facility-based phase TB cases who resided within the high-risk group of zones and a corresponding 95% confidence interval, assuming a binomial distribution. We compared demographic, clinical, and behavioral risk factors among cases residing in the high-risk vs. low-risk zones using Fisher's exact tests for categorical variables and non-parametric Wilcoxon rank-sum tests for continuous variables.

Estimation of expected spatial distribution of TB cases

To estimate the number of facility-based TB cases that would be expected to occur in the high-risk zones based on chance alone, we conducted 1,000 stochastic simulations in which we assumed that the only driver of spatial heterogeneity in TB notification rates was random variation. For each simulation, we randomly assigned to each zone a number of TB notifications based on population size by drawing a value from a Poisson distribution with mean of (total number of TB cases in study area during facility-based phase * proportion of total population residing in that zone). As with the observed data above, we then sorted the zones by the simulated TB rate (simulated number TB notifications per 100,000 population per month) and identified the "high-risk" zones as those representing the 20% of the simulated study population with the highest simulated TB notification rates. These simulated high-risk zones therefore occurred randomly throughout the study area, varying from one simulation to the next, and did not correlate with the actual observed high-risk zones. For each simulation, we then calculated the cumulative proportion of TB notifications occurring among residents of these simulated high-risk zones – thereby providing an estimate of the proportion of TB notifications that would be expected to occur in high-risk zones if the only determinant of "high-risk" were random variation in the spatial distribution of TB notifications. We used the 2.5 and 97.5 percentiles of our simulations to define the corresponding 95% uncertainty range around this proportion.

Stability of facility-based notifications over time

We compared cases diagnosed passively at the health facilities during the facility-based and community-based phases to determine whether there were changes in the spatial distribution of facility-diagnosed cases over time. We calculated the proportion of passively-diagnosed community-phase cases with 95% confidence intervals using a binomial distribution and compared this proportion to the proportion from the facility-based phase using a chi-square test.

Prediction of community-based prevalence using facility-based notifications

We used all cases from the community-based phase to represent the true underlying distribution of prevalent TB. For each zone, we used data from the facility-based phase to calculate an expected number of TB cases that would be found during the community-based phase, by multiplying the proportion of facility-based phase TB cases residing in each zone by the total number of TB cases found in the community phase. The expected number of community-based phase TB cases in each zone was compared to the observed number of TB cases found using a chi-squared test. The observed proportion of community-based phase TB cases residing within the high-risk zones (as defined during the facility-based phase) was calculated, with corresponding 95% confidence intervals using a binomial distribution, and compared to the proportion from the facility-based phase using a chi-square test. We also conducted a sensitivity analysis using only community-phase cases that were diagnosed via community-based active case finding (excluding those diagnosed at the health facilities during the

community-based phase) to represent the cases that would be expected to be found via a case finding intervention informed by notification data from the facility-based phase.

Results

Facility-based TB notifications

During the facility-based phase, 45 cases were notified at the four participating facilities through routine care. These cases resided in 15 different zones in the study area; among those zones, the average monthly TB notification rate ranged from 3.9 to 39.4 TB cases per 100,000 population per month (Figure 1, panel A). One zone in Bukasa parish accounted for 11 of the 45 (24%) TB cases diagnosed during this phase (Table 1). The five zones with the highest TB notification rates were classified as “high-risk.” These zones accounted for 22% of the population but 62% (95%CI 47-75%) of routinely diagnosed TB cases during the facility-based phase.

Compared to facility-based cases from other zones, facility-based TB cases from the high-risk zones were more likely to be female (11/28 [39%] vs. 3/17 [18%]), self-employed (10/28 [36%] vs. 2/12 [12%]), lower income (median monthly income 340,000 Ugandan Shillings [UGX] vs. 600,000 UGX), and HIV positive (11/38 [39%] vs 2/12 [12%]) (Table 3). They were less likely to be able to read and write without difficulty (13/28 [46%] vs. 5/17 [71%]) or to have known any other TB cases (7/28 [25%] vs. 8/17 [47%]). None of these results was statistically significant due to the small sample size.

Expected spatial distribution of TB cases

Under the assumption that the only variation in spatial distribution of TB cases was random chance, we estimated that 47% (95% simulation interval 39-58%) of TB cases would come from “high-risk” zones accounting for the same fraction of the population (22%), a lower percentage than the observed 62%. The results of sensitivity analyses using cutoffs of 10%, 15%, 25%, and 30% of the population are shown in Table 2.

Stability of facility-based notifications over time

Among passively-diagnosed (health facility) cases during the community-based phase, 32% (95% CI 18-50%) were residents of the high-risk zones as defined by the facility-based phase, significantly lower than would be expected if facility-based diagnoses were constant over time (p=0.009).

Prediction of community-based prevalence using facility-based notifications

During the community-based phase, 128 people were diagnosed with TB; these individuals resided in 27 different zones. Among these 27 zones, the average monthly TB notification rate ranged from 8.3 to 120.0 TB cases per 100,000 population (Figure 1, panel B). The five zones classified as “high-risk” based on the facility-based phase (22% of the study population) accounted for 42% (95% CI 34-51%) of the TB cases in the community-based phase, which was significantly higher than the 22% expected by

chance ($p<0.001$) but lower than the 62% of cases notified from those zones during the pre-intervention period ($p=0.02$).

The location of the five high risk zones is shown in Figure 2. Three of the five form a contiguous area in Bukasa parish. If this area were to be defined as a single intervention zone, this area would account for 18% of the total population, 51% (95% CI 36-66%) of the routinely diagnosed TB cases in the facility-based phase and 40% (95% CI 32-49%) of TB cases diagnosed in the community-based phase.

Sensitivity analyses of case definition

When considering only microbiologically confirmed cases (32/45 facility-based phase cases and 125/126 community-based phase cases), six zones accounting for 21% of the population had 59% (95% CI 41-75%) of facility-based phase TB cases; three of these zones were the same as in the primary analysis. We estimated that 53% (95% simulation interval 43-66%) of TB cases would come from “high-risk” zones accounting for the same fraction of the population (21%), based on random variation and population size alone. In the community-based phase, 40% (95%CI 32-49%) of cases came from these 6 “high-risk” zones.

Sensitivity analyses for active case finding

In the community-based phase, 34 (27%) cases were diagnosed at one of the four health facilities via routine services. In our sensitivity analysis excluding these cases, the five high-risk zones from the facility-based phase in the primary analysis

accounted for 46% (95% CI 36-56%) of cases detected via active case finding activities (door to door testing, venue based screening events, and contact investigation).

Discussion

This study in Kampala, Uganda, found evidence of spatial heterogeneity of TB burden within an urban, densely-populated area using routinely collected TB notification data, with 22% of the population accounting for 62% of cumulative TB notifications. Data from a subsequent community-based active case finding activity demonstrated that routine TB notifications can be used to identify geographic areas with a high underlying burden of TB; for example, the same 22% of the population accounted for 42% of the cases diagnosed during a subsequent case-finding intervention. Geographic targeting could therefore double the yield of active case finding interventions in this setting.

Interventions targeted at small geographical scales have not been widely implemented for TB, but locally focused prevention and case finding interventions have been shown to reduce the burden and transmission of HIV (24), malaria (25), and other neglected tropical diseases (26). Based on our results, targeting 22% of the population in an urban high-burden area could identify 42% of TB cases in that population. While we chose a cutoff of 20% of the population as a reasonable size to screen, targeted interventions even in this subpopulation would be resource intensive and logistically challenging. To further improve the feasibility of geographically targeted interventions, it may make sense to focus on a single contiguous area. In this study, three of the five “high-risk” zones (Figure 2) were geographically contiguous, suggesting a possible intervention area. However, this analysis does not account for the increased cost and

human resources required to conduct comprehensive interventions in targeted (often underserved) areas with populations that may be highly mobile; in other studies, the per-case-detected costs of active case finding in high TB burden areas have been shown to be high (27,28). Intervention-specific cost and epidemiological data would be needed to estimate the impact and cost-effectiveness of any particular intervention in this setting.

Spatial analyses of TB have been primarily limited to using TB notification data (29) and are therefore unable to assess whether high notification rates are due to high prevalence of TB in the community or improved access to TB diagnosis (30). Numerous studies in high-burden countries have shown that TB notifications are limited by underdiagnosis and under-reporting (14,15,31–35), but it is not clear whether the location of residence of the reported TB cases represents that of the missed cases. Our analysis suggests that, in this setting, facility-based TB notifications can reasonably predict the location of prevalent TB cases, suggesting that geographically targeted active case finding using routine notifications to define the target zones could be effective in this area. This is a strength of small-scale geographic analysis in our 2.2 km^2 study area, as access to health care may be relatively homogeneous. In settings where low notification rates may represent poor access to services, notifications are likely to be less useful in targeting areas for further TB-related interventions.

The population denominators on which our estimates of zone-level TB rates are based used census estimates collected by our research team; official population estimates are not available from the Uganda Bureau of Statistics at this scale, which may limit the ability of other regions to apply these methods. While our population

estimates may be imprecise, they are the first to be estimated at the zone level in this area, and there is no *a priori* reason to expect that any biases in population estimates would be differential from one zone to the next. Our community-based phase was conducted shortly after the facility-based phase, reflecting how a geographically targeted case finding intervention may be implemented, but the lack of stability in geographic distribution of facility-based notifications over time may make it difficult to accurately predict the location of undiagnosed cases. Our sample size was small, leading to imprecise estimates – but such sample sizes are likely to be representative of real-world interventions that might seek to target TB activities on small geographic scales over realistic time frames. Finally, given the urban, densely population nature of our study setting, these results may not be generalizable to rural settings or different epidemiological contexts; however, these methods could be applied in different settings using routinely available data.

In conclusion, we show that there is substantial geographic heterogeneity in the residence of routinely diagnosed TB patients. We identified high risk zones using data routinely collected at health facilities and show that it may be possible to detect more than 40% of undiagnosed TB cases in the community by screening approximately 20% of the population. Comparison of the spatial distribution of passively diagnosed cases with those identified via community-wide active case finding suggests that geographically prioritized case finding may be an efficient way to detect prevalent TB in urban high-burden settings.

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Tables and Figures

Figure 2.1. Average Monthly TB Notifications, by zone (per 100,000 population)
This figure shows the average monthly TB notification rate per 100,000 population by zone as estimated in (A) the facility-based phase, where TB cases were passively diagnosed via routine standard of care practices from May 2018 to January 2019 and (B) the community-based phase, where additional active case finding activities were implemented throughout the study area from February to December 2019. Numbers indicate each zone's rank (from 1-15) based on average monthly TB notification rates during the facility-based phase – with no numbers assigned to zones in which no TB cases were diagnosed during that phase. High-risk zones (outlined in bold) were selected using notifications from the facility-based phase by starting with the zone reporting the highest TB notification rate and including additional zones with the next-highest rates until the "high-risk" category accounted for at least 20% of the population, resulting in five zones. Two zones did not have population data available to inform denominators and were thus excluded from this analysis.

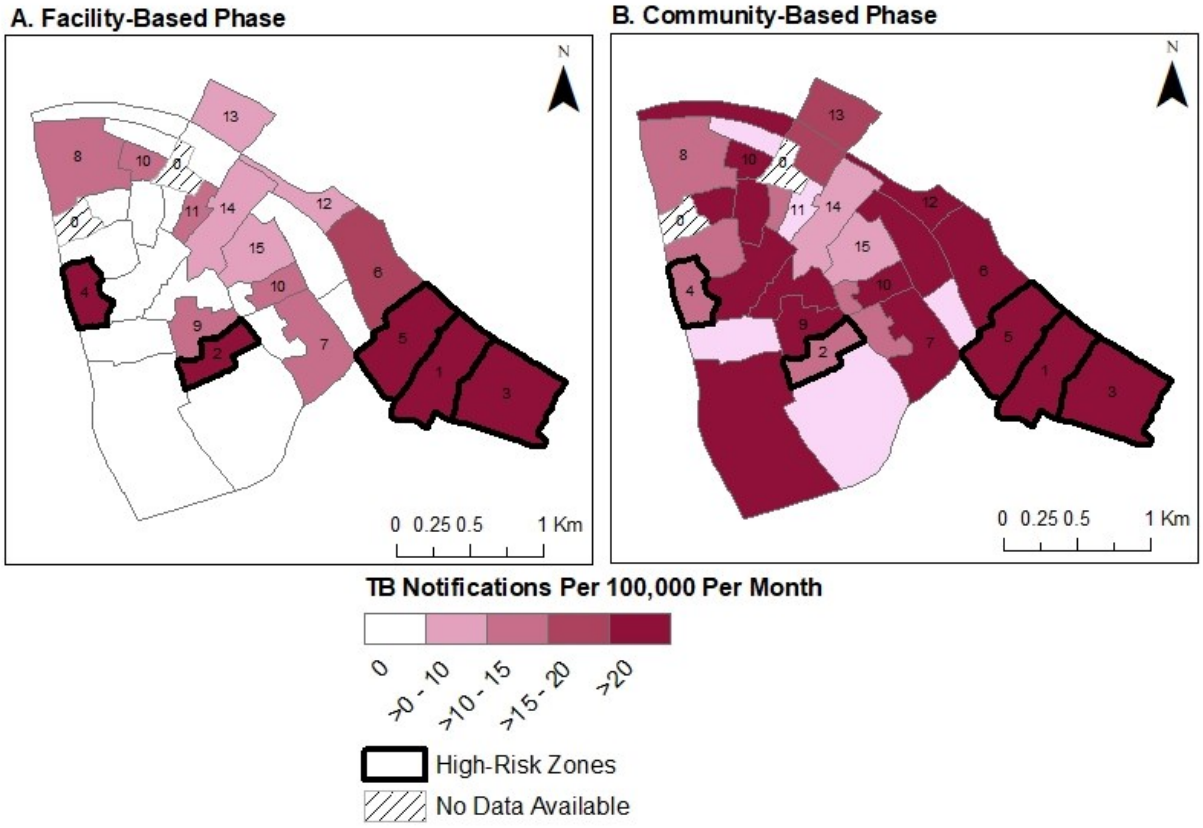


Table 2.1. Observed TB Notifications by Zone and Phase of Case Detection in Urban Uganda

		Facility-based (routine) phase						Community-based (active) phase		
Parish	**Zone**	**Observed TB Cases**	**Population**	**Monthly TB Notification Rate (per 100,000)**	**Rank (Fig. 1)**	**Cumulative Proportion of Population**	**Cumulative Proportion of TB Cases**	**Observed TB Cases**	**Monthly TB Notification Rate (per 100,000)**	**Cumulative Proportion of TB Cases**
Bukasa	Namuwongo A	11	3299	39.4	1	0.07	0.24	31	120.0	0.25
Kisugu	South B	3	906	39.1	2	0.08	0.31	1	14.1	0.25
Bukasa	Yoka	7	2793	29.6	3	0.14	0.47	13	59.4	0.36
Wabigalo	Klezia	2	950	24.9	4	0.16	0.51	1	13.4	0.37
Bukasa	Namuwongo B	5	2705	21.8	5	0.22	0.62	8	37.8	0.43
Kisugu	Kasanvu	4	2471	19.1	6	0.26	0.71	10	51.7	0.50
Kisugu	South AC	1	809	14.6	7	0.28	0.73	4	63.1	0.53
Wabigalo	Project	2	1739	13.6	8	0.32	0.78	2	14.7	0.55
Kisugu	Upper Zone	2	1742	13.6	9	0.35	0.82	4	29.3	0.58
Wabigalo	Central	2	1898	12.4	10	0.39	0.87	11	74.0	0.66
Wabigalo	Kitooro	1	1166	10.1	11	0.41	0.89	0	0.0	0.66
Kisugu	Go Down	1	1202	9.8	12	0.44	0.91	7	74.3	0.72
Wabigalo	Industrial	1	1302	9.1	13	0.46	0.93	2	19.6	0.73
Kisugu	Lakeside	2	2701	8.7	14	0.52	0.98	2	9.5	0.75
Kisugu	Mugalasi	1	3062	3.9	15	0.58	1	2	8.3	0.77
18 zones reporting 0 cases in the facility-based phase		0	20,782	0		1.0	1.0	30	18.4	1.0

Table 2.2. Sensitivity Analysis: Different Cutoffs for "High-Risk" TB Population

Cutoff for percentage of population in "high-risk" area	Actual percentage of population in "high-risk" area[1]	Number of zones in the "high-risk" area	Observed percentage of TB cases in the "high-risk" area (95% CI)	Expected (simulated) percentage of TB cases in the "high-risk" area (95% CI)
5%	7%	1	24% (14-39%)	19% (44-26%)
10%	14%	3	47% (32-62%)	35% (28-44%)
15%	16%	4	51% (36-66%)	38% (31-48%)
20%	22%	5	62% (47-75%)	47% (39-58%)
25%	27%	6	71% (56-83%)	55% (46-66%)

[1] The actual percentage is higher than the cutoff percentage because the actual "high-risk" area consists of intact zones, added sequentially to the "high-risk" area until the cutoff is surpassed.

Figure 2.2. Potential Implications of Geographic-Targeted Screening
High-risk zones as defined by the facility-based phase TB notification rates are indicated in purple. Numbers indicate each zone's rank (from 1-15) based on average monthly TB notification rates during the facility-based phase – with no numbers assigned to zones in which no TB cases were diagnosed during that phase. While targeted active case finding at each selected zone may not be feasible for logistical and political reasons, we highlight that the easternmost three of the five high-risk zones are contiguous and within Bukasa parish (parish boundaries are designated in bold). If this area were to be defined as a priority for case finding activities, it would represent 18% of the total population, 23/45 (51%) of facility-based phase TB cases, and 52/128 (40%) of the community phase TB cases. Two zones did not have population available and were excluded from this analysis.

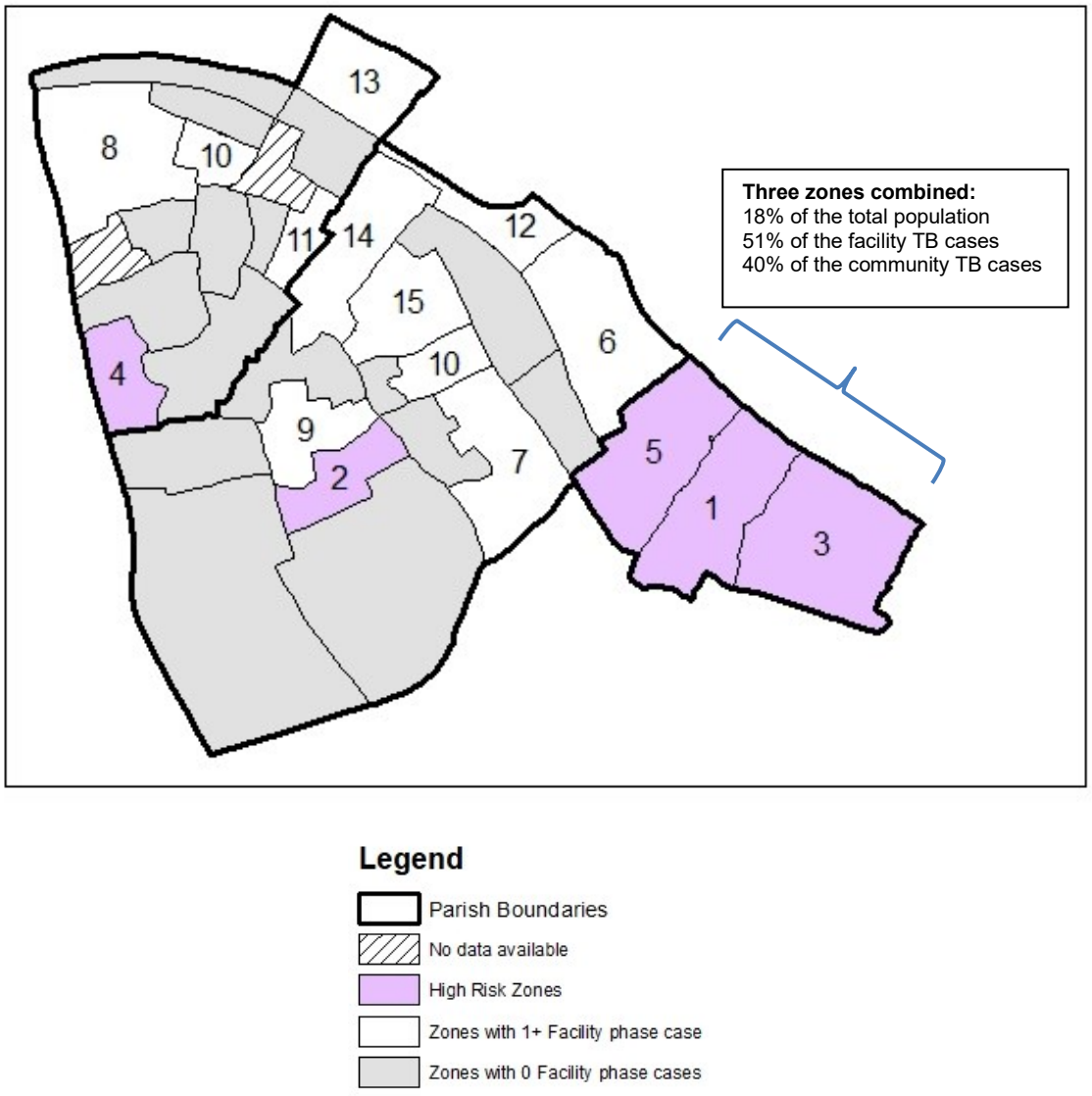
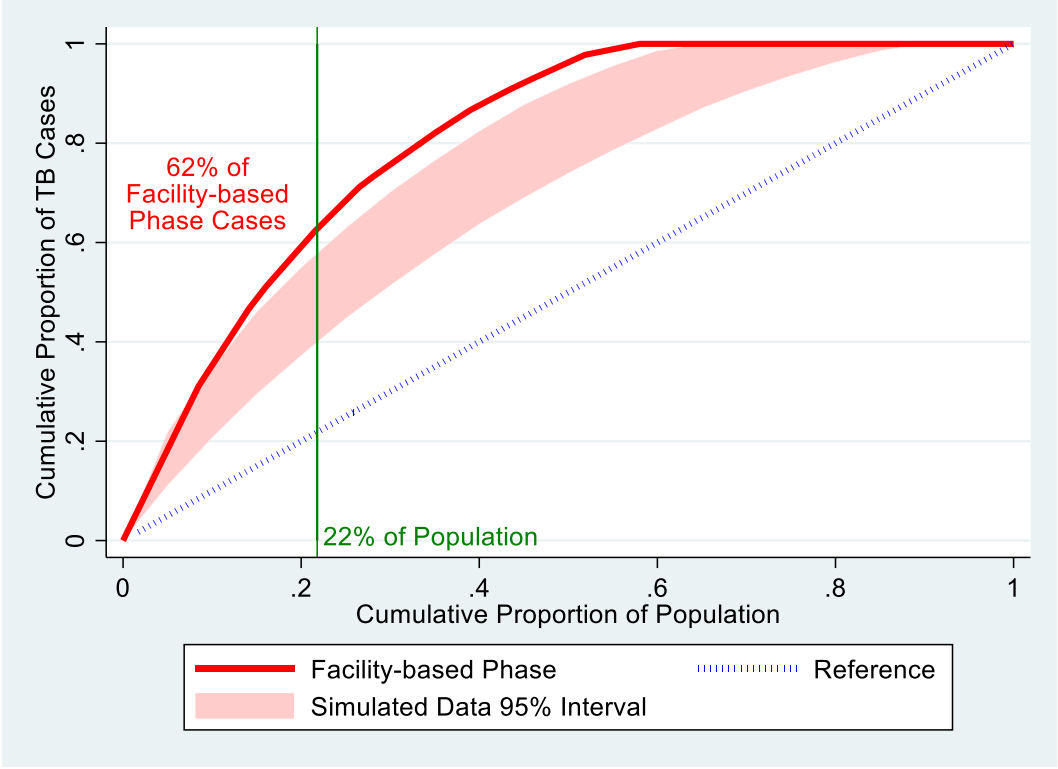


Figure 2.3. Comparison of observed TB notifications in high-risk zones to expected cases due to chance

Panel A orders the 35 zones the study area according to each zone's facility-based phase TB notification rate (also provided in Table 1); the red line shows the cumulative proportion of TB cases notified who reside in "high-risk" zones (y-axis) according to the cumulative proportion of the population in the "high-risk" zone (x-axis). The shaded area corresponds to the 95% simulation interval (2.5^{th} and 97.5^{th} percentiles) from 1,000 simulations that assume the observed population size in each zone and observed total number of TB notifications, but assign TB cases to zones under the assumption that spatial heterogeneity of TB notifications in the area is driven only by population size and random chance. The vertical line at 22% of the cumulative population represents the cutoff for "high-risk" zones used in our primary analysis and shows that 62% of facility-based cases resided in "high-risk" zones, significantly higher than the corresponding simulation interval of 40-59%. Panel B compares the same observed facility-based phase cases from Panel A (red line) with the cumulative proportion of TB cases identified through active case finding during the community-based validation phase (blue line), with the zones ordered according to TB notification rates during the facility-based phase. The vertical line in this panel shows that 42% of community-based phase cases resided in the "high-risk" zones (22% of the population) identified based on notifications during the facility-based phase.


Cumulative Proportion of TB Cases
0
.2
.4
.6
.8
1
62% of
Facility-based
Phase Cases
22% of Population
0
.2
.4
.6
.8
1
Cumulative Proportion of Population
Facility-based Phase
Reference
Simulated Data 95% Interval

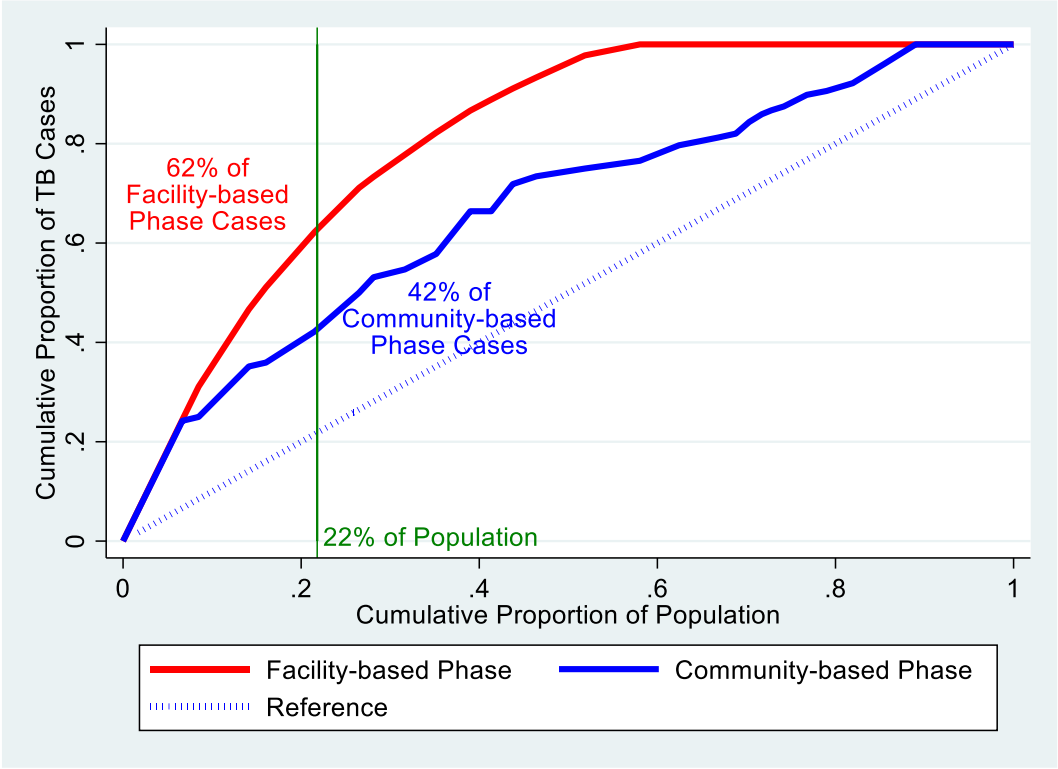

Cumulative Proportion of TB Cases
0
.2
.4
.6
.8
1
62% of
Facility-based
Phase Cases
42% of
Community-based
Phase Cases
22% of Population
0
.2
.4
.6
.8
1
Cumulative Proportion of Population
Facility-based Phase
Community-based Phase
Reference

Table 2.3. Demographic and clinical comparison between routinely diagnosed cases residing in high risk and low risk zones during the facility-based phase

	Residents of High- Risk Zones (N=28)	Residents of Low-Risk Zones (N=17)	p-value
	N (%)	N (%)	
Female	11 (39%)	3 (18%)	0.19
Age at TB diagnosis			0.46
15-24 years	4 (14%)	3 (18%)	
25-34 years	10 (36%)	8 (47%)	
35-44 years	11 (39%)	3 (18%)	
45-54 years	3 (11%)	3 (18%)	
Literacy			0.28
Can read & write without difficulty	13 (46%)	12 (71%)	
Can read & write, but one or both are difficult	13 (46%)	5 (29%)	
Can neither read nor write	2 (7%)	0 (0%)	
Occupation			0.52
Self-employed	10 (36%)	2 (12%)	
Student	1 (4%)	1 (6%)	
Salaried worker	7 (25%)	6 (35%)	
Occasional work (piece jobs)	4 (14%)	4 (24%)	
Unemployed but able to work	3 (11%)	3 (18%)	
Unemployed and unable to work	3 (11%)	1 (6%)	
Monthly income (Ug Shillings x1000), median (IQR)	340 (136)	600 (350, 750)	0.06
Skipped 1+ Meals in the last month[1]	19 (68%)	7 (41%)	0.12
Household Size, median (IQR)	2 (1, 3)	3 (1, 5)	0.35
Duration of cough (weeks), median (IQR)	5 (3, 12)	8 (4, 20)	0.08
HIV Positive	11 (39%)	2 (12%)	0.09
Ever lived with a TB Case	6 (21%)	5 (29%)	0.37
Ever known a TB Case	7 (25%)	8 (47%)	0.08

[1] Participant or other adults in their household reported skipping at least one meal or eating smaller meals than wanted because there wasn't enough money for food

Chapter 3: Characterization of Geographic Mobility among patients at TB Diagnosis and Control Units in Kampala, Uganda

Abstract

Background: International and internal migration are key risk factors for tuberculosis (TB). Geographic mobility, including small-scale travel for work, education, or personal reasons, may also play a role in TB but is poorly defined. We aimed to describe geographic mobility patterns among patients seeking TB diagnostic services in Kampala, Uganda and to assess the associations of this mobility with TB disease and access to care.

Methods: This was a facility-based case control study conducted at four outpatient health facilities providing TB diagnostic and treatment services in Kampala, Uganda. We enrolled confirmed TB cases age ≥15 residing in the study catchment area; each case was matched with 2 controls. Participants self-reported seven characteristics of geographic mobility which were used to conduct a latent class analysis (LCA) and create a definition of mobility. We assessed association of mobility and delays in diagnosis using non-parametric Wilcoxon rank-sum tests for cases and controls separately. We evaluated the association of mobility and TB case status using conditional logistic regression.

Results: We enrolled 101 cases and 202 matched controls. Cases were more likely than controls to have lived in their neighborhood for more than a year (p=0.02); there was no difference between cases and controls in the remaining mobility characteristics. The LCA model with the best fit had 2 classes; the “mobile” class was largely driven by travel > 3 km from residence ≥9 times per month (84% vs. 2%) and spending ≥6 hours away from home when traveling >3

km from residence (78% vs 17%). Mobility was not associated with TB case status (adjusted odds ratio 0.85, 95% CI 0.44, 1.6), duration of symptoms (cases: p=0.73; controls p=0.6) or number of healthcare visits (cases: p=0.42; controls p=0.03) prior to the visit of enrollment.

Conclusions: We provide the first description of mobility characteristics in a TB care seeking population and developed a definition of mobility based on frequency and duration of travel > 3 km from home. While this definition of mobility was not associated with TB case status or barriers to care, more research is needed to understand the drivers of mobility in this population.

Introduction

Tuberculosis (TB) is a leading cause of morbidity and mortality globally, contributing to an estimated 10.0 million cases and 1.2 million deaths in 2018 (1,2). Mobile and migratory individuals are a key population at risk for TB infection and disease (3). Mobile individuals may be more likely to acquire or transmit TB (4,5) and often experience barriers to TB diagnosis and treatment (6,7). While most research on TB and migration is focused on international migration (3), internal mobility such as rural-urban migration (8,9), labor migration (10), and nomadic populations (11–13) have also been shown to be at high risk for TB and to experience barriers to TB care.

Many studies on mobility have focused on HIV in defined populations that are known to experience high mobility. For example, studies have shown truck drivers to be at high risk of acquiring (14–16) and transmitting HIV (17) and to have limited access to health care (18). Agricultural migrant workers have also been shown to be at increased risk for HIV (19,20). However, mobility may exist in less defined scenarios, such as due to marriage, work, or education (21), and there is no single definition of this geographic mobility. Studies of mobility and HIV have considered frequency (20,22–24) and duration of travel from home (22), number of nights spent away from home (20,22–25), circular or temporary migration (26), as well as distance traveled or internal borders crossed (21,22,24), but no studies have applied these definitions to TB.

We aimed to develop a broader understanding of generalized mobility patterns. We described mobility patterns among patients seeking care at four TB

diagnostic and treatment units in Kampala, Uganda. We also assess the relationship between mobility and access to care and TB risk. Identifying mobility characteristics that affect health seeking behaviors or disease transmission is important for providing services in this hard to reach population.

Methods

Study population

We prospectively enrolled patients presenting for TB testing at one public and three private outpatient TB Diagnosis and Treatment Units in Kampala between May 22, 2018, and January 31, 2019. Eligibility criteria included age ≥15 years and residence within the study area, consisting of three parishes (Kisugu, Wabigalo, and part of Bukasa; estimated population: 49,527, total area 2.2 km^2). For the time period between June 25, 2018, and January 1, 2019, we also enrolled participants from Kisugu Health Center (the public facility) regardless of their residence. TB cases were defined as patients diagnosed with pulmonary TB by the treating clinician, regardless of microbiological test result; however, most cases were confirmed with sputum Xpert MTB/RIF. For each case, two controls matched by facility and location of residence (within study area vs. outside study area, for the participants from Kisugu Health Center) were enrolled. Controls were randomly selected from eligible individuals who presented to the same treating facility and were tested for pulmonary TB but had a negative Xpert MTB/RIF result and were not empirically treated for TB. Data collection included participant interviews and abstraction from clinical and laboratory records.

Measurement of components of geographic mobility

We defined *a priori* seven components of mobility and collected information through patient self-report. These measures and their categorization are shown in Table 3.1. As a sensitivity analysis for the continuous variables (frequency and duration of travel further than 3km from home), in addition to using the median to dichotomize the variable, we also considered the 25th and 75th quartiles as cutoffs.

Classification of mobility

We used a latent class analysis (LCA) to inform our definition of mobility. The construct of mobility as a latent variable is shown in Figure 3.1. We conducted latent class analysis with a logit link using these seven variables as defined above using our entire study population. To determine the number of classes that provided the best model fit, we considered models with 1-4 classes and selected the model with the lowest Bayesian Information Criterion (BIC). We then characterized the classifications of mobility based on the LCA marginal means and assigned each participant to a mobility class.

As described below, the results of the LCA were very similar to a dichotomous definition of geographic mobility. We compared a calculated definition of mobility (observed, rather than latent) to the classes predicted by the LCA and used the calculated classes of mobility for further analyses.

Mobility and Access to Care

We defined two variables to indicate barriers to care. Symptom duration prior to current visit was calculated as the time from the self-reported start of the first symptom (cough, fever, night sweats, or weight loss) to the date of the patient's interview. We also elicited the number of self-reported health care visits during this time. Both symptom duration and number of health care visits were compared for mobile vs. non-mobile patients (based on the definition of mobility above) in cases and controls separately using non-parametric Wilcoxon rank-sum tests.

Mobility and TB case status

Using our calculated definition of mobility, we described the characteristics of mobile vs. non-mobile persons, stratified by TB case status, using chi-squared tests. We then assessed the association of mobility with TB case status (case vs. control) using conditional logistic regression, adjusting for possible confounders. Due to the large number of potential confounders, covariates with p-value<0.05 in the bivariate analysis were included in the final model.

Results

Study population

We enrolled a total of 303 participants (101 TB cases and 202 matched controls). Cases generally had similar mobility characteristics compared to

controls, although they were less likely to have lived in their current neighborhood for less than 1 year (p=0.02) (Table 3.1). Cases were less likely to be female (39% vs 60%, p<0.001) or to live in a household with 3 or more people (38% vs. 55%, p=0.006) and were more likely to report limitation in at least one of the 5 EQ-5D domains (physical mobility, self-care, usual activities, pain/discomfort, anxiety/depression) (75% vs. 57%, p=0.002) compared to controls. Cases were also more likely to have been to prison (46% vs 23%, p<0.001) and to have been treated for TB in the past (26% vs 10%, p<0.001).

Classification of mobility

We selected the model with two latent classes as the best fit based on BIC (Table 3.S1 and Figure 3.S1 in Supplement). One class was characterized as "mobile" based on higher marginal means for the following characteristics: travel more than 3 km from residence ≥9 times per month (84% vs. 2%), spending ≥6 hours away from home when traveling more than 3 km from residence (78% vs 17%), and traveling outside Kampala at least once in the last year (81% vs 68%) (Figure 3.2, Table 3.S3 in Supplement). People in this mobile class were more likely to have lived in the current neighborhood of residence at least one year (13% vs. 29%). These results did not change in sensitivity analyses that varied the cutoffs for dichotomizing frequency and durations of travel >3 km. Applying these classes to our patient population, we categorized 175 (57.8%) participants as mobile.

Calculation of Mobility

Based on the results of the LCA, we considered a definition of geographic mobility as traveling further than 3 km from home at least 9 times per month or spending at least 6 hours away from home when traveling further than 3 km. Using this definition classified 94% (N=284/303) of patients in the same mobility category as predicted by the LCA. The remaining 19 patients were categorized as non-mobile in the LCA but mobile based on this calculation; however, the probability of being in the non-mobile class from the LCA was lower among these 19 patients (63%, 95% CI 53-80%) compared to all patients categorized as non-mobile (90%, 95% CI 53-99%).

Characteristics associated with mobility

Among both cases and controls, mobile patients were more likely to be men (cases: 76% vs. 38%, p<0.001; controls: 48% vs. 26%, p=0.002) and employed (cases: 87% vs. 51%, p<0.001; controls: 77% vs. 57%, p=0.011); mobile patients were also less likely to report limitations in any of the five EQ-5D domains (cases: 66% vs. 90%, p=0.007; controls: 53% vs. 66%, p=0.083) (Table 3.3). Among controls only, mobile patients were more likely to have difficulty reading or writing (67% vs. 42%, p=0.004) and were less likely to have known (24% vs. 37%, p=0.04) or lived with a TB case (16% vs. 30%, p=0.019).

Mobility and access to care

While the median duration of symptoms among cases (8 weeks [IQR 4-12]) was higher than among controls (3 weeks [IQR 2-8]), there was no significant difference between mobile and non-mobile patients among either cases or controls (Table 3.S5 in Supplement).

The median number of symptom-related visits was 4 (IQR 2-7) among cases and 3 (2-6) among controls. There was no significant difference between mobile and non-mobile cases; among controls, the number of visits was slightly higher in non-mobile populations (p=0.03) (Table 3.S5 in Supplement).

Mobility and TB Case Status

Among TB cases, 61% (n=62) were classified as mobile compared to 65% (n=132) controls (p=0.50). Mobility was not associated with TB case status (adjusted odds ratio 0.85, 95% CI 0.44, 1.6). In multivariable analysis, previous treatment for TB (aOR 2.8, 95% CI 1.3, 5.9) or limitation in any of the EQ-5D domains (aOR 2.0, 95%CI 1.1, 3.8) were associated with TB case status. Female patients (aOR 0.40, 95% CI 0.20, 0.8) were less likely to have TB.

Discussion

Mobility may be a key factor in infectious disease epidemics, as it may be related to transmission of disease or represent a population that faces challenges in accessing health care. In this analysis of over 300 individuals presenting for

TB diagnosis in urban Uganda, we found that mobility was best defined by the frequency and number of trips further than 3 km from home residence. However, we did not find an association between this definition of mobility and delays in TB evaluation or risk of TB disease.

There is no consistently applied definition of mobility, but our definition of mobility was similar to that used in other studies of mobility in sub-Saharan Africa (20,22–24). A strength of our definition is that it was determined using a data driven approach based on our latent class analysis. Some studies distinguish between internal migration and travel as components of mobility (21); we considered both in our LCA but ultimately only used travel in our final definition. Additionally, our use of a 3 km cutoff, designed to capture travel beyond the participants' neighborhood, was unique in the definition of mobility. We did consider longer travel distance (outside of Kampala), which is similar to inter-district travel used in other studies (21) but found that shorter distance better distinguished the classes of mobility. However, we did not collect information on nights spent away from the home, which is a common component of mobility in other studies (20,22–25).

While we hypothesized that mobile populations would be at increased risk for TB disease (due to increased range of contacts) and may experience barriers to care due to an unstable lifestyle, we did not observe such associations in our analysis. The effect of mobility on disease outcomes and barriers to care is likely

driven by the cause and context of mobility, which we are unable to assess in this simplified analysis. There has been conflicting evidence as to whether mobile populations have more or less exposure to education campaigns and whether they experience greater or fewer barriers to care (27,28). Our analysis suggests that mobile individuals are more likely to be employed and less likely to report limitations on any of the EQ-5D domains, which may suggest that they are healthier and of higher socioeconomic status (supported by the result that mobile individuals were more likely to be in the highest quartile of income among both cases and controls) than non-mobile individuals, putting them at lower risk for disease and experiencing barriers to care. Other mobile populations have been shown to be at increased risk for TB, and interventions targeting these populations have been successful in providing TB diagnostic and treatment services for truck drivers in India (29) and nomadic populations in Nigeria (13) and Iran (12). Migrant-centered care, including mobile clinics, expanding service hours, flexible treatment options, or health passports may be appropriate services for this population (3).

Limitations of our study primarily center on the measurement of mobility. Mobility questions were assessed via self-report in patient interviews and may be subject to misclassification or bias. Additionally, we asked a set of questions that may not capture every component of mobility; for example, we did not elicit number of nights spent away from home and reasons for travel. GPS trackers have been used in other studies and can capture continuous information that can

be used to calculate additional indicators (30,31) and may provide more reliable information (30,32). However, our approach using an LCA contributes to the development of a mobility definition that may be applied to other populations. Our interviews were conducted only at the time of seeking TB diagnostic services; participants, particularly those who were diagnosed with TB, may therefore have been symptomatic for substantial periods of time. A lack of mobility may thus reflect the effects of TB disease itself (i.e., be subject to reverse causality), which could counterbalance any increased TB risk that might be associated with increased mobility; a similar relationship has been suggested for HIV (33). Prospective data collection may help clarify these causal relationships between mobility and risk of disease. Additionally, our population of patients seeking TB diagnostic services at urban health facilities may not represent the general population and therefore our definition of mobility may not be appropriate for other populations.

Conclusion

We developed a data-driven definition of mobility among patients seeking care at health facilities in Kampala, Uganda. While we found no association between this definition of mobility and delays in TB diagnostic evaluations or risk of TB disease, mobile populations remain critical to infectious disease control. Additional research to better measure and classify mobility is warranted to understand the drivers of mobility in order to mitigate any increased risk that for disease that certain mobile populations may experience.

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Tables and Figures

Table 3.1. Components of Geographic Mobility

Question	Categorization	Sensitivity Analysis
Where were you born?	in Kampala vs. outside Kampala	n/a
How long have you lived within 3km of your current residence?	new residents: < 1 year	n/a
Is there another place that you stay, other than the residence you have just described?	yes vs. no	n/a
How often do you typically visit each of the following places* for any reason?	Visit any taxi park at least 1 time per month vs. less than 1 time per month	n/a
How often do you go somewhere more than about 3km from your residence?	<9 times per month vs. ≥9 times per month (median)	<2 times per month vs. ≥2 times per month (25th percentile) <24 times per month vs. ≥24 times per month (75th percentile)
When you go more than about 3km from your residence, how many hours do you usually spend >3km away?	<6 hours per trip vs. ≥6 hours per trip (median)	<4 hours per trip vs. ≥4 hours per trip (25th percentile) <9 hours per trip vs. ≥9 hours per trip (75th percentile)
How many times did you travel outside of Kampala in the past 12 months, to your best recollection?	0 trips in the last year vs. ≥1 trip in the last year	n/a

*Kisugu Taxi stage, Namuwongo Taxi Stage, Old Taxi Park, New Taxi par, Ssali Stage Wabigalo

Figure 3.1. Construct of Geographic Mobility as a Latent Variable

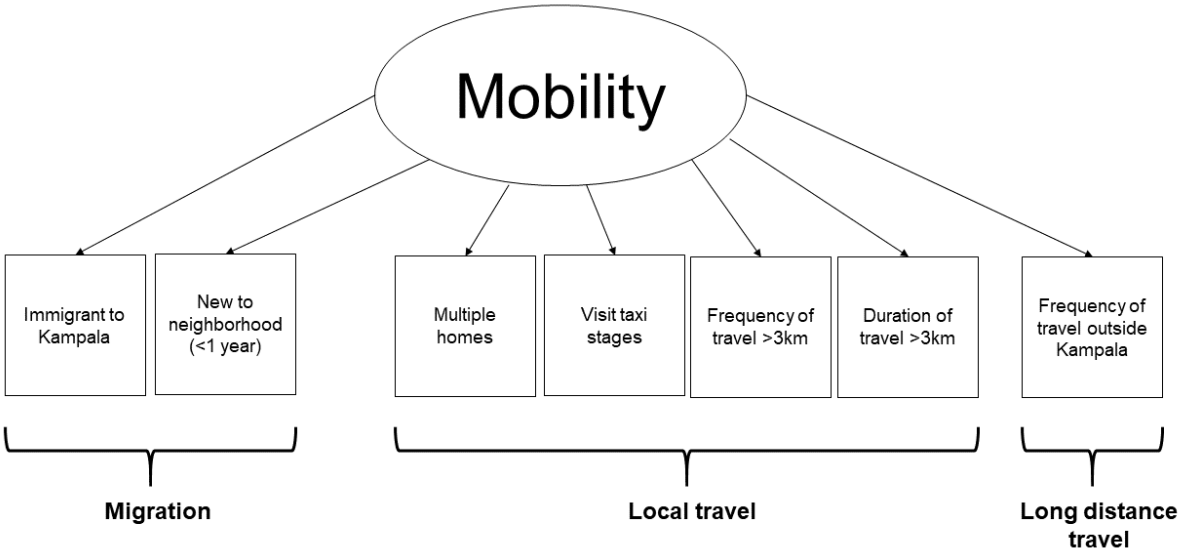


Table 3.2. Mobility and Sociodemographic and Risk Factor Characteristics by TB

case status

	TB Case N=101	Control N=202	p-value
	N (%)	N (%)	
Mobility Characteristics			
Born in Kampala	15 (15%)	26 (139%)	0.63
Lived in neighborhood <1 year	12 (12%)	47 (23%)	0.02
Have another residence	8 (8%)	19 (9%)	0.67
Visited taxi stage ≥1 times per week	27 (27%)	47 (23%)	0.51
Travel 3km ≥9 times per month (median)	50 (50%)	101 (50%)	0.94
Spend ≥6 hours away when traveling 3km (median)	52 (52%)	107 (53%)	0.81
Ever traveled outside Kampala in last year	73 (72%)	156 (77%)	0.34
Other Sociodemographic Characteristics			
Age in years			0.17
15-24	19 (19%)	44 (22%)	
25-34	46 (46%)	67 (33%)	
35-44	22 (22%)	48 (24%)	
≥45	14 (14%)	43 (21%)	
Female sex	39 (39%)	121 (60%)	<0.001
Parish of Residence			0.75
Kisugu	14 (14%)	36 (18%)	
Wabigalo	9 (9%)	18 (9%)	
Bukasa (within study area)	22 (22%)	36 (18%)	
Other (Kisugu health Center Only)	56 (54%)	112 (55%)	
Location of Birth			0.76
Kampala	15 (15%)	26 (13%)	
Northern Uganda	10 (10%)	17 (8%)	
Eastern Uganda	25 (25%)	41 (20%)	
Western Uganda	20 (20%)	40 (20%)	
Central Uganda (outside Kampala)	29	69 (34%)	

	(289%)		
Outside Uganda	2 (2%)	9 (5%)	
Literacy			0.46
Can read/write without difficulty	45 (45%)	81 (40%)	
Difficulty or in ability in reading/writing	56 (55%)	121 (60%)	
Highest completed education			0.37
None	43 (43%)	72 (36%)	
Certificate	52 (52%)	110 (55%)	
Degree/further studies	6 (6%)	20 (10%)	
Occupation			0.14
Employed	74 (73%)	142 (70%)	
Unemployed	23 (23%)	39 (19%)	
Other	4 (4%)	21 (10%)	
Income quartile			0.69
1st (lowest)	30 (30%)	61 (30%)	
2nd	17 (17%)	45 (22%)	
3rd	32 (32%)	57 (28%)	
4th (highest)	22 (22%)	39 (19%)	
Ever Been to Prison	46 (46%)	47 (23%)	<0.001
HIV Positive	34 (34%)	61 (30%)	0.54
Previous TB Treatment	26 (26%)	21 (10%)	<0.001
Ever had household TB contact	21 (21%)	42 (21%)	0.98
Ever known a TB case	24 (24%)	57 (28%)	0.44
Household has ≥3 people	38 (38%)	110 (555%)	0.006
Limitations in any of the EQ-5D domains	76 (75%)	116 (57%)	0.002

Figure 3.2. Marginal Means for Latent Classes of Mobility

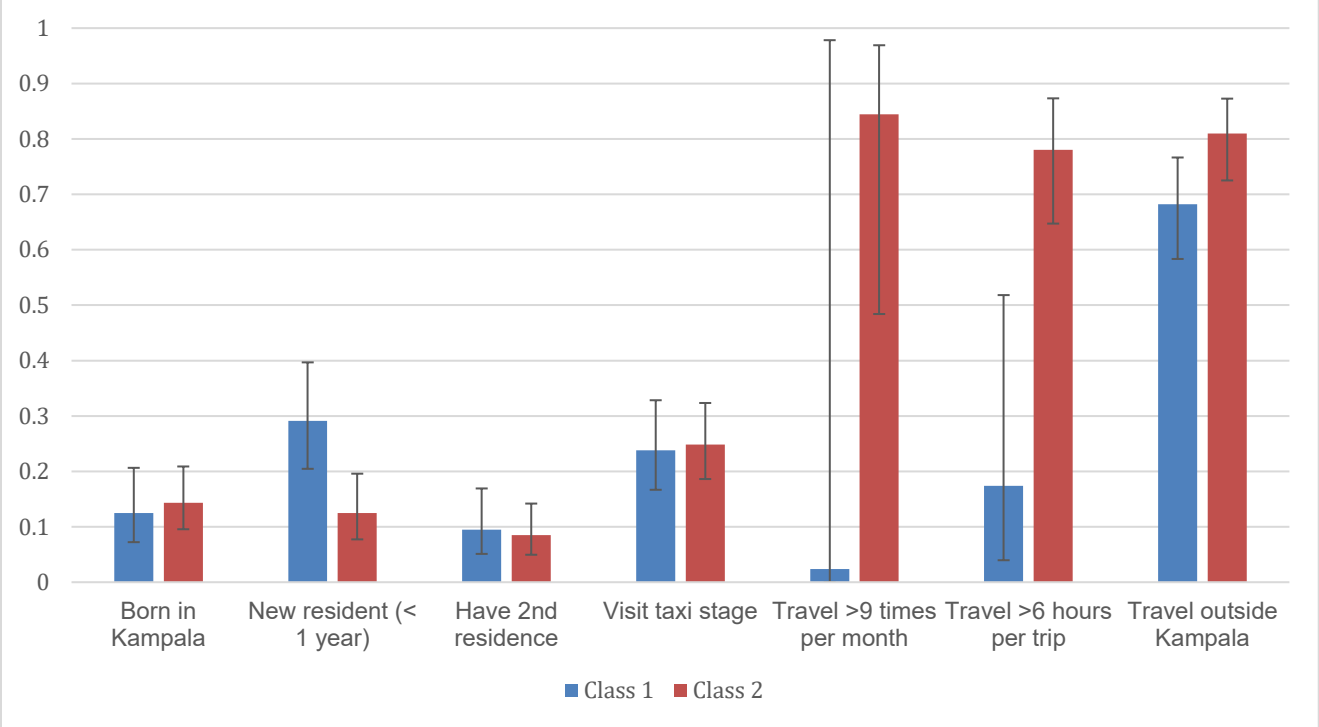


Table 3.3. Association of sociodemographic characteristics with mobility classification

	TB Cases			Controls		
	Mobile N=62	**Non mobile N=39**	**p-value**	**Mobile N=132**	**Non mobile N=70**	**p-value**
	N (%)	N (%)		N (%)	N (%)	
Age in years			0.059			0.35
15-24	7 (11%)	12 (31%)		26 (20%)	18 (26%)	
25-34	28 (45%)	18 (46%)		47 (36%)	20 (29%)	
35-44	16 (26%)	6 (15%)		28 (21%)	20 (29%)	
≥45	11 (18%)	3 (8%)		31 (24%)	12 (17%)	
Female Sex	15 (24%)	24 (62%)	<0.001	69 (52%)	52 (74%)	0.002
Parish of Residence			0.016			0.25
Kisugu	11 (18%)	3 (8%)		23 (17%)	13 (19%)	
Wabigalo	9 (15%)	0 (0%)		11 (8%)	7 (10%)	
Bukasa (within study area)	13 (21%)	9 (23%)		19 (14%)	17 (24%)	
Other (Kisugu health Center Only)	29 (47%)	27 (69%)		79 (60%)	33 (47%)	
Location of Birth			0.78			0.8
Kampala	9 (15%)	6 (15%)		19 (14%)	7 (10%)	
Northern Uganda	6 (10%)	4 (10%)		13 (10%)	4 (6%)	
Eastern Uganda	17 (27%)	8 (21%)		25 (19%)	16 (23%)	
Western Uganda	14 (23%)	6 (15%)		26 (20%)	14 (20%)	
Central Uganda (outside Kampala)	15 (24%)	14 (36%)		44 (33%)	25 (36%)	
Outside Uganda	1 (2%)	1 (3%)		5 (4%)	4 (6%)	
Literacy			0.54			0.004
Can read/write without difficulty	26 (42%)	19 (49%)		43 (33%)	38 (54%)	
Difficulty or in ability in reading/writing	36 (58%)	20 (51%)		89 (67%)	32 (46%)	
Highest completed education			0.2			0.018
None	22 (35%)	21 (54%)		39 (30%)	33 (47%)	
Certificate	36 (58%)	16 (41%)		76 (58%)	34 (49%)	
Degree/further studies	4 (6%)	2 (5%)		17 (13%)	3 (4%)	
Occupation			<0.001			0.011
Employed	54 (87%)	20 (51%)		102 (77%)	40 (57%)	
Unemployed	7 (11%)	16 (41%)		19 (14%)	20 (29%)	
Other	1 (2%)	3 (8%)		11 (8%)	10 (14%)	
Income quartile			0.19			0.1
1st (lowest)	15 (24%)	15 (38%)		35 (27%)	26 (37%)	
2nd	9 (15%)	8 (21%)		26 (20%)	19 (27%)	

3rd	21 (34%)	11 (28%)		41 (31%)	16 (23%)	
4th (highest)	17 (27%)	5 (13%)		30 (23%)	9 (13%)	
Ever Been to Prison	31 (50%)	15 (38%)	0.26	31 (24%)	16 (23%)	0.92
HIV Positive	20 (32%)	14 (36%)	0.71	41 (31%)	20 (29%)	0.71
Previous TB Treatment	16 (26%)	10 (26%)	0.99	12 (9%)	9 (13%)	0.4
Ever had household TB contact	15 (24%)	6 (16%)	0.35	21 (16%)	21 (30%)	0.019
Ever known a TB case	17 (28%)	7 (18%)	0.26	31 (24%)	26 (37%)	0.04
Household has >=3 people	23 (37%)	15 (38%)	0.89	71 (54%)	39 (56%)	0.79
Limitation in any of the EQ-5D domains	41 (66%)	35 (90%)	0.007	70 (53%)	46(66%)	0.083

Table 3.4. Association of mobility and sociodemographic and clinical risk factors with TB case status

	Unadjusted Odds Ratio (95% CI)	**Adjusted Odds Ratio (95%CI)**
Mobility	0.85 (0.52, 1.4)	0.85 (0.44, 1.6)
Age in years		
15-24	*Reference*	*Reference*
25-34	1.6 (0.83, 3.1)	0.75 (0.31, 1.8)
35-44	1.1 (0.51, 2.2)	0.49 (0.17, 1.4)
≥45	0.75 (0.34, 1.7)	0.39 (0.14, 1.1)
Female Sex	0.42 (0.26, 0.69)	0.40 (0.20, 0.78)
Parish of Residence		
Kisugu	*Reference*	
Wabigalo	1.3 (0.47, 3.5)	
Bukasa (within study area)	1.6 (0.7, 3.6)	
Other (Kisugu health Center Only)	1.3 (0.64, 2.6)	
Location of Birth		
Kampala	*Reference*	
Northern Uganda	1.0 (0.37, 2.8)	
Eastern Uganda	1.0 (0.47, 2.4)	
Western Uganda	0.87 (0.38, 2.0)	
Central Uganda (outside Kampala)	0.73 (0.34, 1.6)	
Outside Uganda	0.39 (0.07, 2.0)	
Literacy		
Read/write no difficulty	1.2 (0.74, 2.0)	
Can't read/write or do w/difficult	*Reference*	
Highest completed education		
None	*Reference*	
Certificate	0.79 (0.48, 1.3)	
Degree/further studies	0.5 (0.19, 1.4)	

Occupation		
Employed	*Reference*	*Reference*
Unemployed	1.1 (0.63, 2.0)	1.4 (0.6, 3.0)
Other	0.37 (0.12, 1.1)	0.34 (0.08, 1.4)
Income quartile		
1st (lowest)	*Reference*	
2nd	0.77 (0.38, 1.6)	
3rd	1.1 (0.62, 2.1)	
4th (highest)	1.2 (0.58, 2.3)	
Ever Been to Prison	2.8 (1.7, 4.6)	1.7 (0.87, 3.2)
HIV Positive	1.2 (0.70, 2.0)	
Previous TB Treatment	3.0 (1.6, 5.6)	2.8 (1.3, 5.9)
Ever had household TB contact	1.0 (0.56, 1.8)	
Ever known a TB case	0.80 (0.46, 1.4)	
Household has >=3 people	0.50 (0.31, 0.82)	0.67 (0.37, 1.2)
Limitation in any of the EQ-5D domains	2.3 (1.3, 3.8)	2.0 (1.1, 3.8)

Supplemental Materials

Table 3.S1. Model selection

Number of Latent Classes	df	AIC	BIC
1	7	2247.703	2273.699
2	15	2174.194	2229.9
3	22	2173.285	2254.987
4	30	2179.721	2291.133

Table 3.S2. Marginal Probabilities for Latent Classes

Class	Probability
1	0.42 (0.24-0.62)
2	0.58 (0.38-0.76)

Figure 3.S1. Plot of Information Criteria Values for Models with 1-4 Latent Classes

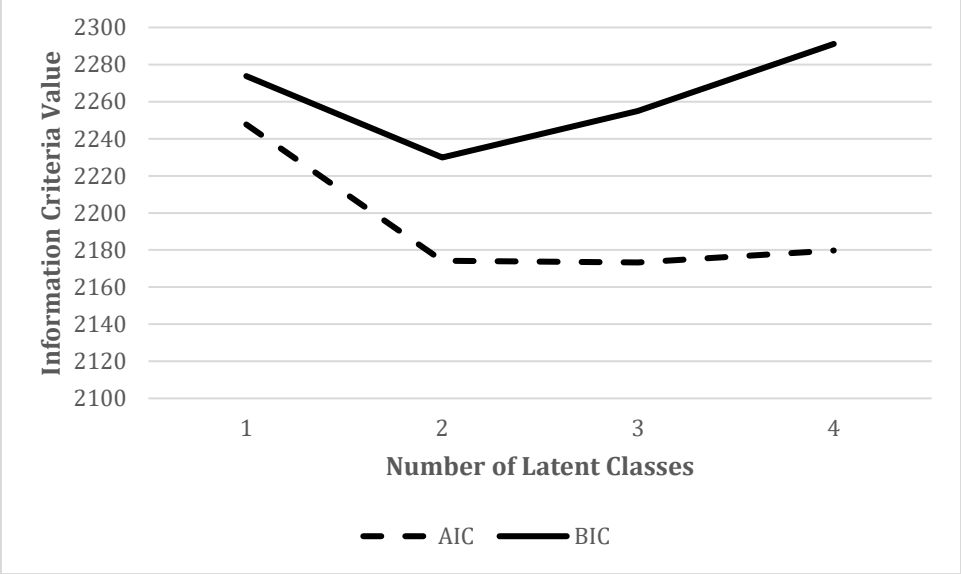


Table 3.S3. Marginal Means for Latent Classes of Mobility (with 95% Confidence Intervals)

	Class 1	Class 2	Total*
Born in Kampala	0.12 (0.07-0.21)	0.14 (0.1-0.21)	0.14 (0.1-0.18)
Lived in neighborhood < 1 year	0.29 (0.2-0.4)	0.13 (0.08-0.2)	0.2 (0.15-0.24)
Have another residence	0.09 (0.05-0.17)	0.08 (0.05-0.14)	0.09 (0.06-0.13)
Visited taxi stage ≥1 time per week	0.24 (0.17-0.33)	0.25 (0.19-0.32)	0.24 (0.2-0.3)
Travel 3km ≥9 times per month (median)	0.02 (0-0.98)	0.84 (0.48-0.97)	0.5 (0.44-0.55)
Spend ≥6 hours away when traveling ≥3km	0.17 (0.04-0.52)	0.78 (0.65-0.87)	0.52 (0.47-0.58)
Ever traveled outside Kampala in the last year	0.68 (0.58-0.77)	0.81 (0.73-0.87)	0.76 (0.7-0.8)

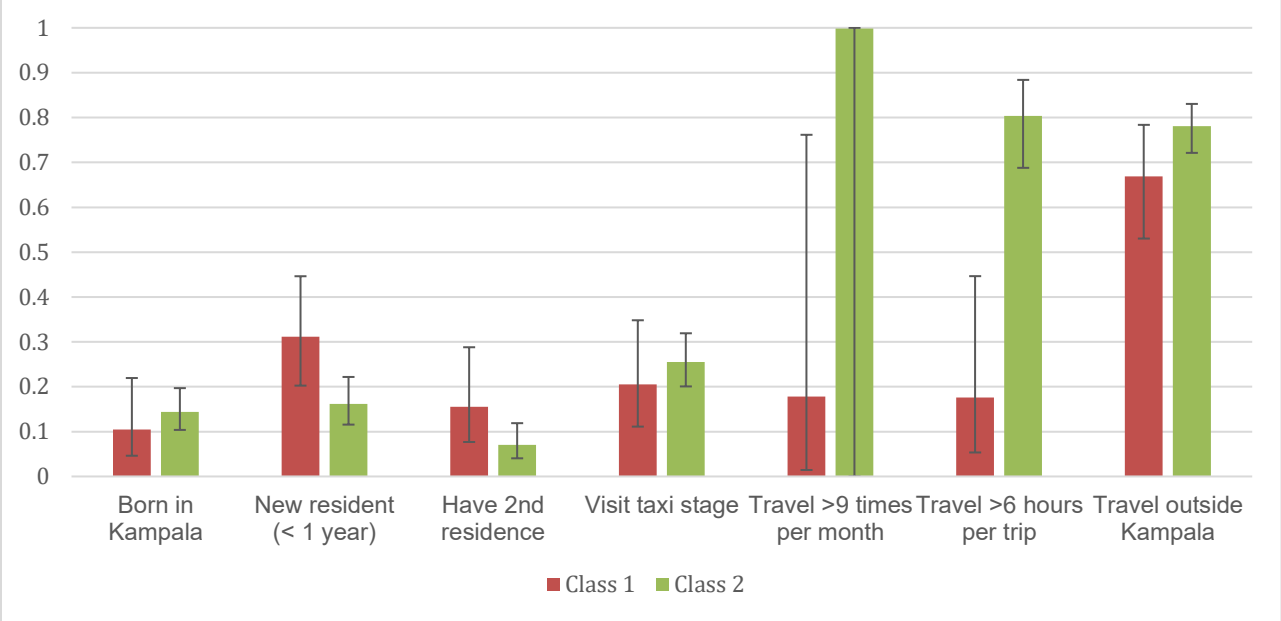
*observed proportion

Table 3.S4. Marginal Means for Latent Classes of Mobility Mobility (with 95% Confidence Intervals) - sensitivity analysis (different cutoffs for frequency & duration of travel)

	25th percentile		75th percentile		
	Class 1	**Class 2**	**Class 1**	**Class 2**	**Total**
Born in Kampala	0.1 (0.05-0.22)	0.14 (0.1-0.2)	0.14 (0.09-0.21)	0.13 (0.08-0.2)	0.14 (0.1-0.18)
Lived in neighborhood < 1 year	0.31 (0.2-0.45)	0.16 (0.12-0.22)	0.25 (0.18-0.33)	0.14 (0.09-0.21)	0.43 (0.38-0.49)
Have another residence	0.16 (0.08-0.29)	0.07 (0.04-0.12)	0.09 (0.05-0.15)	0.09 (0.05-0.15)	0.09 (0.06-0.13)
Visited taxi stage ≥1 time per week	0.21 (0.11-0.35)	0.26 (0.2-0.32)	0.2 (0.14-0.28)	0.29 (0.22-0.38)	0.24 (0.2-0.3)
Travel 3km ≥9 times per month (median)	0.18 (0.01-0.76)	1 (0-1)	0 (0-1)	0.66 (0.55-0.76)	0.5 (0.44-0.55)
Spend ≥6 hours away when traveling ≥3km	0.18 (0.05-0.45)	0.8 (0.69-0.88)	0 (0-1)	0.55 (0.45-0.64)	0.52 (0.47-0.58)
Ever traveled outside Kampala in the last year	0.67 (0.53-0.78)	0.78 (0.72-0.83)	0.69 (0.61-0.76)	0.82 (0.75-0.88)	0.76 (0.7-0.8)

Figure 3.S2. Marginal Means for Latent Classes of Mobility – sensitivity analysis (different cutoffs for frequency & duration of travel)

a. 25th percentile
b. 75th percentile



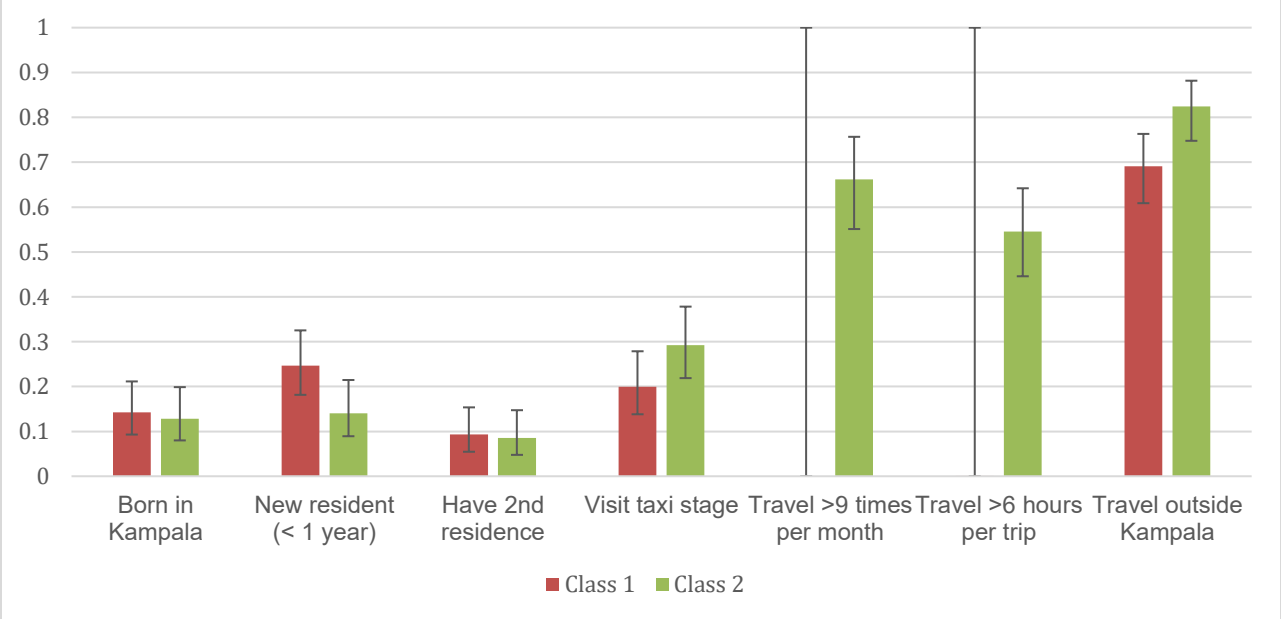


Table 3.S5. Duration of TB-related symptoms among mobile vs. non-mobile patients (median, IQR)

	Mobile	**Non-mobile**	**p-value**
	(median, IQR)	(median, IQR)	
Cases	8 (3, 16)	8 (4, 12)	0.7
Controls	3 (2, 8)	4 (2, 8)	0.6

Table 3.S6. Number of symptom-related health care visits among mobile vs. non-mobile patients

	Mobile	**Non-mobile**	**p-value**
	(median, IQR)	(median, IQR)	
Cases	4 (3, 7)	4 (2, 7)	0.42
Controls	3 (2, 4)	3 (2, 6)	0.03

Chapter 4: Is Distance associated with Tuberculosis Treatment Outcomes? A Retrospective Cohort Study in Kampala, Uganda

Abstract

Introduction: Barriers to accessing nearby health facilities may hinder initiating and completing tuberculosis (TB) treatment. We aimed to evaluate whether distance from residence to health facility chosen for treatment is associated with TB treatment outcomes.

Methods: We conducted a retrospective cohort study of all patients initiating TB treatment at six health facilities in Kampala from 2014-2016. We investigated associations between distance to treating facility and unfavorable TB treatment outcomes (death, loss to follow up, or treatment failure) using multivariable Poisson regression.

Results: Unfavorable treatment outcomes occurred in 20% (339/1,691) of TB patients. The adjusted relative risk (aRR) for unfavorable treatment outcomes (compared to treatment success) was 0.87 (95% confidence interval [CI] 0.70, 1.07) for patients living ≥ 2 km from the facility compared to those living closer. When we separately compared each type of unfavorable treatment outcome to favorable outcomes, those living ≥2 km from the facility had increased risk of death (aRR 1.42 [95%CI 0.99, 2.03]) but decreased risk for loss to follow-up (aRR 0.57 [95%CI 0.41, 0.78]) than those living within 2 km.

Conclusions: Distance from home residence to TB treatment facility is associated with increased risk of death but decreased risk of loss to follow up. Those who seek care further from home may have advanced disease, but once enrolled may be more likely to remain in treatment.

Introduction

Although tuberculosis (TB) is both preventable and treatable, it is the leading cause of death due to a single pathogen worldwide (1). One challenge in TB control is maintaining adherence to a minimum of six months of treatment. The World Health Organization estimates that 82% of patients worldwide who start treatment for TB experience treatment success (defined as treatment completion or cure); this percentage has not improved substantively in the past decade (1). People with restricted access to health care may not be able to initiate and complete TB treatment as recommended. Risk factors for unfavorable treatment outcomes include demographic, clinical, and health systems characteristics (2–4).

Geographic barriers to care, including physical distance to a health facility, may contribute to poor treatment outcomes. Distance from home to health facility has been associated with decreased access to a wide range of health services and outcomes, including poor HIV treatment clinic attendance (5) and antiretroviral adherence (6), lower likelihood of facility-based childbirth (7), and maternal (8) and child mortality (9). Geographic barriers to care have been linked to delays (6,10), loss-to follow up (11), and lack of adherence during the TB diagnostic evaluation and treatment processes (10). Whether these associations translate into worse treatment outcomes remains uncertain. As the effect of geographic barriers has primarily been noted in rural areas where patients likely have limited options as to where they seek care and even the closest health care facilities may require more than an hour of travel, we aimed to understand the effect of these barriers on TB treatment outcomes in the context of a

densely populated, urban setting where there are many TB treatment facilities available and patients may choose to seek care at facilities other than the ones closest to them.

Understanding links between geographic barriers to care and TB treatment outcomes may help identify a population at risk for unfavorable treatment outcomes that could be targeted with interventions to reduce barriers to care and improve outcomes. We therefore sought to characterize the association of distance from home to health facility and TB treatment outcomes in six public and private health facilities in Makindye division, Kampala district, Uganda.

Study population and Methods

Study Overview and Population

We conducted a retrospective cohort study of TB patients at one public (Kisugu Health Center, the primary public TB treatment facility in this area) and five private urban outpatient health facilities serving the population of Kisugu and Wabigalo parishes of Makindye division, Kampala, Uganda. Facilities were included if they provided TB care to an average of at least one patient per month from Kisugu or Wabigalo parish. At each of the selected facilities, all patients initiating TB treatment from January 1, 2014 to December 31, 2016 and who lived in Uganda were included. The National TB Control Program oversees all TB care and patients may seek treatment at any facility of their choosing. Treatment of adult TB is largely decentralized in Uganda; TB cases requiring hospitalization or advanced clinical care, such as pediatric TB or drug-resistant TB, may be diagnosed at these facilities in the community

but are referred to referral hospitals for their treatment and management and would not be included in this analysis. All facilities providing TB treatment in Uganda are expected to follow the national guidelines for TB treatment, although variation in implementation may exist and additional services (such as laboratory tests) may incur additional charges at private facilities. In urban settings, the national guidelines recommend that patients or their treatment supporters report to the treating facility to receive their anti-TB drugs every two weeks during the intensive phase and every four weeks during the continuation phase.

Data Collection

Demographic and clinical data were abstracted retrospectively from the Facility TB Registers, including treatment facility, parish of residence, age at diagnosis, sex, HIV status, site of disease (pulmonary vs. extrapulmonary), treatment regimen, diagnostic test results (sputum microscopy and Xpert MTB/RIF [Cepheid, Inc., Sunnyvale, California, USA]), date of treatment initiation, and treatment outcome. Data were abstracted directly as written in the registers with guidance from health facility staff as needed. Study data were collected and managed using REDCap (Research Electronic Data Capture) (12,13) hosted at Johns Hopkins Bloomberg School of Public Health.

Measurement of Primary Exposure and Outcome

We used reported area of residence to calculate two measures of distance from residence to the health facility where the patient chose to receive TB treatment. The TB registers do not capture patient addresses but do have information on the administrative area of residence, the smallest of which is the parish with a median size of 0.13 km^2 and median population of 23,041 within Kampala. The centroid of the parish of residence was used to estimate each patient's location of residence based on parish boundaries provided by Uganda Bureau of Statistics 2014 census data. We calculated Euclidean distance as a straight line from parish centroid to each health facility using ArcGIS (ESRI, Redlands, California, USA). Additionally, we used OpenStreetMap (OpenStreetMap Foundation, Cambridge, United Kingdom) to define road networks and calculated travel distance based on the shortest available route using the Network Analysis tool in ArcGIS.

Treatment outcomes following the World Health Organization (WHO) definitions were abstracted from the Facility TB Registers. "Unfavorable" outcomes included treatment failure, death, and loss to follow-up (including those with a documented outcome of default); patients with no documented outcome were not included in the analysis, although we performed a sensitivity analysis in which these patients were considered to have unfavorable outcomes. These were compared to favorable treatment outcomes of treatment completion or cure (also called treatment success). Patients with an outcome of "transferred out" (with no additional treatment outcome information from their receiving facility) were excluded.

Facility TB Notification Rate

We calculated an average annual "facility TB notification rate" for each parish, which we defined as the annual average number of cases from the parish reported at the six facilities divided by the parish's 2014 population from the Uganda Bureau of Statistics (14). We used Poisson regression to assess the association of Euclidean distance from the parish centroid to the facility where the patients received TB treatment on facility TB notification rates.

Distance to TB treatment facility and Treatment Outcomes

To measure the association between distance from residence to TB treatment facility and treatment outcome at the individual level, our primary exposure was Euclidean distance divided into four categories: <2 km, 2 to <5 km, 5 to <10 km, and ≥10 km. These categories were chosen based on the following rationale: <2 km is walking distance and therefore distance should not represent significant barriers to care; 2 to <5 km is still quite close but may require additional means of transport or additional travel time; 5 to <10 km is within the urban area but may take significant time and/or resources to travel; ≥10 km represents a significant investment in time and resources to reach the facility. For additional analyses using shortest available route travel distance, we used the same four distance categories. We also considered a binary exposure with distance dichotomized as <2 km or ≥2 km. Our outcome of interest was unfavorable treatment outcome, which was defined as above.

Patient characteristics were compared across the four exposure categories for Euclidean distance using chi-square tests. Risk factors of interest were defined *a priori* as characteristics known to be associated with TB treatment outcomes and that conceivably could lead to differences in care-seeking behavior and choice of TB treatment facility, and included: age, sex, HIV status, site of disease (pulmonary vs. extrapulmonary), lack of bacteriologic confirmation (positive sputum microscopy or GeneXpert), year of treatment, and treatment facility. We estimated the relative risk as a measure of association between unfavorable treatment outcomes and Euclidean distance, modeling distance both in four categories (with reference to the <2 km category) and as binary, using simple and multivariable Poisson regression with robust variance. All risk factors of interest were included in the multivariable model regardless of statistical significance. We analyzed associations between travel distance and unfavorable treatment outcomes in similar fashion. In a sub-analysis, we also analyzed death and loss to follow up as separate outcomes compared to favorable treatment outcomes.

Results

Study Population

From 2014 to 2016, 2,251 patients initiated TB treatment at the six study facilities, of whom 2,146 (95.3%) had a documented residential information in the Facility TB register. Patients came from 181 parishes in 28 districts throughout Uganda. We excluded 261 (12.2%) patients whose listed parish of residence information could

not be matched to a parish listed in the 2014 Uganda Bureau of Statistics Census and an additional 16 participants from analyses of travel distance who could not be linked due to lack of road network connectivity. We excluded 109 (5.8%) TB patients who were transferred out as we were unable to determine their final treatment outcome. Among 1,691 patients with reported outcomes, favorable treatment outcomes were seen in 1,352 (80.0%) of TB patients; 85 (4.8%) TB patients had no documented treatment.

Facility TB Notification Rate

Average annual parish-level facility TB notification rates ranged from 0 to 327 TB cases per 100,000 population (Figure 1). Facility notification rates decreased by 4% with each additional kilometer from the parish centroid to the health facility where the patient received TB treatment (rate ratio 0.96 [95% CI 0.95, 0.97]).

Distance to TB treatment facility and Treatment Outcomes

The median Euclidean distance from the centroid of parish of residence to health facility where the patient chose to receive TB treatment was 3.7 km. While many patients lived <2 km from their chosen facility (34%), nearly half of patients lived 2-10 km from their facility (49%), and 17% lived ≥ 10 km from their facility. Across the four distance exposure groups, there were differences in age, sex, HIV status, disease site, laboratory confirmation of disease, year of treatment initiation, and health facility (all $p<0.05$) (Table 1). People living ≥2km from the facility were more likely to be female (42% vs 34%), HIV positive (53% vs 46%), have extrapulmonary disease (17% vs. 8%),

and lack bacteriologic confirmation of disease (37% vs. 24%) compared to those living <2 km from the facility.

In simple and multivariable Poisson regression models, no significant association was seen between the four categories of distance and unfavorable treatment outcomes (Table 2). In analysis of a binary measure of distance, the adjusted relative risk [aRR] for unfavorable treatment outcomes was 0.87 (95% CI 0.70, 1.07) for patients who lived ≥2 km from the facility where they chose to receive TB treatment compared to those living within 2 km. Patients who were HIV positive (aRR 1.72 [95%CI 1.36, 2.17]), over the age of 65 years (aRR 2.53 [95%CI 1.59, 4.04]), or lacked bacteriologic confirmation of TB (aRR 1.57 [95%CI 1.27, 1.94]) were more likely to have unfavorable treatment outcomes. Patients aged less than 14 years (aRR 0.44 [95%CI 0.21, 0.90]) or receiving TB treatment at St. Francis Nsambya Hospital (aRR 0.60 [95%CI 0.45, 0.80], compared to Kisugu Health Centre) had lower risk of unfavorable treatment outcomes.

In a sub-analysis evaluating death and loss to follow-up separately, distances of ≥ 2 km from residence to facility chosen for TB treatment were associated with an increased risk of death but decreased risk of loss to follow up (Table 3). Comparing those living ≥2 km from the facility to those living within 2 km, the adjusted RR for death was 1.42 (95% CI 0.99, 2.03) and the adjusted RR for loss to follow up was 0.57 (95% CI 0.41, 0.78). Risk factors for death included older age (55-64 years or 65+ years), being HIV positive, and lacking bacteriologic confirmation of disease (Table 3).

Travel distance

Travel distance using the shortest available route was strongly correlated with Euclidean distance (R^2=0.98) but was on average 19% further than Euclidean distance (95% CI 18%, 20%). While 31.1% of participants were reclassified to a different distance category if travel distance was used instead of Euclidean distance, there were no substantive differences in the association between distance from facility chosen for TB treatment and treatment outcomes when using travel distance as the exposure compared to Euclidean distance (Tables in supplement).

Discussion

This analysis of 1,774 patients treated for TB across six urban clinics in the Makindye division of Kampala, Uganda, was suggestive of a protective association between longer distance from home to chosen treatment facility and composite unfavorable treatment outcomes. Facility notification rates for the included treatment facilities were high in parishes nearest to the facilities but were also high for some parishes far from the facilities. Nevertheless, despite the high density of TB treatment facilities in Kampala, 66% of patients starting TB treatment in these six facilities lived more than ≥2 km from the treating facilities (Table 1); compared to those who lived within 2 km of the facility, those living more remotely were 42% more likely to die but 43% less likely to be lost to follow-up.

Most patients in our study setting live within 2 km of multiple facilities and therefore can choose where they want to receive TB care. Patients may choose to seek

care at a facility further away due to stigma against TB and a desire to hide their TB status (15–17), convenience due to work or other travel (18), or perception of better care, particularly at private facilities (18). This dynamic may explain the differences seen when considering death versus loss to follow up as an outcome. Death during TB treatment in this setting (where multidrug resistance is uncommon) likely reflects a patient's severity of illness when diagnosed, whereas loss to follow-up may more closely reflect patient motivation and health system investment. Thus, patients who choose to travel more than 2 km to be treated may be those who experience other barriers to seeking care (e.g., stigma, job-related time limitations, unease with the healthcare system) which can cause delays in diagnosis and treatment. Such delays are associated with increased disease severity (19) and higher corresponding mortality rates (20–22). However, once treatment is initiated, these patients who are sicker and willing to travel longer distances may be more motivated to adhere to treatment, thereby reducing losses to follow-up. These findings illustrate how important distinctions between these two outcomes may be obscured when considering unfavorable treatment outcome as a composite measure.

Our study fills an important gap in knowledge regarding barriers to care and TB treatment outcomes. Prior studies have had mixed results regarding the effect of distance on delays in TB diagnosis and initiation of TB treatment (2–4). Our study suggests that, once treatment is initiated, distance is not associated with overall unfavorable treatment outcomes. Other studies have highlighted economic, socio-cultural, and health system barriers to care in high-burden settings as access-related risk factors for poor treatment outcomes (23); the current research suggests that

geographic distance to treatment facility may not be a strong measure of access to care, particularly in the urban sub-Saharan African setting. Additionally, our finding that travel distance using the shortest available route does not change our results compared to using Euclidean distance is in contrast with other research (24). This may reflect the high population density and informal road network in our setting, such that travel paths are generally direct and the differences between Euclidean and travel distances are small, particularly if walking or using boda bodas (motorbike taxis) for transport.

This analysis does have some key limitations, largely due to the limited data available in facility TB registers. For example, these registers do not contain data on precise address of residence, thus limiting our measurement of distance to that of the parish centroid. Nevertheless, on average, participants will live within 500 meters of the parish centroid, making major bias at the scale of our distance categories less likely. Additionally, while Euclidean distance does not directly capture the distance traveled to seek care, our assessment of travel distance yielded comparable results. Due to the limited data available in the TB registers, we are unable to assess the contribution of broader barriers to health care access, including economic, socio-cultural, and health system barriers. These factors may overlap or interact with geographic barriers. Additionally, we could not assess patients' reasons for choosing particular facilities; further qualitative research could help to elucidate these motivations. Our study includes patients attending facilities in a densely crowded urban area, and our findings may not generalize to other settings (e.g., rural areas) where facilities are further apart and patients have fewer treatment options. While we do not have complete capture of any geographic region (e.g., people living in Kisugu and Wabigalo parishes) due to our

sampling frame based on health facilities, we do have full capture of every patient seeking care at these facilities. Our final models excluded more than 20% of TB cases seen at these facilities due to missing data on either residence or treatment outcome; while our sensitivity analysis showed no major effect of excluding those missing treatment outcomes, we may have selection bias if those included in our analysis are not representative of those missing residential information in regards to the association of distance on treatment outcomes. Finally, since we only considered patients enrolled in care, we could not assess the role of geographic barriers in limiting initial access to care.

Conclusion

Distance from home residence to TB treatment facility was not associated with overall unfavorable treatment outcomes in this urban Ugandan population, but was associated with increased risk of death and decreased risk of loss to follow up. These findings suggest that those who seek care further from home may do so at a more advanced disease state, but once enrolled they may be more likely to remain in treatment. This is important for TB control programs to consider, as they may need to invest in programs that decrease delays in diagnosis among those living further away and improving treatment adherence among those who live closer to facilities. A detailed understanding of the patient population and the varying experiences of that population is key to appropriately focusing resources to improve TB treatment outcomes.

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Tables and Figures

Table 4.1. Patient characteristics by distance from residence to TB health facility

	Total	Euclidean Distance Categories				p-value
		< 2km	2 to <5 km	5 to <10 km	≥ 10 km	
	n (%)	n (%)	n (%)	n (%)	n (%)	
Total	1,776	606	459	407	304	
Age (years)						<0.001
0-14	87 (5)	21 (3)	20 (4)	26 (6)	20 (7)	
15-24	366 (21)	142	95 (21)	81 (20)	48 (16)	
25-34	627 (35)	224	177	140	86 (29)	
35-44	398 (22)	122	113	93 (23)	70 (23)	
45-54	200 (11)	66 (11)	37 (8)	48 (12)	49 (16)	
55-64	61 (3)	21 (3)	12 (3)	11 (3)	17 (6)	
≥65	35 (2)	10 (2)	4 (1)	7 (2)	14 (5)	
Male (N=1,773) [1]	1,079 (61)	401	286	219	173	0.001
HIV Positive	887 (50)	275	263	202	147	0.002
Pulmonary TB (N=1,765)	1,513 (86)	552 (92)	395 (86)	323 (80)	242 (80)	<0.001
Lack of bacteriologic confirmation	569 (32)	142 (23)	132 (29)	168 (41)	127 (42)	<0.001
Year of treatment initiation (N=1,773) [1]						0.289
2014	622 (35)	200	171	149	102	
2015	558 (31)	212	131	126	89 (30)	
2016	593 (33)	194	156	132	111	
Facility (N=1,776)						<0.001
Kisugu Health Center (public)	441 (24)	284 (47)	84 (18)	51 (13)	22 (7)	
Alive Medical Services	383 (22)	112	149	55 (14)	67 (22)	
International Hospital Kampala	178 (10)	92 (15)	27 (6)	37 (9)	22 (7)	
Kibuli Muslim Hospital	184 (10)	49 (8)	28 (6)	63 (15)	44 (14)	
St. Francis Hospital - Nsambya	578 (33)	60 (10)	169 (37)	201 (49)	148 (49)	

Meeting Point	12 (1)	9 (2)	2 (0)	0 (0)	1 (0)	
Treatment Outcome (N=1,776)						<0.001
Cured	919 (51)	342	239	194	144	
Complete	433 (24)	101	108	127	97 (32)	
Failure	21 (1)	4 (1)	9 (2)	7 (2)	1 (0)	
Died	167 (9)	38 (6)	48 (10)	44 (11)	37 (12)	
Lost to Follow Up	151 (9)	88 (15)	29 (6)	22 (5)	12 (4)	
Unknown/Missing	85 (5)	33 (5)	26 (6)	13 (3)	13 (4)	

[1] Ns below the total of 1,776 indicate data missing for that particular variable

Table 4.2. Crude and Adjusted Relative Risks for unfavorable TB treatment outcomes (death, treatment failure, or loss to follow-up)

	Crude RR (95% CI)	Adjusted RR (95% CI)
Euclidean Distance		
<2 km	*Reference*	*Reference*
2 to <5 km	0.88 (0.69, 1.12)	0.91 (0.70, 1.17)
5 to <10 km	0.82 (0.63, 1.06)	0.88 (0.68, 1.15)
>10 km	0.76 (0.56, 1.02)	0.77 (0.57, 1.04)
Age at diagnosis		
0-14 years	0.42 (0.20, 0.87)	0.44 (0.21, 0.90)
15-24 years	0.63 (0.46, 0.87)	0.79 (0.57, 1.08)
25-34 years	*Reference*	*Reference*
35-44 years	1.03 (0.80, 1.32)	0.97 (0.75, 1.25)
45-54 years	1.35 (1.02, 1.77)	1.18 (0.89, 1.57)
55-64 years	1.25 (0.79, 1.98)	1.23 (0.79, 1.92)
>65 years	1.96 (1.25, 3.06)	2.53 (1.59, 4.04)
Male sex	1.12 (0.92, 1.36)	1.08 (0.88, 1.32)
HIV Positive	1.83 (1.50, 2.24)	1.72 (1.36, 2.17)
Pulmonary TB	0.85 (0.66, 1.10)	1.06 (0.80, 1.40)
Lack of bacteriologic confirmation	1.47 (1.22, 1.78)	1.57 (1.27, 1.94)
Treatment Start year		
2014	*Reference*	*Reference*
2015	0.89 (0.71, 1.12)	0.88 (0.70, 1.11)
2016	0.86 (0.69, 1.09)	0.89 (0.71, 1.11)
Facility		
Kisugu Health Center (public)	*Reference*	*Reference*
Alive Medical Services	1.19 (0.93, 1.53)	0.97 (0.74, 1.27)

International Hospital Kampala	0.99 (0.70, 1.40)	0.84 (0.59, 1.20)
Kibuli Muslim Hospital	1.01 (0.72, 1.40)	0.97 (0.70, 1.35)
St. Francis Hospital - Nsambya	0.63 (0.48, 0.83)	0.60 (0.45, 0.80)
Meeting Point	0.76 (0.21, 2.72)	0.55 (0.15, 2.03)

Table 4.3. Adjusted relative risks for Death and Loss to Follow up during TB treatment

	Death	Lost to Follow Up
	Adjusted RR (95% CI)	**Adjusted RR (95% CI)**
Euclidean Distance		
<2 km	*Reference*	*Reference*
2 to <5 km	1.48 (0.99, 2.22)	0.59 (0.38, 0.89)
5 to <10 km	1.38 (0.90, 2.12)	0.61 (0.39, 0.95)
>10 km	1.35 (0.86, 2.10)	0.45 (0.25, 0.81)
Age at diagnosis		
0-14 years	0.59 (0.24, 1.46)	0.28 (0.07, 1.12)
15-24 years	0.59 (0.30, 1.14)	0.80 (0.53, 1.22)
25-34 years	*Reference*	*Reference*
35-44 years	1.38 (0.94, 2.02)	0.65 (0.42, 0.99)
45-54 years	1.68 (1.11, 2.54)	0.64 (0.36, 1.12)
55-64 years	2.08 (1.23, 3.51)	0.51 (0.16, 1.58)
>65 years	6.44 (3.69, 11.27)	0.77 (0.20, 3.02)
Male sex	0.98 (0.74, 1.31)	1.31 (0.94, 1.83)
HIV Positive	3.28 (2.23, 4.81)	1.05 (0.73, 1.51)
Pulmonary TB	0.93 (0.66, 1.30)	1.50 (0.78, 2.86)
Lack of bacteriological confirmation	2.14 (1.59, 2.89)	1.45 (0.99, 2.13)
Treatment Start year		
2014	*Reference*	*Reference*
2015	0.78 (0.55, 1.10)	0.88 (0.61, 1.26)
2016	0.81 (0.59, 1.13)	0.88 (0.61, 1.27)
Facility		
Kisugu Health Center (public)	*Reference*	*Reference*

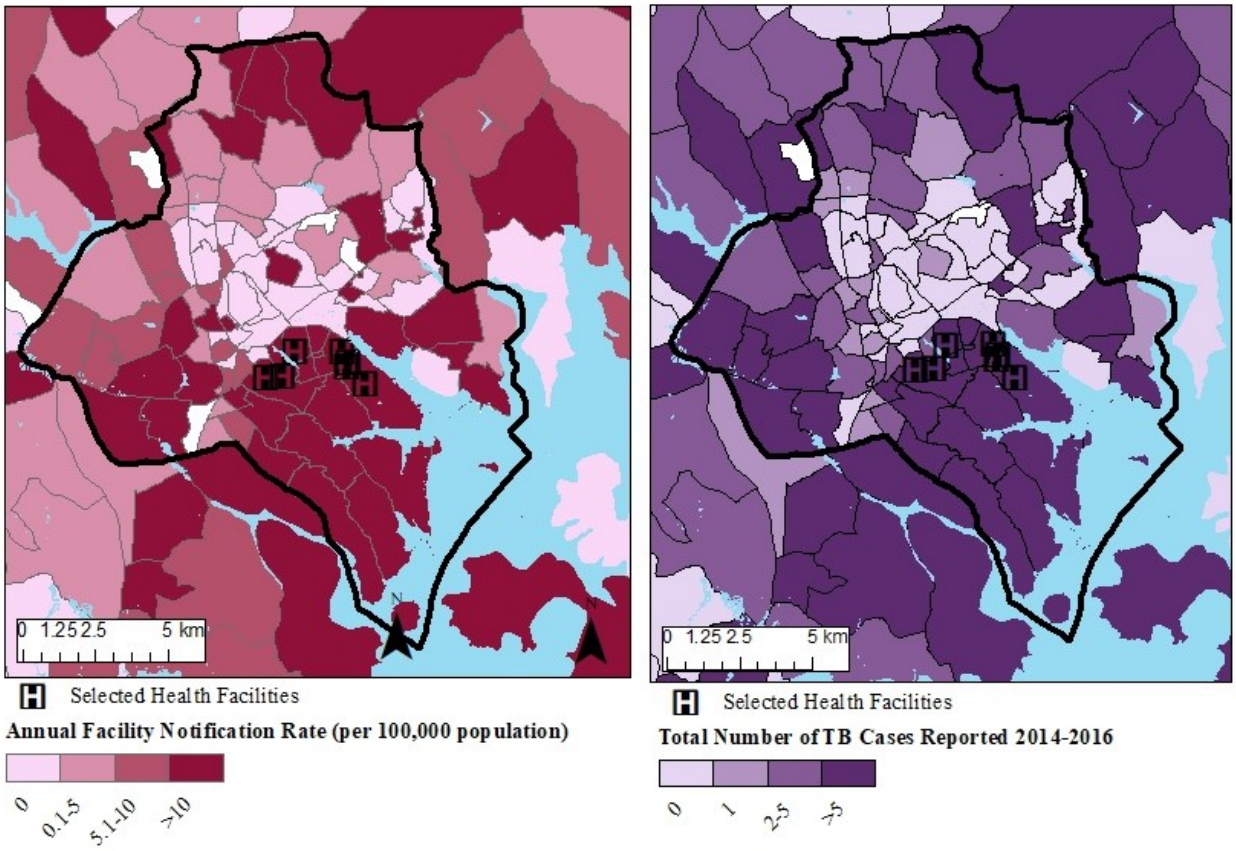
Alive Medical Services	1.02 (0.63, 1.66)	1.10 (0.74, 1.62)
International Hospital Kampala	1.41 (0.83, 2.39)	0.60 (0.34, 1.08)
Kibuli Muslim Hospital	1.48 (0.90, 2.44)	0.83 (0.49, 1.41)
St. Francis Hospital - Nsambya	0.92 (0.59, 1.45)	0.25 (0.14, 0.46)
Meeting Point	1.72 (0.51, 5.77)	*excluded*

Note: *Meeting Point reported no patients lost to follow up*

Figure 4.1. TB Facility Notification by Parish in Kampala District[1] and surrounding areas for six Facilities serving Kisugu and Wabigalo Parishes[2], 2014-2016

a. Annual Facility Notification Rate per 100,000 population (based on 2014 census)

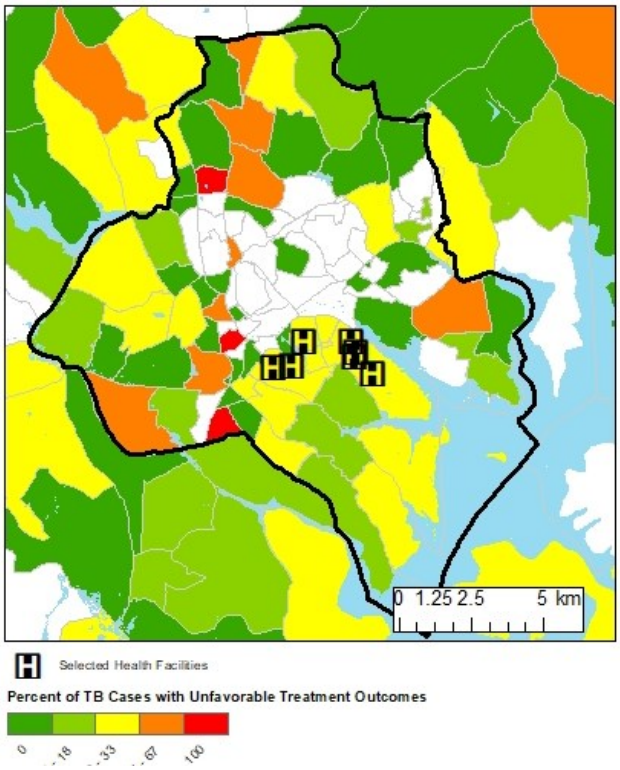
b. Total Count of Facility Notified TB Cases



[1] Parishes further outside Kampala not displayed. Dark line indicates Kampala District boundary

[2] Facility Notification Rates and Total Number of TB Cases Reported are from six study facilities providing TB treatment and do not represent all TB cases diagnosed at all facilities within each parish

Figure 4.2. Percentage of TB Cases with unfavorable treatment outcomes by Parish in Kampala District and surrounding areas, 2014-2016



Note: *Parishes further outside Kampala not displayed. Dark line indicates Kampala District boundary.*

Supplemental Material

Table 4.S1 Adjusted relative risks for unfavorable TB treatment outcomes using Euclidean and travel distance

	Euclidean Distance	**Travel Distance**
	Adjusted RR (95% CI)	**Adjusted RR (95% CI)**
Distance		
<2 km	*Reference*	*Reference*
2 to <5 km	0.91 (0.70, 1.17)	0.94 (0.70, 1.26)
5 to <10 km	0.88 (0.68, 1.15)	0.96 (0.71, 1.31)
>10 km	0.77 (0.57, 1.04)	0.79 (0.56, 1.10)
Age at diagnosis		
0-14 years	0.44 (0.21, 0.90)	0.44 (0.21, 0.91)
15-24 years	0.79 (0.57, 1.08)	0.79 (0.57, 1.09)
25-34 years	*Reference*	*Reference*
35-44 years	0.97 (0.75, 1.25)	0.97 (0.75, 1.25)
45-54 years	1.18 (0.89, 1.57)	1.19 (0.90, 1.59)
55-64 years	1.23 (0.79, 1.92)	1.25 (0.80, 1.95)
>65 years	2.53 (1.59, 4.04)	2.54 (1.59, 4.04)
Male	1.08 (0.88, 1.32)	1.09 (0.89, 1.33)
HIV Positive	1.72 (1.36, 2.17)	1.71 (1.35, 2.16)
Pulmonary TB	1.06 (0.80, 1.40)	1.05 (0.79, 1.39)
Lack of bacteriological confirmation	1.57 (1.27, 1.94)	1.58 (1.28, 1.95)
Treatment Start year		
2014	*Reference*	*Reference*
2015	0.88 (0.70, 1.11)	0.89 (0.71, 1.12)
2016	0.89 (0.71, 1.11)	0.89 (0.71, 1.12)
Facility		
Kisugu Health Center (public)	*Reference*	*Reference*
Alive Medical Services	0.97 (0.74, 1.27)	0.94 (0.72, 1.23)

International Hospital Kampala	0.84 (0.59, 1.20)	0.84 (0.59, 1.20)
Kibuli Muslim Hospital	0.97 (0.70, 1.35)	0.93 (0.67, 1.30)
St. Francis Hospital - Nsambya	0.60 (0.45, 0.80)	0.57 (0.43, 0.75)
Meeting Point	0.55 (0.15, 2.03)	0.54 (0.14, 2.05)

Table 4.S2. Sensitivity Analysis comparing adjusted relative risks for unfavorable TB treatment outcomes including and excluding patients with no documented outcomes

	Unfavorable Outcomes	**Unfavorable + Unknown Outcomes**
	Adjusted RR (95% CI)	**Adjusted RR (95% CI)**
Euclidean Distance		
<2 km	*Reference*	*Reference*
2 to<5 km	0.91 (0.70, 1.17)	0.94 (0.78, 1.14)
5 to <10 km	0.88 (0.68, 1.15)	0.90 (0.73, 1.10)
>10 km	0.77 (0.57, 1.04)	0.90 (0.72, 1.12)
Age at diagnosis		
0-14 years	0.44 (0.21, 0.90)	0.69 (0.45, 1.05)
15-24 years	0.79 (0.57, 1.08)	0.90 (0.72, 1.13)
25-34 years	*Reference*	*Reference*
35-44 years	0.97 (0.75, 1.25)	0.96 (0.80, 1.17)
45-54 years	1.18 (0.89, 1.57)	1.06 (0.85, 1.33)
55-64 years	1.23 (0.79, 1.92)	1.11 (0.78, 1.59)
>65 years	2.53 (1.59, 4.04)	1.93 (1.31, 2.83)
Male	1.08 (0.88, 1.32)	1.09 (0.94, 1.26)
HIV Positive	1.72 (1.36, 2.17)	1.40 (1.18, 1.66)
Pulmonary TB	1.06 (0.80, 1.40)	1.01 (0.82, 1.24)
Lack of bacteriological confirmation	1.57 (1.27, 1.94)	1.56 (1.33, 1.84)
Treatment Start year		
2014	*Reference*	*Reference*
2015	0.88 (0.70, 1.11)	0.94 (0.78, 1.12)
2016	0.89 (0.71, 1.11)	1.04 (0.88, 1.23)
Facility		
Kisugu Health Center	*Reference*	*Reference*

Alive Medical Services	0.97 (0.74, 1.27)	1.09 (0.89, 1.33)
International Hospital	0.84 (0.59, 1.20)	1.15 (0.91, 1.45)
Kibuli Muslim Hospital	0.97 (0.70, 1.35)	0.96 (0.75, 1.24)
St. Francis Hospital - Nsambya	0.60 (0.45, 0.80)	0.51 (0.40, 0.65)
Meeting Point	0.55 (0.15, 2.03)	0.45 (0.12, 1.61)

Table 4.S3. Adjusted relative risks for unfavorable TB treatment outcomes by TB Treatment Facility

	Kisugu Health Center	Alive Medical Services	International Hospital Kampala	Kibuli Muslim Hospital	St. Francis Hospital - Nsambya
	Adjusted RR (95% CI)	**Adjusted RR (95% CI)**	**Adjusted RR (95% CI)**	**Adjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Euclidean Distance					
<2 km	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
≥2 km	0.69 (0.47, 1.02)	0.95 (0.65, 1.38)	1.00 (0.56, 1.8)	1.21 (0.63, 2.31)	0.86 (0.47, 1.60)
Age at diagnosis					
0-14 years	0 (0, 0)	0.24 (0.04, 1.62)	0.54 (0.13, 2.16)	1.36 (0.27, 6.82)	0.51 (0.16, 1.58)
15-24 years	0.70 (0.40, 1.21)	1.09 (0.63, 1.88)	0.91 (0.29, 2.85)	0.54 (0.16, 1.81)	0.68 (0.30, 1.51)
25-34 years	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
35-44 years	0.89 (0.56, 1.42)	0.89 (0.56, 1.41)	0.78 (0.34, 1.78)	1.24 (0.60, 2.56)	1.03 (0.59, 1.78)
45-54 years	0.83 (0.38, 1.80)	1.17 (0.73, 1.86)	1.06 (0.47, 2.39)	0.87 (0.42, 1.80)	1.56 (0.86, 2.85)
55-64 years	1.24 (0.48, 3.19)	0 (0, 0)	0 (0, 0)	1.33 (0.67, 2.66)	2 (0.94, 4.25)
>65 years	2.16 (0.96, 4.87)	0 (0, 0)	4.07 (0.62, 26.54)	0.63 (0.08, 5.35)	6.16 (2.99, 12.71)
Male	1.41 (0.92, 2.17)	0.89 (0.61, 1.29)	0.88 (0.48, 1.62)	1.07 (0.61, 1.85)	1.15 (0.76, 1.74)
HIV Positive	1.44 (0.96, 2.16)	1.12 (0.66, 1.90)	1.92 (0.87, 4.27)	2.07 (1.14, 3.76)	2.43 (1.55, 3.81)
Pulmonary TB	2.41 (0.36, 16.22)	0.86 (0.50, 1.50)	2.33 (0.92, 5.95)	1.03 (0.60, 1.77)	0.82 (0.49, 1.38)

No bacteriological confirmation	1.28 (0.76, 2.15)	1.2 (0.78, 1.83)	2.37 (1.12, 4.99)	4.04 (2.05, 7.97)	1.36 (0.82, 2.24)
Treatment Start year					
2014	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
2015	1.01 (0.65, 1.57)	0.79 (0.49, 1.26)	0.75 (0.38, 1.49)	0.54 (0.27, 1.07)	1.22 (0.75, 1.96)
2016	1.11 (0.71, 1.73)	1.08 (0.72, 1.61)	0.68 (0.23, 2.00)	0.63 (0.36, 1.10)	0.7 (0.42, 1.16)

Chapter 5: Conclusions and Public Health Significance

Summary of Key Findings

In order to achieve the End TB vision of a world free of TB (1), there need to be substantial improvements to the efficiency and implementation of current TB control interventions. This research used the application of spatiotemporal epidemiology in the context of local TB epidemics to investigate approaches to improving TB control methods in urban, high-burden settings.

In aim 1, we used routinely collected data and small-scale administrative units to assess the potential yield of targeted, community based active case finding interventions. We demonstrated that even within a very small area (2.2 km^2) where access to care is expected to be homogeneous, there is substantial heterogeneity in the spatial distribution of TB cases presenting at the local health facilities such that more than 60% of cases come from areas accounting for only 20% of the population. Additionally, through a subsequent active case finding activity, we showed that the facility-based TB notifications reasonably predict the location of undiagnosed TB in the community; more than 40% of cases found during our community-based case finding intervention came from those same areas accounting for 20% of the population. Therefore, in this setting it may be feasible to detect nearly half of undiagnosed TB cases in the community by targeted case finding interventions to only 20% of the population. Additionally, the application of these methods may be useful in other urban, high-burden settings.

In aim 2, we investigated geographic mobility, which complements aim 1 by considering the potential TB risk that occurs way from one's home residence.

Using six a priori defined questions regarding routine movement beyond the study boundaries, we developed a definition of geographic mobility using latent class analysis. We found that frequency and duration of travel more than 3 km from home were the driving components of this case definition. However, we found no association between this definition of mobility and TB case status (compared to TB negative controls) (adjusted odds ratio 0.85 [95% CI 0.44-1.6]) or between mobility and delays in TB diagnosis among TB cases ($p>0.05$). This is one of the first attempts to characterize mobility in the context of TB; further research should address other potential measures and causes of mobility in order to develop a better understanding of mobility that can be used more broadly to identify potential risk groups for TB or other diseases.

In aim 3, we used a broader study population to assess the association of distance between home residence and TB treatment facility and unfavorable TB treatment outcomes. We found that patients residing further from the facility where they received their care were more likely to die before completing treatment (adjusted risk ratio [aRR] 1.42 (95% CI 0.99-2.03) but less likely to be lost to follow-up (aRR 0.57 [95% CI 0.41-0.79]). This suggests that patients who live further away from the health facility may delay seeking care, and thus have more advanced disease leading to increased mortality, but that once patients from further away are engaged in care they are more invested and less likely to be lost to follow-up.

These aims together demonstrate that spatiotemporal epidemiology, including location of residence and movement behavior occurring outside that

residence, is an important consideration for TB control programs. In aim 1, we show that using small-scale administrative area of residence to target active case finding may efficiently identify undiagnosed cases in the community. However, the impact may be limited if those case finding activities fail to capture the mobile individuals identified in aim 2, who may not be home during door-to-door testing. Similarly, if those cases identified reside too far from a health facility to receive timely treatment and are at increased risk of mortality as shown in aim 3, the effect of the case finding on treatment outcomes may be minimal. Incorporating spatiotemporal epidemiology is an important consideration in the development of targeted TB interventions.

Public health implications

This research was designed to not only to advance understanding of geography and movement as it relates to TB, but also to directly inform TB control in this setting in urban Uganda and to inform approaches to understanding local spatiotemporal epidemiology of TB in other settings. For example, from our results in aim 1, we can recommend that this study area implement case finding activities in areas with high TB facility-based notification rates; we can also recommend that other areas consider a similar approach to identifying high-risk locations based on their own data. We can also suggest that our study facilities consider TB treatment adherence interventions that focus on reducing loss to follow-up among people living close to the facility, who may be less invested in their care, based on the results from aim 3; facilities in other

settings could replicate our analysis using their own treatment data to see if their patient population is at similar risk for loss to follow-up.

A major strength of this research is its hyper-local context. While there is increasing interest in applying spatial approaches to TB research and control programs, this is generally done at the national or district level (2). Research at this geographic level can give broad context to the epidemic but cannot inform locally appropriate interventions. Therefore, there is a need for high-quality routinely collected spatiotemporal data at the local level. This includes improved quality of GIS data as well as improved timeliness and accessibility in order to detect areas with high burden or limited healthcare access in an actionable timeframe (3). Supplementing health system data with additional data sources, such as Open Street Map (4), can support more complex analyses of the relationship between geography and health (5,6). Given the sensitive nature of spatiotemporal data, as more data becomes available considerations regarding maintaining confidentiality will become increasingly important (7–9).

We present one of the first attempts to investigate geographic mobility at the individual level among people at risk for TB; previous research has focused on using population-level mobility in transmission models for TB and other infectious diseases (10–13). The importance of this mobility in relation to infectious disease transmission is increasingly recognized; for example, Uganda is currently implementing control measures for Ebola due to the outbreak in bordering Democratic Republic of Congo (14) and is applying new methods to collecting data on population movement in order to plan those efforts. As better

data collection tools and measures of mobility are developed, these should be applied across disease programs to supplement spatial analyses based on residence, particularly in scenarios where transmission is likely to occur outside the home.

Limitations

We posit the role of location in TB risk as being a combination of local transmission and local barriers to care. In this research, we are not able to distinguish the causes for associations seen between location and TB. For example, in Aim 1 we identified areas with high TB notification rates and undiagnosed TB, but we could not determine whether there in ongoing transmission or if these cases represent recent reactivation or undiagnosed active TB. However, by framing our approach from the perspective of implementing active case finding interventions, we were able to show potential impact of such interventions without explicitly understand the cause of the local epidemic. Molecular sequencing technologies are rarely used in this type of setting but could help understand transmission (15).

Fixing the “delivery gap” (16) in TB between effective interventions and the highest-need is only one piece of the solution to the TB epidemic. Models suggest that in high-burden settings, even broad scale-up of a single intervention will not be sufficient to reach the End TB targets; in some settings, even scale-up of all the major interventions would not achieve these goals (17). While,

improvement in the implementation of established TB interventions (18) will contribute to these goals, this needs to be done in parallel with additional research on preventive vaccines, therapeutic solutions to latent TB infection, rapid point of care diagnostics, and shorter drug regimens (18) in order to end the TB epidemic.

Conclusions

Despite substantial investments and efforts, the annual reduction in TB incidence is too slow to meet the End TB targets (18). Interventions targeted at established high-risk populations have shown effectiveness and efficiency; the incorporation of spatiotemporal risk factors in defining and identifying high-risk populations may improve TB control efforts. Using detailed local epidemiology, we describe how the location of residence as well as movement outside that residence play a role in TB risk and access to care in an urban, high-burden setting. Further understanding of these risk factors in this setting as well as others is critical to targeting TB control interventions to high-risk populations that are being missed by current practices and to reduce the global incidence of TB as per the vision of the End TB goals.

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Appendix A: Curriculum Vitae

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Education

Johns Hopkins University (2016-2020)
Doctorate of Philosophy in Infectious Disease Epidemiology, Bloomberg School of Public Health *(expected)*

University of California, Berkeley (2007-2009)
Master of Public Health in Infectious Diseases, School of Public Health
Certificate in International Health

Boston University (2003-2007)
Bachelor of Science in Human Physiology, Sargent College of Health and Rehabilitation Sciences
Bachelor of the Arts in Biology, College of Arts and Sciences

Work Experience

TB Research Assistant (October 2016-March 2020)
Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, Baltimore, MD
Provided logistical and technical support to the STOMP-TB Study. Responsibilities included: supporting application for ethical reviews, participation in team coordination meetings, monitoring field work, conducting site visits, and supporting data management.

Center for Health and Human Rights Research Assistant (September 2018-October 2018)
Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, Baltimore, MD
Abstracted human rights data from published reports for data triangulation project of the Rohingya refugee crisis

Senior TB/HIV Advisor (February 2016-August 2016)
U.S. Centers for Disease Control and Prevention, Windhoek, Namibia
Served as the primary technical expert and point-of-contact for CDC Namibia on TB/HIV operational research and monitoring & evaluation activities. Provided technical assistance to Namibia Ministry of Health and Social Services (MoHSS) counterparts

regarding evaluation and research methodology, data management and analysis (including Epi Info and/or Stata), report writing and development of scientific products.

ASPPH/CDC Allan Rosenfield Global Strategic Information Fellow (September 2013-September 2015)
U.S. Centers for Disease Control and Prevention, Windhoek, Namibia
Managed two operational research projects assessing the integration of TB and HIV clinical systems, in collaboration with the Namibia Ministry of Health and Social Services (MoHSS) and other partners. Responsibilities included finalizing scientific protocols, staff hiring and training, field supervision, data quality control, and data analysis and dissemination.

Surveillance and Informatics Coordinator (October 2010-August 2013)
California Department of Public Health, Tuberculosis Control Branch, Richmond, CA
Led the Tuberculosis Control Branch to implement, coordinate, and improve information systems including CalREDIE, an award-winning (Digital Government Achievement Award, Government to Government category 2012) web-based disease reporting and surveillance system for TB and other communicable diseases in California. Conducted surveillance-based epidemiologic research, involving conceiving, planning, and conducting advanced epidemiologic analyses.

Public Health Technical Assistance Fellow (June 2009-July 2010)
Global Health Access Program, Mae Sot, Thailand
Provided technical support to community-based relief organizations operating along the Thai-Burma (Myanmar) border, developing health workers' capacity to coordinate public health activities benefitting internally displaced persons in conflict zones of Burma. Areas of focus included tuberculosis, malaria, and population-based surveys.

Student Epidemiologist (May 2008-April 2009)
California Department of Public Health, Tuberculosis Control Branch, Richmond, CA
Conducted epidemiologic data analysis on characteristics of foreign-born TB cases for the state of California, which was used to inform programmatic decisions by senior leadership. Conceived and conducted analysis plan and presented results to local health jurisdictions that participated in data collection.

Teaching Experience

Lead Teaching Assistant, Johns Hopkins Bloomberg School of Public Health

- Public Health 340.753, Epidemiologic Methods III, Term 3 2018

Teaching Assistant, Johns Hopkins Bloomberg School of Public Health

- Public Health 600.601, Seminars in Public Health, Term 1 2019
- Public Health 340.658, Critical Reading of Epidemiologic Literature, Summer Institute 2019
- Public Health 340.612, Epidemiologic Basis for Tuberculosis Control, Summer Institute 2019
- Public Health 140.698, Spatial Analysis III: Spatial Statistics, Term 3 2018
- Public Health 340.612, Epidemiologic Basis for Tuberculosis Control, Term 3 2019

- Public Health 340.612, Epidemiologic Basis for Tuberculosis Control, Term 1 2018
- Public Health 340.601, Principles of Epidemiology, Summer Term 2018
- Public Health 340.613, Design and Conduct of Clinical Trials, Summer Institute 2018
- Public Health 340.658, Critical Reading of Epidemiologic Literature, Summer Institute 2018
- Public Health 340.612, Epidemiologic Basis for Tuberculosis Control, Summer Institute 2018
- Public Health 340.752, Epidemiologic Methods II, Term 2 2017
- Public Health 340.751, Epidemiologic Methods I, Term 1 2017

Tutor, Johns Hopkins Bloomberg School of Public Health
- Public Health 340.752, Epidemiologic Methods II, Term 2 2018

Graduate Student Instructor, University of California, Berkeley
- Public Health 162A, Public Health Microbiology Lab, Spring 2009
- Integrative Biology 132, Human Physiology Lab, Fall 2008
- Integrative Biology 128, Sports Medicine, Spring 2008

Undergraduate Teaching Fellow, Boston University
- Biology 108, Introductory Biology II, Spring 2005

Awards and Honors

- Charlotte Silverman Fund, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health (2020)
- Fulbright Fogarty Award in Public Health, J. William Fulbright Foreign Scholarship Board (2019)
- Diversity Recognition Award, Johns Hopkins Diversity Leadership Council (2019) – *Epidemiology Inclusion, Diversity, Equity & Science Workgroup*
- Student Travel Support Fund, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health (2018)
- Abraham Lilienfeld Teaching Assistantship in Epidemiologic Methods (2017-2018)
- Global Health Established Field Placement Grant, Center for Global Health, Johns Hopkins Bloomberg School of Public Health (2017)
- U.S. Centers for Disease Control and Prevention, Namibia Certificate of Appreciation (2016) – *In recognition of your contribution to the TB/HIV program in Namibia. Your commitment and leadership of the TB/HIV evaluation over the past two years will have a lasting impact on the program and health of Namibians.*

- Embassy of the United States of America, Windhoek, Namibia Certificate of Appreciation (2015) – *for professionalism, skills in public health evaluation, flexibility, and passion for public health work in Namibia*
- U.S. Mission Namibia Honor Award (2015) – *for exceptional team work, dedication, and collaboration toward achieving the goal of COP 15 approval for CDC Namibia and PEPFAR*
- U.S. Mission Namibia Honor Award (2014) – *for exceptional team work, dedication, and collaboration toward achieving the goal of COP 14 approval for CDC Namibia and PEPFAR*
- American Public Health Association – Abstract Review Panel, HIIT Section (2013)
- Council of State and Territorial Epidemiologists Public Health Informatics Scholarship (2012)
- California Department of Public Health, Public Health Acknowledging My Efforts Award (2011) – *TB Registry Unit*
- Interexchange Foundation Christianson Grant (2009)
- University of California, Berkeley Center for Health Leadership Internship Award (2008)
- Sargent College Professional Contribution Award, Boston University (2007)
- Undergraduate Research Opportunity Program Summer Grant, Boston University (2006)
- America East Academic Honor Roll (2005-2007)
- Boston University Merit Scholarship (2003-2007)

Academic and Community Service

- Peer Reviewer, Society for Epidemiologic Research Conference 2020 (January 2020)
- Peer Reviewer, Epidemiology and Infection (May 2019-present)
- This is Public Health Ambassador, Association of Schools and Programs of Public Health (June 2019-present)
- Member, Epidemiology Inclusion, Diversity, Equity & Science Workgroup, Johns Hopkins Bloomberg School of Public Health (September 2018-present)
- Teaching Assistant Training Chair, Epidemiology Student Organization, Johns Hopkins Bloomberg School of Public Health (May 2018-present)
- Member, Student Planning Committee for SER Conference (December 2017-June 2018)
- Member, Department of Epidemiology Doctoral Teaching Assistant Curriculum Working Group, Johns Hopkins Bloomberg School of Public Health (December 2017-present)
- Student Mentor, Epidemiology Student Organization, Johns Hopkins Bloomberg School of Public Health (August 2017-present)
- Member, Surveillance and Outbreak Response Team, Johns Hopkins Bloomberg School of Public Health (June 2017-present)

- Team Captain, Hopkins Marathon Team, Johns Hopkins University (June 2017-present)
- Sports Chair, Epidemiology Student Organization, Johns Hopkins Bloomberg School of Public Health (May 2017-May 2018)

Papers and Reports

1. Kendall, Kamoga,Kitonsa, Nalutaaya, Salvatore, **Robsky**, Nakasolya, Mukiibi, Isooba, Cattamanchi, Kato-Maeda, Katamba, Dowdy. "Empiric treatment of pulmonary TB in the Xpert era: Correspondence of sputum culture, Xpert MTB/RIF, and clinical diagnoses." *PLoS One*. July 2019. 14(7):e0220251.
2. Duque-Silva, **Robsky**, Flood, Barry. "Risk Factors for Central Nervous System Tuberculosis." *Pediatrics.* November 2015. 136(5):e1276-84.
3. Chitnis, **Robsky**, Schecter, Barry. "Trends in Tuberculosis Cases among Nursing Home Residents, California, 2000-2009." *Journal of the American Geriatrics Society.* June 2015. 63(6):1098-1104.
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9. **Robsky**. "Analyzing Highly Infectious Tuberculosis in Mexican-born and Other Foreign-born Cases in California, 2001-2006." Master's Comprehensive Paper, UC Berkeley. May 2009.

Presentations and posters

1. **Robsky**, Kitonsa, Mukiibi, Nakasolya, Isooba, Nalutaaya, Salvatore, Kendall, Katamba, Dowdy. **"**Using spatial heterogeneity of facility-based TB notification rates to identify areas with high burden of undiagnosed TB in Kampala, Uganda." Delta Omega Poster Competition, Johns Hopkins Bloomberg School of Public Health (February 2020)
2. **Robsky**, Kitonsa, Mukiibi, Nakasolya, Isooba, Nalutaaya, Salvatore, Kendall, Katamba, Dowdy. "Using spatial heterogeneity of TB notification rates to identify

high-risk areas for in Kampala, Uganda." 50th Union World Conference on Lung Health (October 2019)

3. **Robsky,** Hughes, Kityamuwesi, Kendall, Kitonsa, Dowdy, Katamba. "Is Distance associated with Tuberculosis Treatment Outcomes? A Retrospective Study in the Kisugu and Wabigalo Neighborhoods of Kampala, Uganda." Johns Hopkins TB Centre Annual Meeting (June 2019)
4. Shisana, **Robsky**, Zuma, Zungu, Celentano. "Association of Perceived Risk, HIV Status and Behavioral Risk Factors, South Africa." AIDSImpact (July 2019)
5. **Robsky,** Hughes, Kityamuwesi, Kendall, Kitonsa, Dowdy, Katamba. "Is Distance associated with Tuberculosis Treatment Outcomes? A Retrospective Study in the Kisugu and Wabigalo Neighborhoods of Kampala, Uganda." 49th Union World Conference on Lung Health (October 2018)
6. Mungunda, Roscoe, Lockhart, de Klerk, Baughman, Agolory, Gawanab, Menzies, Jonas, Salomo, Taffa, Lowrance, **Robsky**, Tollefson, Pevzner, Hamunime, Mavhunga. "Assessing the Tuberculosis Preventive Therapy Cascade for People Living with HIV in Namibia and Identifying Challenges Associated with Its Implementation." 49th Union World Conference on Lung Health (October 2018)
7. **Robsky,** Hughes, Dowdy, Katamba. "A Retrospective Study of TB Treatment Outcomes in the Kisugu and Wabigalo Neighborhoods of Kampala, Uganda." Johns Hopkins Global Health Day (March 2018)
8. **Robsky**, Hamunime, Tjituka, Mavhunga, Menzies, Gawanab, Tollefson, Mungunda. "Assessment of Intensified Case Finding and Isoniazid Preventative Therapy at Health Facilities Providing HIV Care and Treatment Services in Namibia." 47th Union World Conference on Lung Health (October 2016).
9. Mavhunga, Menzies, Gawanab, Nandjebo, Taffa, Pathmanathan, **Robsky**, Mungunda. "Assessment of Uptake of Antiretroviral Therapy among HIV-Infected TB Patients in Namibia." 47th Union World Conference on Lung Health (October 2016).
10. Chitnis, **Robsky**, Schechter, Barry, Flood. "Trends in Tuberculosis Cases among Nursing Home Residents, California, 2000-2009." Infectious Disease Society of American Conference (November 2013).
11. **Robsky**, Shah, Moore, Pascopella, Barry Flood. "Tuberculosis Treatment Outcomes among Individuals Born in Mexico and Central America Compared with other Foreign-Born Persons in California, 2000-2009." Infectious Disease Society of American Conference (November 2013).
12. Duque-Silva, **Robsky**, Flood, Barry. "Epidemiology of Pediatric Central Nervous System (CNS) Tuberculosis (TB) – California, 1993-2011." International Union Against Tuberculosis and Lung Disease North America Region Conference (February 2013).
13. "Epidemiology of Tuberculosis." Tuberculosis Clinical Intensive Training. Curry International Tuberculosis Center (September 2012).
14. **Robsky**, Shah, Pascopella, Barry, Flood. "Tuberculosis among Individuals Born in Mexico and Central America Compared with Other Foreign-Born Persons in California, 2001-2010." American Thoracic Society / Centers for Disease Control and Prevention (May 2012).

15. Lwin, Yone, Mahn, Moo, Benjamin-Chung, Smith, Mullany, T.Lee, Richards, C.Lee, **Robsky**, Chowdbury. “Diagnosis: Critical. Health and human rights survey in eastern Burma.” Global Health Council International Conference (June 2011).
16. Thura, Benjamin-Chung, Smith, Mullany, C.Lee, Richards, T.Lee, **Robsky**. “Health and Human Rights Survey in Western Burma.” Global Health Council International Conference (June 2010).
17. **Robsky**, Forget, M.Richard, Wah Wah Paw, Eh Kalu Shwe Oo, A.Richard, Leigh, Lee. “Community-based tuberculosis care in Eastern Myanmar's chronic conflict zone: Challenges and solutions in meeting program objectives.” American Public Health Association Annual Meeting (November 2010).
18. “Epidemiology of TB Among Mexican-born in California.” Presentation with Lisa Pascopella, California Department of Public Health TB Control Branch (April 2009).
19. **Robsky**, Pascopella, Flood. “Tuberculosis in Mexican-born, California, 2001-2007.” California Tuberculosis Controllers Association (April 2009).
20. Oh, Pascopella, **Robsky**, Salcedo, et al. “Immigration visa status and identification of foreign-born tuberculosis cases in California.” California Tuberculosis Controllers Association (April 2009).
21. “Alameda County Foreign Born Data.” Presentation with Peter Oh, Alameda Public Health Department (August 2008).
22. “Santa Clara County Foreign Born Data.” Presentation with Peter Oh, Santa Clara Tuberculosis Clinic (July 2008).