EVALUATING THE IMPACT OF STRATEGIES FOR TUBERCULOSIS PREVENTION AND CONTROL IN HIGH-BURDEN, LOW-RESOURCE SETTINGS: DATA FOR EVIDENCE-BASED DECISION-MAKING IN LOCAL CONTEXTS

By

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ABSTRACT

Background: While incidence rates of tuberculosis (TB) are on the decline globally, the TB burden in sub-Saharan Africa and Southeast Asia remains high. If the goal of reducing the global TB incidence rate to < 10/100,000 population per year is to be achieved by 2035, additional TB control interventions will need to be deployed in high burden settings. Research is needed to identify effective, efficient interventions that prevent additional TB cases, identify and properly diagnose incident cases, as well as to provide timely, appropriate treatment and ensure treatment completion. We sought to evaluate several TB control interventions as implemented in local contexts, including a household contact tracing in rural South Africa, a cost-effectiveness analysis of interferon-γ release assays (IGRAs) in India, and predictors of isoniazid preventive therapy (IPT) completion in rural Malawi. This research aims to provide data for policy-makers and government officials tasked with the deployment of scarce TB control resources in local contexts, with the goal of identifying strategies to integrate TB case finding and prevention activities into programs with limited resources.

Methods: We recruited 130 newly diagnosed TB patients ("index cases") from public clinics in Vhembe District, Limpopo Province, South Africa, and visited their homes to test their household contacts for TB via sputum smear microscopy and culture. Clinical and demographic characteristics, including HIV status, were assessed via self-report. We calculated the yield of previously undiagnosed TB disease among household contacts (defined as the number of new TB cases identified for every 100 index cases

traced) and evaluated risk factors for TB disease among household contacts using multilevel logistic regression.

Next we evaluated the incremental cost-effectiveness of IGRAs compared to a base-case scenario of empirical diagnosis (without microbiological testing), as well as sputum smear microscopy and Xpert MTB/RIF. We performed our analysis from the perspective of the Indian TB Control Program, and evaluated the cost, disability-adjusted life years, deaths, and secondary cases averted, and false positive diagnoses resulting from the use of these diagnostics in a hypothetical cohort of 1 million adult Indian TB suspects. We performed one-way sensitivity analyses, as well as a probabilistic sensitivity analysis to generate uncertainty ranges around our estimates.

Finally we evaluated factors associated with IPT completion in a cohort of 974 newly diagnosed adult HIV patients in Malawi who were started on IPT after active TB disease was excluded. Participants were recruited as part of a larger cluster randomized trial of TB screening being conducted in 12 clinics across rural Malawi. IPT completion was defined as receipt of ≥150 doses of isoniazid during routine clinical visits. We assessed factors associated with IPT completion using a multilevel logistic regression model adjusted for patient clinical and demographic characteristics.

Results: A total of 282 household contacts were enrolled in our household contact tracing study between December 1, 2013 and September 30, 2014. A total of 11 individuals tested positive for TB disease, for a household TB disease prevalence of 3.9% (95% CI: 2.0-6.9%) and a yield of 8.5 cases per 100 index cases traced (95% CI: 4.2-15.1).

The majority of TB cases identified by the study (10/11, 90.9%) were smear-negative/culture-positive. The presence of TB symptoms was not significantly associated with increased odds of active TB disease in our population (aOR: 0.3, 95% CI: 0.1-1.4).

Our cost-effectiveness analysis found that IGRAs were less cost-effective than sputum smear microscopy or Xpert MTB/RIF when diagnosing active TB in India. This was largely due to the poor specificity of IGRAs for active TB in a setting with high background rates of latent TB infection. Relative to sputum smear microscopy, IGRAs resulted in 315,700 (95% uncertainty range [UR]: 118,300 – 388,400) false-positive TB diagnoses, at an incremental cost of US$49.3 million (95% UR: $34.9 - $58.0 million) per 1 million population tested. Relative to Xpert MTB/RIF (including the cost of treating drug resistant TB), IGRAs averted 70,400 (95% UR: [-7,900] – 247,200) fewer disability adjusted life years and cost US$14.6 million (95% UR: [-$7.2] - $28.7 million) more.

In Malawi, 732 of the 974 (75%) individuals who started IPT completed their course of therapy. Individuals completing IPT were significantly older than non-completers (34 vs. 31, $p<0.01$) and less likely to have experienced an interruption of >2 months (7.1% vs. 80%, $p=0.01$). After controlling for potential confounders, participants younger than 25 years (compared to those over 45 years, aOR: 0.33, 95% CI: 0.18-0.60) and males (compared to non-pregnant women, aOR: 0.57, 95% CI: 0.37-0.88) had significantly lower odds of IPT completion. Concomitant receipt of ART drugs, being a current or

former smoker, and self-reported alcohol use were not significantly associated with IPT completion in our study.

Discussion: Identification of effective and cost-effective interventions operationalizing case finding and prevention of TB will be vital in controlling TB and meeting ambitious global targets by 2035, especially in high-burden settings. We evaluated potential prevention and case-finding interventions in local settings, providing data useful to TB control programs and governments in sub-Saharan Africa and Southeast Asia, where high TB burdens and scarce resources present substantial challenges to meeting global TB control targets.

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Preface

This work could not have been completed without the efforts of dedicated field staff, the attention of knowledgeable study coordinators, and the input of compassionate advisers. I want to thank all of them, as well as my friends and family who have supported me (both emotionally and, sometimes, financially) throughout my training. You are—no doubt—both excited and relieved to see it coming to an end. I also want to take a moment to thank the many individuals who participated in the studies included in this dissertation. I do my work with the lofty hopes of, at least indirectly, improving your health. But it is your time, openness, and willingness to share that makes it all possible. Thank you for all that you have taught me.

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CHAPTER 1:

INTRODUCTION AND REVIEW OF THE LITERATURE

Tuberculosis Epidemiology

Mycobacterium tuberculosis, the bacterium that causes tuberculosis (TB), infects approximately a third of the global population [1,2]. *M. tuberculosis* is transmitted through the air via droplets when an infectious individual talks, sings [3], or coughs [4,5]. Tuberculosis infections can be classified as either "latent" (non-transmissible TB infection) or "active" (generally symptomatic, transmissible TB disease). While those with latent TB infections are asymptomatic and non-infectious [6,7], approximately 5-15% of these individuals will progress to active disease over the course of their lifetimes [8]. Active TB disease most often affects the lungs (known as "Pulmonary TB"), causing a constellation of symptoms including cough, fever, night sweats, weight loss, and lethargy. Extra-pulmonary TB can also occur, and may effect a range of body systems [9]. Untreated, up to two-thirds of those with active TB disease will die [10]. On average, infectious individuals will transmit TB to between 10-15 susceptible individuals over the course of a year [11], though evidence suggests that so-called "super-spreaders" can infect many more [12,13].

Close contact with an individual suffering from untreated, pulmonary TB is the predominant risk factor for infection with *M. tuberculosis*. As many as half of the household contacts of an infectious TB case will themselves become latently infected, especially if the infectious case has smear positive TB disease [8]. A number of agent, host, and environmental factors are associated with progression from latent infection to active TB disease. These include recent infection with TB, being less than 5 years old [14], being homeless [15], living/working in a congregate setting such as hospitals [16–

18] or prisons [19,20], smoking [21], alcohol [22] and substance abuse [23], diabetes [24], end stage renal disease [25], low body weight [26], and a number of other conditions that weaken the immune system [27–29].

Most notably, human immunodeficiency virus (HIV) infection increases the risk of TB disease by an estimated 29 times [23,30]. Globally TB remains the leading cause of death among people living with HIV (PLHIV), a third of whom are infected with latent TB and at high risk of progression to active TB disease. This dual epidemic has been most pronounced in sub-Saharan Africa, home to nearly 80% of TB/HIV co-infected individuals worldwide and 9 of the 22 countries classified as "high-burden" for TB by the World Health Organization (WHO) [31]. In countries such as South Africa, high HIV prevalence rates have led to a more than 3-fold increase in the number of TB case-notifications since 1990, and annual TB incidence rates peaked as high as 1,000 per 100,000 per population in 2012 [32]. This has led to large-scale morbidity and mortality, and has strained already fragile healthcare systems in South Africa and other high TB/HIV burden countries.

While annual TB incidence rates per population are highest in South Africa and neighboring Swaziland and Lesotho, globally India contributes the largest number of incident cases each year. In 2013 India had an estimated 2.0-2.3 million incident TB cases; approximately 2.2% (1.9-2.6%) of new TB cases had multi-drug resistant (MDR) TB, and 15% (11-19%) of retreatment cases were diagnosed as having MDR-TB [33]. Unlike South Africa, however, the TB epidemic in India is not driven primarily by HIV infection. Just over 5% of the incident TB cases in 2013 were estimated to have been

HIV-infected in India, compared to about 60% of all TB cases in South Africa [34]. Despite these differences, in both India and South Africa (as well as other low- or middle-income countries) TB control is hindered by a number of factors including resource constraints, large rural populations, and limited healthcare infrastructure.

Global TB Control

An estimated 9 million incident cases of TB occurred globally in 2013, for an average worldwide TB incidence rate of 126 cases per 100,000 population [31]. Just over a million of these cases were thought to have been co-infected with HIV. While annual TB incidence continues to decline slowly worldwide, the vast majority of new cases still occur in the WHO Africa Region (29% of all new cases) and Asia (56% of all new cases) [31]. Incident rates in the Africa Region have fallen far more slowly than global averages, likely because of the HIV co-epidemic in that region. While global TB incidence rates have fallen from nearly 150 per 100,000 in 2002 to approximately 125 per 100,000 in 2011, TB incidence rates in the WHO Africa Region generally, and in South Africa specifically, remain far higher, at 275 and 993 per 100,000 population, respectively [31]. Consistently high rates of TB in this region can be attributed in part to population growth and accelerating urbanization, poverty, inadequate health infrastructure, insufficient case-detection rates, and the high prevalence of HIV/AIDS [35]. Given these challenges (and despite slow global reductions in both TB incidence and prevalence) it does not appear that the 2015 Millennium Development Goal (MDG) target of a 50% reduction in the TB prevalence from 1990-2015 will be met worldwide.

Though the 2015 goals were not met, there has been substantial progress worldwide in controlling TB, and the WHO has set ambitious post-2015 targets as a part of their "End TB Strategy". This strategy include a goal of ending TB by 2035 (defined as a 95% reduction in the number of annual TB deaths from 2015-2035 and a global TB incidence rate of less than 10/100,000 population per year) [36]. The first pillar of this strategy comprises a focus on "integrated, patient-centered care and prevention" of TB, including "early diagnosis of tuberculosis…and systematic screening of contacts and high-risk groups" as well as "preventive treatment of persons at high risk" of TB disease [36]. The strategy also recognizes the need for research into the potential impacts and optimal implementation of prospective interventions.

Given that 85% of all incident cases of TB continue to occur in the Asian and African Regions, identifying efficient, cost-effective interventions adapted to local contexts is particularly important if ambitious global TB targets are to be met. However, in these settings inadequate health infrastructure and limited resources often present further challenges to TB control, especially in rural areas. Epidemiological data, as well as implementation science and operational research, are crucial to the development and evaluation of potential interventions for TB control under real-world conditions.

Potential interventions may be designed to address different aspects of the TB prevention and case finding pathway; to prevent TB disease in high-risk individuals, to find a greater proportion of all TB cases (and to diagnose them earlier in the disease course), to effectively screen and treat those at highest risk for active disease, and to ensure that those on preventive or curative treatment complete their course of

medication (**Figure 1.1**). Interventions at each phase of this prevention, diagnosis, and treatment pathway need to be evaluated rigorously under operational conditions to ensure the efficient deployment of scare TB control resources, especially in rural settings, where resource and infrastructure constraints may complicate implementation.

We sought to evaluate interventions implemented in rural high-burden areas targeting points along the TB case-finding and prevention pathway (**Figure 1.1**); specifically 1) Active case-finding to identify and screen individuals at high risk for TB disease, 2) Evaluation of the incremental cost-effectiveness of diagnostic tests for active pulmonary TB, and 3) Identification of predictors for isoniazid preventive therapy (IPT) completion among adults newly diagnosed with HIV. While each of these analyses focuses on a different point on the pathway, together the interventions evaluated work to prevent TB disease and correctly identify additional TB cases under real-world conditions in low-resource settings. Ultimately the widespread implementation of such evidence-based, cost-effective interventions for TB control is needed to reduce the burden of TB in high-burden rural settings, and maximize the value of limited TB resources.

TB Case-Finding

Timely diagnosis and prompt treatment initiation have been linked to reductions in TB-related morbidity and mortality. However, in low-resource, high-burden settings, TB case-finding typically consists of passive case detection methods, strategies which

rely on symptomatic individuals self-presenting at health facilities [37]. Self-presentation is frequently delayed by barriers including distance to health facilities, poverty, lack of education or awareness of TB, and other competing needs (e.g. school, work) [38,39]. These barriers may be of even greater concern in rural areas where health facilities are more sparsely located and transport options are more limited in comparison to urban/peri-urban areas. As a result of such barriers, estimates suggest that individuals with active pulmonary TB may go more than a year between symptom onset and diagnosis (or death) [40]. These diagnostic delays lead to increased morbidity and mortality, further secondary disease transmission, higher costs to healthcare systems, and inadequate case-detection rates [41–43]. As a result, passive case-detection alone has not been adequate to control epidemics of TB, especially in settings with high rates of HIV [44].

Strategies to boost TB case-finding rates above and beyond that of passive case-detection alone have been developed. Generally these strategies fall into one of two categories; Enhanced case-finding (ECF) or active case-finding (ACF). Like passive case-detection, ECF methods are still patient-initiated, but include educational or informational campaigns by the health system to inform communities of TB, the importance of testing, and the availability of TB diagnostics and treatment at local clinics. Unfortunately the population-level impact of ECF on community TB prevalence remains unclear [45].

ACF methods, on the other hand, are initiated by the health system and involve actively searching for additional cases in a particular time period, location, or group.

While ACF can take many forms (household contact tracing, case-driven contact referral, systematic screening of high risk populations, etc.), these methods have been shown to effectively identify more cases of TB, and to find them earlier in the disease course, than passive case detection methods alone [46,47]. However, like ECF strategies, the effects of ACF on community-level burden of TB have not been clearly demonstrated, and more research is needed. While ACF strategies are frequently employed in many high-resource, low TB burden settings, they have traditionally been considered too resource intensive to implement in high burden settings, which are often resource constrained. Recently, however, the WHO began scaling up its "3 Is Policy" for TB/HIV, which includes ACF and recommends TB screening for all HIV-infected individuals (so-called *"*intensified" [active] case-finding), as well as provision *of isoniazid preventive therapy* (IPT) for HIV-infected individuals in whom active TB is not suspected and the introduction of additional infection control measures in settings with a high risk of TB exposure [48]. South Africa has also been at the forefront of promoting ACF strategies for TB, virtually the only high burden country to do so at a population level. Unfortunately, research into the efficiency and yield of the various forms of ACF is lacking, especially in rural areas where these interventions may be more logistically difficult to implement.

Despite these concerns, early evidence suggests that household contact tracing may be one potentially cost-effective ACF strategy that could feasibly be implemented in a rural, high-burden setting [49]. Previous research has found higher rates of TB among the household contacts of adults with recently-diagnosed active TB disease as

compared to the general population [50,51], suggesting that the household is an important setting for TB transmission. However, the role of TB transmission within the household—and thus the yield and efficiency of household contact tracing—may differ according to the underlying TB incidence rate in the wider community.

Increasing TB case-notification rates in rural, high-burden areas presents unique logistical and implementation challenges that need to be better understood. ACF interventions such as household contact tracing may provide efficient, cost-effective approaches to bolster TB diagnosis and treatment rates in these settings, but need to be rigorously evaluated under operational conditions. The objective of **Aim 1** of this analysis is to estimate the yield (defined as the number of new cases of TB identified among household contacts per index case traced) of a household contact tracing intervention implemented in a rural South African setting, and compare our findings to a similarly structured intervention conducted in a high-burden, peri-urban area in South Africa. To accomplish this, adults newly diagnosed with active, pulmonary TB ("index cases") were recruited from public clinics, after which study staff visited the household and collected sputum from all household contacts to be tested for TB via sputum smear microscopy and culture. Individuals under the age of five and/or positive for TB were referred to routine health services for further evaluation/treatment. Our findings will inform government officials and policy makers in this and other similar settings regarding potential implementation and scale-up of household contact tracing interventions in high TB/HIV burden settings.

Diagnostic Tests for TB

Appropriate diagnostic tests for TB are another vital part of TB case-finding and prevention in high-burden settings. Quality assured diagnostic tests are a crucial to the appropriate care of TB patients, and their improper deployment can lead to missed TB cases (resulting in preventable morbidity, mortality, and further disease transmission), unnecessary TB treatment for false-positive cases, as well as an over-burdening of the health system and wasted healthcare resources. The number of TB diagnostics available to healthcare providers has also increased markedly in recent years. However, their effectiveness use depends on the development of new TB screening and diagnostic algorithms, training for laboratory staff and healthcare providers on the tests' proper use, improvement of laboratory infrastructure, and country-level policy reform. These activities should be informed by research on the impact and cost-effectiveness of various diagnostic tests and testing algorithms in specific settings.

The use—and potential misuse—of interferon-gamma release assays (IGRAs) provides one such opportunity for research. IGRAs, including QuantiFERON-TB Gold in Tube (Cellestis, Carnegie, Australia) and T-SPOT.TB (Oxford Immunotec, Oxfordshire, UK) are immunological tests designed to detect latent tuberculosis infection (LTBI) in high-income, low TB-burden settings. IGRAs offer a number advantages over tuberculin skin testing (TST, the traditional test for LTBI), including a higher specificity and a lower risk of Bacille Calmette-Guerin (BCG) vaccine cross-reaction [54]. Unlike TST, IGRA testing utilizes a blood sample for testing, and does not require patients to return to the clinic 24-48 hours later to have the test read, making it easier to implement. Like TST,

however, IGRAs cannot differentiate between latent TB infection and active TB disease [55].

Because of this inability to distinguish between latent and active TB, the WHO does not recommend the use of IGRAs as a test for the detection of active pulmonary TB, nor does the WHO recommend IGRAs a TST replacement in low- and middle-income countries [56]. Despite recommendations against the use of IGRAs in these settings, concern is mounting in countries such as India and China that IGRAs are being used off-label as a test for active TB [57–60]. The use of IGRAs for the diagnosis of active disease in a setting like India, with background rates of LTBI as high as 40% or more [61], would result in large numbers of false positive TB diagnoses [18,62,63] (a test that is positive among all people with LTBI is likely to have a specificity of 60% or less when used for active TB in this context). Over-diagnosis of TB due to the utilization of tests with a poor specificity for active TB represents a potential waste of scarce healthcare resources, and may expose patients to avoidable risks resulting from unnecessary treatment.

The population level outcomes of various TB diagnostic tests can be quantified through the use of decision analysis, an algorithmic approach that allows researchers to estimate the incremental costs and consequences of various courses of action (here, TB diagnostic algorithms) [64]. Decision analysis also enables researchers to incorporate uncertainty into their estimates through probabilistic sensitivity analyses, and to identify factors that have the greatest influence on the outcome of interest [64]. This approach is especially useful for comparing multiple alternatives, and provides an estimate for the

incremental cost-effectiveness of various options compared to an appropriate baseline scenario.

For Aim 2 we used decision analysis to estimate the incremental costs (from the Indian healthcare sector perspective) and consequences (including deaths, DALYs, false-positive diagnoses, and secondary TB cases averted) of 4 different diagnostic algorithms: A reference scenario of clinical examination and non-microbiological tests, clinical diagnosis plus sputum smear microscopy, clinical diagnosis plus IGRA, and clinical diagnosis plus Xpert MTB/RIF (with and without the additional cost of multidrug-resistant TB (MDR-TB) treatment). This analysis was based on a hypothetical cohort of 1 million adult Indian TB suspects, similar in HIV prevalence/access to ARVs to that observed amongst adults tested for TB each year in India.

We hypothesized that, in a setting with high background rates of LTBI, IGRAs would be less cost-effective than other diagnostic tests with a higher specificity for active TB, due in large part to the cost of treating the substantial number of false-positive cases generated. These results will provide quantitative data to support training and advocacy efforts around the proper use (or non-use) of IGRAs in India, and other low-/middle-income country settings where LTBI prevalence is high.

Isoniazid Preventive Therapy

After high-risk individuals are screened for active TB, appropriate therapy (either curative, for those with active TB disease, or preventative, for those without active disease) is vital in preventing TB related morbidity and mortality, as well as further

secondary disease transmission. This is particularly true for people living with HIV (PLHIV), who are at high risk for TB reactivation and TB-related death [65]. While antiretroviral therapy can reduce the risk of TB disease in PLHIV (through reconstitution of the immune system), the risk of TB reactivation remains higher among PLHIV on ARVs compared to HIV-uninfected individuals [66,67]. This differential risk is greatest during the first six months of ARVs [68]. Isoniazid preventive therapy (IPT) has been shown to reduce the risk of TB disease in PLHIV (in whom active TB disease has been excluded) [69] above and beyond the effects of ARVs alone [68,70,71], and can be safely administered concurrently with ARVs [72]. When administered this way, IPT and ARVs have demonstrated a synergistic effect in reducing the risk of TB reactivation among PLHIV.

The WHO recommends 6 months of IPT be offered to all PLHIV in whom active TB disease is not suspected [73], though globally IPT coverage remains stubbornly low [74]. The first HIV diagnosis may represent an effective opportunity to initiate IPT, since these appointments occur in-person and typically involve counseling and referrals to routine healthcare services. An on-going cluster-randomized trial of TB diagnostics for the exclusion of active TB among newly diagnosed PLHIV in rural Malawi has demonstrated high rates of acceptability of IPT when prescribed in this manner; of the 1,011 individuals eligible for IPT, more than 99% initiated therapy during the first two phases of the study (*Unpublished data*). Importantly, strategies for IPT eligibility screening and provision at the time of the first HIV diagnosis offer the opportunity to identify individuals at highest risk of TB disease (and who therefore stand to benefit the

most from IPT) in a routine clinical setting. Such an approach has the potential to better integrate TB/HIV care in high dual-burden settings in an efficient, cost-effective manner.

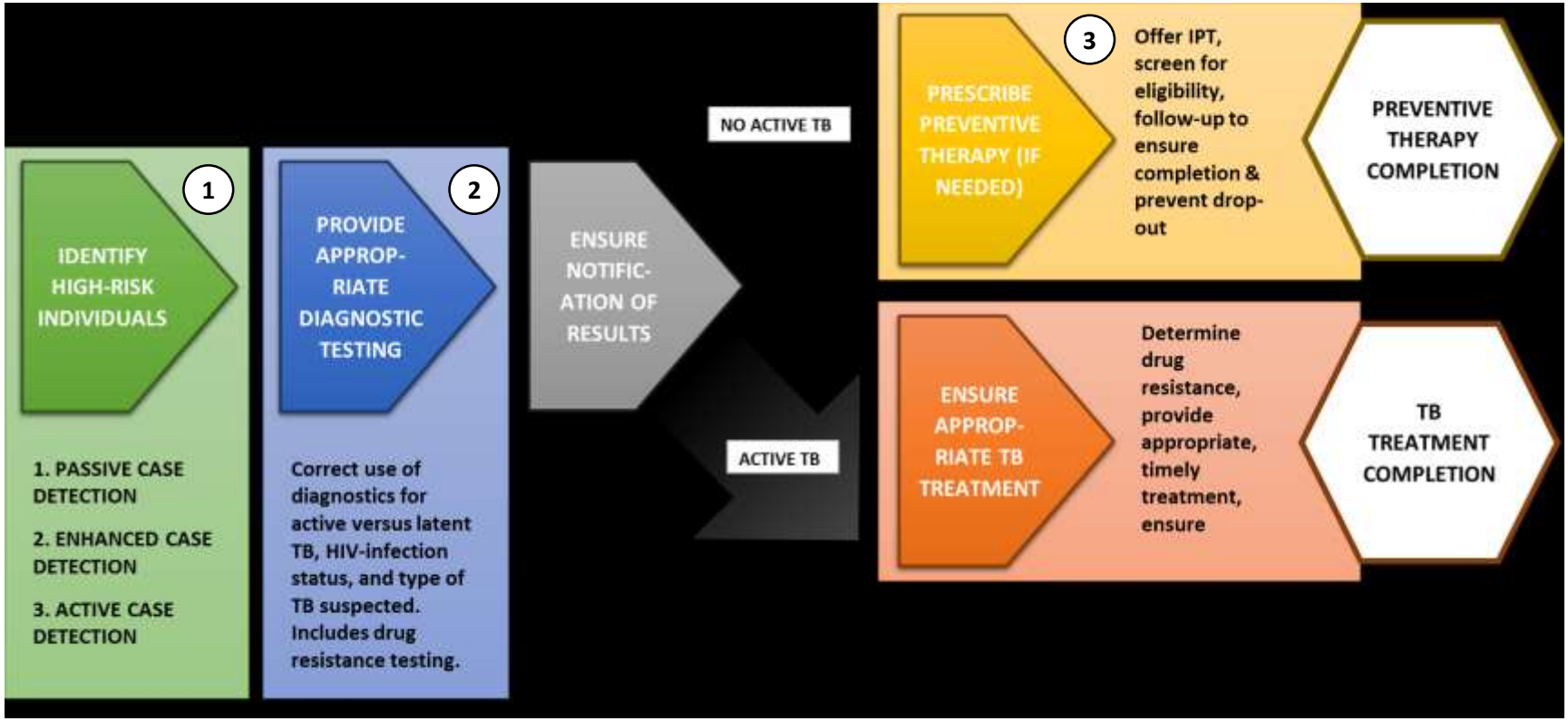
While IPT initiation rates may increase if isoniazid is prescribed to PLHIV when HIV is first diagnosed, monitoring for side-effects and ensuring IPT completion remains a source of concern. Even among successful initiators, IPT completion may be hindered by fears of stigma, limited funds for transportation, and a desire to avoid taking medications when symptoms are absent [75]. Identifying risk factors for non-completion may help inform targeted interventions that could boost completion rates and reduce TB risk among PLHIV, especially during the crucial months before and immediately after ARV initiation. Characterizing individuals most at risk of IPT non-completion, or particular groups that may most benefit from targeted support during preventive treatment, may help improve rates of IPT completion, thereby reducing incident TB disease among newly diagnosed PLHIV.

In an effort to inform such interventions, for **Aim 3** we explored factors associated with IPT completion among a cohort of recently diagnosed HIV patients in rural Malawi, a high TB/HIV burden country. This analysis is nested within a larger cluster randomized trial of TB diagnostics in newly diagnosed PLHIV. Participating individuals were screened for symptoms of active TB at the time of their first HIV diagnosis. Asymptomatic individuals were offered IPT if they were eligible, while symptomatic individuals underwent additional microbiological testing for TB. Those testing negative were considered eligible for IPT if/when their TB symptoms resolved. Individuals initiating IPT were followed-up during routine clinical visits over the year

following their HIV diagnosis. We explored clinical and demographic factors associated with IPT completion among all individuals starting IPT during the first two phases of the study. We hypothesized that individuals initiating ARVs would be more likely to complete IPT, which was dispensed during routine clinical visits, since these individuals were attending regular clinic appointments to receive their antiretroviral drugs. Possible risk factors (all of which are easily assessed during routine clinical contact) identified by this analysis could be used to design and target interventions to support individuals most at risk treatment default.

These analyses focus primarily on interventions deployable in low-resource, rural settings, where TB prevention, diagnosis, and treatment are hampered by limited infrastructure, human and financial resource constraints, low population densities, long distances to health facilities, and high rates of poverty. Most research on TB control, conversely, has been conducted in urban, and peri-urban settings where infrastructure and epidemic conditions may differ substantially. Ensuring the feasibility and effectiveness of TB control interventions in rural, high-burden settings requires operational and implementation science research at every step of the TB case-finding and prevention pathway.

Figure 1.1: TB Case-Finding and Prevention Pathway - Conceptual Framework



Interventions can be targeted to points along the pathway, including 1) case detection strategies for improved TB case-finding, 2) the use of appropriate diagnostic tests for the cost-effective identification of active TB disease, 3) notification of patients, clinics, and surveillance systems of new TB cases, 4) the use of appropriate treatments for active TB disease or prevention of active disease among those eligible for preventive therapy. Interventions to reduce treatment default and increase treatment completion help ensure that therapy is continued until cure to prevent relapse, the development and/or spread of drug resistance, and further secondary disease transmission.

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CHAPTER 2:

YIELD OF HOUSEHOLD CONTACT TRACING FOR TUBERCULOSIS IN RURAL SOUTH AFRICA

INTRODUCTION TO CHAPTER 2:

The TB case-finding and prevention pathway begins with the identification of high risk populations in need of TB testing. Previous research has demonstrated an increased risk of TB disease among the household contacts of active TB patients, especially those that are smear positive. Household contact tracing, a form of active contact tracing, has been shown to be feasible and effective in high-income, low TB-burden settings, but has long been considered impractical and infeasible to implement in high-burden, low-income settings. However, given the challenge of TB control in this context and the potential for high yields of previously undiagnosed TB disease in TB-patient households, these interventions deserve serious consideration as a tool to increase TB case notification rates.

However, because their efficiency and effectiveness depends in part on setting-specific factors such as the underlying transportation infrastructure, community socio-economic status, distance to the health facilities, TB/HIV stigma (among others), the yield and cost-effectiveness of household contact tracing interventions may vary widely. This may be especially true when comparing urban and rural contexts. Operational research on these setting-specific effects, including their influences on yield and cost, will be important in deciding how and where to implement ACF interventions. This study explores the yield of an ACF intervention implemented in rural South Africa, and compares the results to a similarly structured intervention implemented in an urban/peri-urban area.

ABSTRACT

Background: Efficient and effective strategies for identifying cases of active tuberculosis (TB) in rural sub-Saharan Africa are lacking.

Methods: Adults newly diagnosed with active TB were recruited from public clinics in Vhembe District, South Africa. Study staff visited index case households and collected sputum specimens for TB testing via smear microscopy and culture. We calculated the yield and the number needed to screen (NNS) to find one additional case. Predictors of new TB among household contacts were evaluated using multilevel logistic regression, accounting for clustering by household.

Results: We recruited 130 index cases and 282 household contacts. After excluding 3 prevalent cases, we identified 11 previously undiagnosed cases of culture- or smear-confirmed TB, giving a prevalence of 3.9% (95% CI: 2.0-6.9%) among contacts, a yield of 8.5 per 100 (95% CI: 4.2-15.1) index cases traced, and NNS of 12 (95% CI: 7-24). The presence of TB symptoms was not associated with an increased odds of active TB (aOR: 0.3, 95% CI: 0.1-1.4).

Conclusions: Household contacts of recently diagnosed TB patients in rural South Africa have high prevalence of TB and can be feasibly detected through contact tracing, but more sensitive tests than sputum smear are required.

BACKGROUND:

More aggressive approaches to finding cases are essential if we are to accelerate the current slow decline in TB incidence [1]. While most TB control interventions have focused largely on urban, high-burden settings, high TB incidence rates have been observed in rural populations [2,3], where long distances [4], inadequate infrastructure, poor-quality health facilities, and limited human resources present major obstacles to active case finding efforts [5,6]. To date, the majority of research on active TB case finding has been done in urban, peri-urban, or congregate settings [7]; limited research has been done on the efficacy and feasibility of these interventions in rural areas. [8]

Though unproven, it is also reasonable to believe that a higher proportion of TB transmission could occur in the household in rural settings, where fewer people may frequent high-transmission settings such as public transit, shebeens, or major public gatherings [9–11]. We therefore sought to determine the yield of a household-based active case-finding intervention in a rural region of South Africa, a country with high rates of both TB and HIV [12]. We aimed to estimate the prevalence of previously undiagnosed TB among household contacts of recently diagnosed adult TB patients, to calculate the number of index cases needed to screen (NNS) to identify one additional case of previously undiagnosed TB, and to qualitatively compare the yield, prevalence, and NNS of active TB case finding in this rural setting to a higher-burden, peri-urban one [13].

METHODS:

Study setting

This study took place in Vhembe District, a municipality in Limpopo Province, South Africa, that borders Zimbabwe and Botswana. The district has a population of approximately 1.3 million, and a population density of 130 individuals per square mile [14]. At 350 per 100,000/year, Vhembe had the second lowest district-level TB incidence in South Africa in 2012 [15].

Participants

Adults recently diagnosed with TB at public clinics in the district ("index cases") were consecutively asked to participate in the study. Index cases were eligible to participate if they were 18 years of age or older, had a recorded TB diagnosis based on clinical evaluation and/or radiology (with or without bacteriological confirmation), had initiated TB treatment within the previous 30 days, had been a resident of Vhembe District for at least 6 months, had at least one household contact, and consented to a home visit by the study team (**Figure 2.1**). A household contact was defined as any person living on the same residential plot who shared either the same residential structure or frequent meals with the index case. Participating index cases provided written informed consent and completed a short survey that included demographics, TB and HIV clinical history, and directions to their home. TB diagnosis and treatment data were abstracted from the clinic registers and/or patient's clinical records.

Household Visits

Trained study staff visited index case households within 2 weeks of recruitment. Household contacts were eligible to participate in the study if they met the definition of a household contact (described above) and provided informed consent. Trained study staff administered similar brief surveys to all participating household contacts and collected sputum specimens for smear and culture in accordance with national guidelines [16]. TB testing, including fluorescence microscopy with auramine staining and culture (BAC-TEC MGIT 960, BD Diagnostics, Franklin Lakes, USA) was performed by South Africa's National Health Laboratory System. All household contacts under the age of 5 were referred for further clinical evaluation through routine services, according to South African guidelines [16]. Results from the laboratory tests were made available to study personnel, and all positive results were reported to clinical staff for initiation of TB treatment through routine clinical services. Clinic records were evaluated to determine if individuals referred for treatment actually initiated anti-TB therapy. We did not provide HIV testing, but referred individuals who did not know their HIV status, or who had not been recently tested, to the routine health services for voluntary HIV counseling and testing.

If household contacts were not available for recruitment during the first study visit, study staff attempted to make an appointment to return to the home at a later time. Study staff returned to each household up to three times to complete recruitment and deliver all positive test results. If a phone number had been provided and

participants consented to receiving their results via phone, the study team called individuals who had negative smear and culture results.

Statistical Analysis:

Our primary outcome was the proportion of household contacts with newly diagnosed TB, confirmed by smear and/or culture positive for TB. We calculated the yield of active case finding as the number of newly diagnosed TB cases among household contacts identified for every 100 index cases traced and also calculated the number of index cases needed to screen to identify one additional confirmed TB case. We constructed 95% confidence intervals (95% CI) around these estimates by assuming a binomial distribution (for prevalence) or a Poisson distribution (for yield). We examined univariate associations between our outcomes and potential predictors using Fisher's exact tests and Wilcoxon/Mann-Whitney tests. We used multilevel logistic regression modeling to examine the relationship between newly diagnosed TB and variables including demographics, laboratory results, symptom history, and index case characteristics, incorporating a random effects term to account for clustering at the household level. All analyses were performed in Stata 12 (Stata Corp., College Station, USA)

RESULTS:

Index Cases:

Between December 1, 2013 and September 30, 2014, we recruited 130 of 156 (83%) of eligible index cases from 27 participating public clinics in Vhembe District (**Figure 2.1A**). Index cases were 56% male (73/130) and averaged 40 years of age (Interquartile range [IQR]: 31 – 49) (**Table 2.1**). Nearly all participants spoke Tshivenda (126/130, 97%) and were born in Limpopo Province (127/130, 98%). Just over 50% of index cases had completed at least some high school (73/130, 56%), and a similar proportion reported living in a female-headed household (67/130, 52%). On average, household size was five people (IQR: 3-6), and the head of the household earned approximately 2,200 Rands (about US$200 in 2014) per month (IQR: 13-2350) from all formal and informal sources. Index cases had lived in their current homes for 30 years on average (IQR: 20-40); only two reported living in their current home for one year or less.

Of the 95% of index cases with known HIV status, 58 (47%) were living with HIV, less than 20% of whom (n=11) reported receiving antiretroviral therapy at the time of their TB diagnosis, though 71% (n=40) received their HIV and TB test results a month or less apart (40/56, 71%). Only two index cases had documented drug-resistant TB. A great majority of index cases reported having TB symptoms (cough, fever, night sweats, weight loss, and/or fatigue) at diagnosis (112/130, 86%), and a median duration of symptoms of 30 days (IQR: 30-120).

Household Contacts:

From 130 index case households visited, we recruited 282 household contacts (**Figure 2.1B**). Household contacts were somewhat younger than index cases (median age: 26 years, IQR: 17-50, with 23% younger than 15 years old) and were more likely to be female (203/282, 72%) (**Table 2.2**). Among adult participants (>18 years old) half had completed at least some high school (99/198, 50%). Of the 119 household contacts willing to disclose their HIV status, 22 (19%) reported that they were living with HIV, 20 (91%) of whom were receiving antiretroviral therapy. Three participants reported that they were currently receiving treatment for TB and were excluded from subsequent analyses. Only 4% of household contacts (12/279) were unable to produce sputum of a sufficient quantity for testing; these individuals were analyzed as TB-negative.

Yield and Number Needed to Screen:

The intervention identified 11 new cases of confirmed active TB, for a household contact prevalence of 3,940 per 100,000 (95% CI: 1,980-6,940). Of these, only one (9%) was smear-positive; the rest were positive on culture alone. An additional 18 individuals (6,450 per 100,000, 95% CI: 3,870-10,000) had cultures that were positive for non-TB mycobacteria. The intervention therefore yielded 8.5 previously undiagnosed TB cases (95% CI 4.2-15.1) for every 100 index cases traced, giving a number of index cases needed to screen, using culture, of 12 (95% CI: 7-24) to identify one new case of previously undiagnosed TB.

Predictors of TB

Overall, 44% (n=122) of participating household contacts reported at least one TB symptom; these included cough (15%), fever (15%), lethargy (14%), loss of appetite (5%), weight loss (14%), and night sweats (18%), with a median duration of 75 days (IQR: 14-365) and mean of 272 days. Counterintuitively, contacts newly diagnosed with culture-confirmed TB had a markedly lower prevalence of symptoms, though this difference was not statistically significant (18% vs. 45%, p=0.120). Only 29 contacts (24%) reporting seeking care for their symptoms; none of these individuals had confirmed prevalent TB.

Compared to contacts without TB, those with newly diagnosed TB were more likely to live in female-headed households (82% vs. 51%, p=0.063) and to have completed more years of schooling (10 vs 8, p=0.023) on univariate analysis. We detected no differences in terms of BMI, smoking status, history of previous TB, and history of isoniazid preventive therapy (IPT). All of the household contacts diagnosed with TB had started TB treatment by the end of the study period. In a multilevel logistic regression model including both education and female-headed household status, both variables remained independent predictors of newly diagnosed TB (adjusted OR [aOR]: 5.2, 95% CI: 1.1-25.4, for female-headed household, aOR: 8.2, 95% CI: 1.5-46.2, for finishing high school versus having less than eight years of education) (**Table 2.3**).

DISCUSSION:

This study found a high prevalence (nearly 4,000 per 100,000) of previously undiagnosed TB among household contacts of newly diagnosed TB patients, only one-third lower than that (6,075 per 100,000) observed in a similar contact tracing study in an area with nearly three times the background incidence of TB [13]. The sensitivity of smear for culture-confirmed active TB in this population was less than 10%. This analysis demonstrates that, even in rural settings, household contact tracing can feasibly identify cases of active TB, but symptom screening is unhelpful in identifying TB cases. Additionally, we found that sensitive diagnostic tests may be required in order to effectively diagnose TB cases, which may substantially add to the expense of conducting active contact tracing in this setting.

While the WHO recommends TB screening for the household contacts of newly diagnosed TB patients (because of their elevated risk of TB disease), they do not recommend a specific algorithm [17]. Instead WHO provides a range of potential algorithms, such as testing only those individuals with any cough, a cough of more than two weeks, or the presence of any TB symptoms (e.g. cough, fever, weight loss, night sweats, and/or lethargy) [17]. Had we used the presence of any cough to screen for household contacts at greatest risk for TB—and tested only these "highest risk" individuals—we would have missed all of the new TB cases, while screening for the presence of any TB symptoms before testing would have only captured two (18%) of 11 cases.

The fact that the majority of new TB cases identified by this study were asymptomatic and smear negative indicates that household contact tracing in rural areas may identify cases of TB early, before substantial secondary transmission or TB-related morbidity or mortality can occur. Virtually all index cases recruited for our study were symptomatic, whereas household contacts with TB were actually less likely to report symptoms than their family members without active TB. These findings suggest that TB cases captured by active contact tracing interventions are different than the cases captured by the routine system through passive case detection, and that the diagnostic tests and/or screening algorithms required to detect them differ as well. Had household contacts been tested for TB using sputum smear microscopy alone, we would have missed more than 90% of all TB cases in our sample.

Index cases in our study reported mean symptom durations of nearly 250 days before TB diagnosis, while smear/culture positive TB cases averaged only 11 days between symptom onset and the study visit. This discrepancy indicates that substantial TB transmission may be occurring before individuals ever present to care in a passive case-detection setting. This transmission can likely only be averted through active screening strategies such as contact tracing.

We also identified a very high prevalence of non-TB mycobacteria (NTM) among household contacts, nearly three times as high as the prevalence of culture-confirmed TB 11% (95% CI: 7-15%). Other studies from South Africa have also identified high rates of NTM infection [18,19]. This result raises questions regarding the timing of TB treatment initiation among culture-positive individuals identified through contact

tracing. On average speciation takes approximately 5 additional days [20] from the time a culture positive result is returned. Avoiding treatment delays for those with active TB is paramount, but preventing unnecessary treatment should be an important consideration given the poor specificity of culture for TB (92%) in this population.

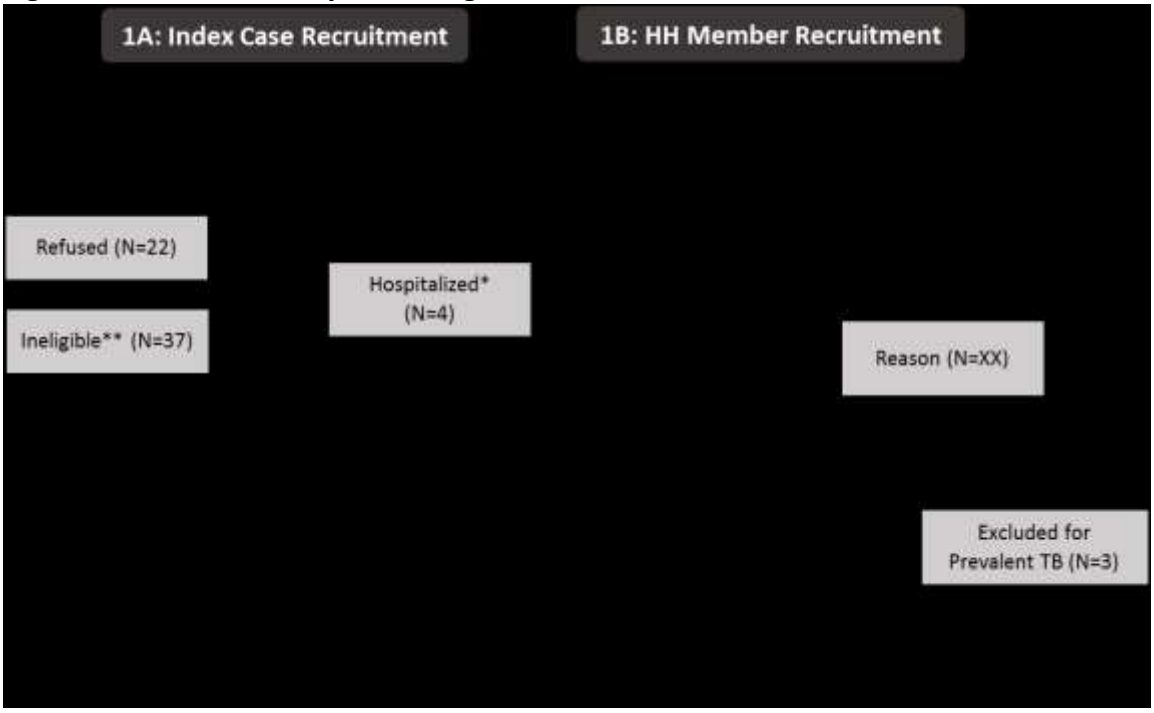
This study has a number of important limitations. First, although we screened more than 280 household contacts, our sample size of TB cases was small, leaving us without power to detect modest differences between those with and without TB. Because we recruited index cases with and without laboratory-confirmed TB, it is possible that some of the participating index cases did not have active TB disease. However, this study sought to explore the feasibility and effectiveness of household contact tracing under operational conditions in which TB is not always bacteriologically confirmed. Finally, we were unable to perform HIV testing or TB testing with Xpert MTB/RIF for household contacts. Further studies of TB contact tracing in rural settings could seek to expand the sample size, evaluate novel diagnostic tools (e.g., Xpert MTB/RIF), study the cost-effectiveness of active contact tracing in this setting, and elucidate the relationships between HIV and TB status among household contacts.

Conclusion:

Household contact tracing of newly diagnosed TB patients in a rural South African setting feasibly found high prevalence of previously undiagnosed TB, nearly all of which was smear-negative. Symptom screening was not an effective strategy for identifying cases in the household. Household contact tracing, using more sensitive

diagnostic tests than smear, should be seriously considered in high-burden settings, including rural areas, if ambitious TB control targets are to be met worldwide.

Figure 2.1A & 2.1B: Study Flow Diagram



* Hospitalized patients were unable to be recruited for this study

** Participants were ineligible due to age <18 years (N=1), a time between TB treatment initiation and study screening of >30 days (N=5), having no household contacts (N=22), or primary residence outside of the study district (N=9).

† NNS: Number (of index cases) needed to screen with culture to find 1 new case of active TB among household contacts

Table 2.1: Index Case Demographic and Clinical Characteristics

Variable	Overall (N=130) N (%)	New TB in HH (N=9) N (%)	No New TB in HH (N=121) N (%)	P-value*
Female Sex	57 (44%)	3 (33%)	54 (45%)	0.731
Age (Median, IQR)	40 (31-49)	36 (31-48)	39 (31-49)	0.831
Female-Headed Household	67 (52%)	7 (78%)	60 (50%)	0.166
Head of HH Income (Median, IQR)	1270 (13-2350)	2500 (1270-6300)	1270 (0-2000)	**0.047**
Education				
8th grade or less	40 (31%)	4 (44%)	36 (30%)	
At least some high school	73 (56%)	3 (33%)	70 (58%)	0.278
More than high school	17 (13%)	2 (22%)	15 (12%)	
Unemployed	73 (56%)	6 (67%)	67 (55%)	0.731
Number of HH members, by Self-Report (Median, IQR)	5 (3-6)	6 (5-6)	4 (3-6)	0.130
Number of HH Contacts Participating in Study (Median, IQR)	2 (1-3)	3 (2-6)	2 (1-3)	**0.005**
Years lived in HH (Median, IQR)	30 (20-40)	37 (28-43)	30 (19-39)	0.235
Previous TB	15 (12%)	1 (11%)	14 (12%)	1.0
TB Symptoms				
Cough	58 (45%)	4 (44%)	54 (45%)	1.0
Fever	45 (35%)	1 (11%)	44 (36%)	0.162
Fatigue	64 (49%)	4 (44%)	60 (50%)	1.0
Loss of appetite	25 (19%)	1 (11%)	24 (20%)	1.0
Weight loss	84 (65%)	5 (56%)	79 (65%)	0.720
Night sweats	55 (42%)	5 (56%)	50 (41%)	0.493
At least one TB symptom	112 (86%)	7 (78%)	105 (87%)	0.611
Symptom duration				
No symptoms	18 (14%)	2 (22%)	16 (13%)	
<1 month	57 (44%)	3 (33%)	54 (45%)	0.357
1-6 months	32 (25%)	1 (11%)	31 (26%)	
>6 months	23 (18%)	3 (33%)	20 (17%)	
Smear Positive**	44 (73%)	2 (29%)	42 (79%)	**0.012**
Xpert Positive†	55 (86%)	2 (67%)	53 (87%)	0.370

* Categorical variables were tested using Fisher's Exact Test, and continuous variables were tested with a Ranksum test

** 70 individuals were missing smear results in the clinic TB register and/or index case TB card (68 index cases living in households with no new TB cases, and 2 individuals living in households with ≥1 new TB case)

† 66 individuals were missing Xpert results in the clinic TB register and/or index case TB card (60 index cases living in household with no new TB cases, and 6 individuals living in households with ≥1 new TB case)

Table 2.2: Household Contact Demographic and Clinical Information

Variable	Overall (N=279) N (%)	Lab-Confirmed TB (N=11) N (%)	No Lab-Confirmed TB (N=268) N (%)	P-value*
Female Sex	201 (72%)	10 (91%)	191 (71%)	0.301
Age Category				
Under 14	60 (22%)	2 (18%)	58 (22%)	
15-39	117 (42%)	6 (55%)	111 (41%)	0.943
40-64	66 (24%)	2 (18%)	64 (24%)	
65 and Older	36 (13%)	1 (9%)	35 (13%)	
Female-Headed Household	146 (52%)	9 (82%)	137 (51%)	0.063
Head of HH Income (Median, IQR)	1270 (0-2500)	1270 (1270-6300)	1270 (0-2350)	0.101
Education				
8th grade or less	140 (50%)	3 (27%)	137 (51%)	
At least some high school	114 (41%)	5 (45%)	109 (41%)	0.079
More than high school	25 (9%)	3 (27%)	22 (8%)	
Unemployed	149 (53%)	8 (73%)	141 (53%)	0.229
Number of HH members (Median, IQR)	5 (4-7)	6 (5-8)	5 (4-7)	0.248
HIV Status				
HIV-Infected	19 (7%)	0 (0%)	19 (7%)	
HIV-Uninfected	97 (35%)	3 (27%)	94 (35%)	0.792
HIV Status Unknown	163 (58%)	8 (73%)	155 (58%)	
TB Symptoms				
Cough	41 (15%)	0 (0%)	41 (15%)	0.377
Fever	42 (15%)	1 (9%)	41 (15%)	1.0
Fatigue	40 (14%)	0 (0%)	40 (15%)	0.374
Loss of appetite	13 (5%)	1 (9%)	12 (4%)	0.414
Weight loss	38 (14%)	1 (9%)	37 (14%)	1.0
Night sweats	51 (18%)	1 (9%)	50 (19%)	0.695
At least one TB symptom	122 (44%)	2 (18%)	120 (45%)	0.120
Symptom duration				
No symptoms	157 (56%)	9 (82%)	148 (55%)	
<1 month	53 (19%)	1 (9%)	52 (19%)	0.465
1-6 months	32 (11%)	1 (9%)	31 (12%)	
>6 months	37 (13%)	0 (0%)	37 (14%)	
Smear Positive	1 (0.4%)	1 (9%)	--	--
Culture Positive	28 (11%)	10 (91%)	18 (8%)	--
MTB Culture Positive	10 (4%)	10 (91%)	--	--
Smear and/or MTB Culture Positive	11 (4%)	11 (100%)	--	--

* Categorical variables were tested using Fisher's Exact Test, and continuous variables were tested with a Ranksum test

Table 2.3: Factors Associated with Newly Diagnosed TB among Household Contacts

Variable	Unadjusted OR (95% CI)	Adjusted* aOR (95% CI)
Female Sex	4.06 (0.49-33.71)	4.51 (0.54-37.65)
Age (per 10 year increase)	0.97 (0.72-1.30)	1.00 (0.71-1.41)
Female-headed household	4.48 (0.87-23.08)	**5.19 (1.06-25.44)**
Head of household income (Per 500 Rands)	1.06 (0.96-1.17)	1.03 (0.94-1.14)
Education**		
8th grade or less	Ref	Ref
At least some high school	2.14 (0.49-9.40)	2.08 (0.47-9.19)
More than high school	**6.05 (1.07-34.40)**	**6.88 (1.19-39.66)**
Unemployed	2.28 (0.56-9.25)	2.48 (0.62-9.96)
Number of HH members (Index case self-report)	1.12 (0.88-1.43)	1.14 (0.92-1.43)
TB Symptoms		
At least one TB symptom	0.26 (0.05-1.30)	0.29 (0.06-1.44)
Symptom duration		
No symptoms	Ref	Ref
<1 month	0.32 (0.04-2.80)	0.35 (0.04-2.98)
>=1 month	0.22 (0.02-1.90	0.25 (0.03-2.13)

* Adjusted for Education status

** Adjusted results for education status after controlling for female head of household

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CHAPTER 3:

COSTS AND CONSEQUENCES OF USING INTERFERON-γ RELEASE ASSAYS FOR THE DIAGNOSIS OF ACTIVE TUBERCULOSIS IN INDIA

INTRODUCTION TO CHAPTER 3

The diagnosis or exclusion of TB disease in high risk individuals in paramount, whether these individuals are identified through passive case finding efforts (such as self-presentation), or active approaches such as symptom screening and the household contact tracing intervention described in **Chapter 2**. The process of diagnosing a TB case has benefited immensely from the development of new TB diagnostics in recent years. While new tests are often more sensitivity and specific than earlier tests, their effective deployment requires additional healthcare provider and laboratory training, as well as the development and dissemination of new diagnostic algorithms and testing guidelines. When any of these are lacking, true TB cases may be missed (leading to increased morbidity and mortality, and further disease transmission), true negatives may be falsely diagnosed and treated, and limited healthcare resources may be wasted. Decisions on the most efficient use of new TB diagnostics may be informed by quantitative analyses, such as the one in **Chapter 3**. This cost effectiveness analysis explores the costs and consequences of the use of interferon-gamma release assays (IGRAs), which are increasingly being used off-label in the Indian private sector to diagnose active TB disease. In this chapter we explore the health system costs and patient consequences associated with the use of IGRAs in India in order to better inform healthcare providers, laboratory professionals, and policymakers on the effects of using IGRAs to diagnose active TB in this setting.

ABSTRACT:

Background:

There is growing concern that interferon-γ release assays (IGRAs) are being used off-label for the diagnosis of active tuberculosis (TB) disease in many high-burden settings, including India, where the background prevalence of latent TB infection is high. We analyzed the costs and consequences of using IGRAs for the diagnosis of active TB in India from the perspective of the Indian TB control sector.

Methods and Findings:

We constructed a decision analytic model to estimate the incremental cost and effectiveness of IGRAs for the diagnosis of active TB in India. We compared a reference scenario of clinical examination and non-microbiological tests against scenarios in which clinical diagnosis was augmented by the addition of either sputum smear microscopy, IGRA, or Xpert MTB/RIF. We examined costs (in 2013 US dollars) and consequences from the perspective of the Indian healthcare sector. Relative to sputum smear microscopy, use of IGRA for active TB resulted in 23,700 (95% uncertainty range, UR: 3,800 – 38,300) additional true-positive diagnoses, but at the expense of 315,700 (95% UR: 118,300 – 388,400) additional false-positive diagnoses and an incremental cost of US$49.3 million (95% UR: $34.9 – $58.0 million) (2.9 billion Indian Rupees). Relative to Xpert MTB/RIF (including the cost of treatment for drug resistant TB), use of IGRA led to 400 additional TB cases treated (95% UR: [-8,000] – 16,200), 370,600 (95% UR: 252,200 – 441,700) more false-positive diagnoses, 70,400 (95% UR: [-7,900] – 247,200) fewer

disability-adjusted life years averted, and US$14.6 million (95%UR: [-$7.2] – $28.7 million) (854 million Indian Rupees) in additional costs.

Conclusion:

Using IGRAs for diagnosis of active TB in a setting like India results in tremendous overtreatment of people without TB, and substantial incremental cost with little gain in health. These results support the policies by WHO and Standards for TB Care in India, which discourage the use of IGRAs for the diagnosis of active TB in India and similar settings.

INTRODUCTION:

Interferon-gamma Release Assays (IGRAs), including QuantiFERON-TB Gold In Tube (Cellestis, Carnegie, Australia) and T-SPOT.TB (Oxford Immunotec, Oxfordshire, UK), are immunological tests that are widely used to detect latent tuberculosis infection (LTBI) in high-income settings. IGRAs have higher specificity than tuberculin skin testing (TST), are less likely than TSTs to cross-react with the Bacille Calmette-Guerin (BCG) vaccine, and correlate well with *M. tuberculosis* exposure [1], though stronger association with progression to active disease has not been conclusively shown [2].

While IGRAs are recommended for the diagnosis of LTBI in many high-income countries, they are not recommended by the World Health Organization (WHO) as a TST replacement for LTBI diagnosis in low and middle income countries [3]. Furthermore, in no setting are IGRAs recommended for detection of active pulmonary TB [3], since IGRAs (like TST) cannot differentiate latent infection from active TB disease [4].

In high-burden settings, where 40% or more of the general population is latently infected with TB [5] and therefore likely to test IGRA-positive [6–8] (i.e., a test that is positive among all people with latent TB is likely to have a specificity of 60% or less when used for active TB), use of IGRAs to diagnose active pulmonary TB is particularly problematic. This concern equally applies to the use of tuberculin skin test (TST) for active TB. Nevertheless, in many high-burden countries, including India, there is growing concern that IGRAs (and, to a lesser extent, TST) are being used off-label, particularly in the private sector, for the diagnosis of active TB [9,10]. In India, QuantiFERON is marketed as “TB Gold,” and another IGRA (Immunoshop, Mumbai,

India) as “TB Platinum,” names that provide poorly-trained healthcare providers little guidance as to their intended use. In China, domestic IGRAs are made by several companies, and publications from China suggest their use to diagnose active TB in that setting as well [11,12].

Although the use of IGRAs and TST for active TB is discouraged by the Indian Revised National TB Control Programme (RNTCP) and the Standards for TB Care in India [13], IGRAs are not banned, and there is growing concern that the use of IGRAs has increased since the ban on antibody-based serological TB tests in 2012 [14,15]. Market research conducted in 2012-2013 by the Clinton Health Access Initiative found that approximately 12% of private laboratories in India offered QuantiFERON TB Gold tests [16]. As the economic and patient consequences of this practice remain unclear, we analyzed the costs and consequences of using IGRAs for the diagnosis of active pulmonary TB in India from the perspective of the Indian TB control sector.

MATERIALS AND METHODS:

Study Design and Population:

To estimate the costs and consequences of IGRAs for the diagnosis of active pulmonary TB in adults, we adapted our prior decision analysis model of serological TB tests in India [17] (**Figure 3.1**). The full model can be seen in the Supplemental Material (**S1 File**). We took as our study population one million Indian adults in whom TB is clinically suspected, with a nationally representative prevalence of latent TB infection, human immunodeficiency virus (HIV) infection, and antiretroviral therapy access. This

hypothetical study cohort is representative of adults in India presenting for TB diagnosis in settings with access to serological testing, and is intended to approximate the annual costs and outcomes among all adult patients in India receiving serological testing for suspected active TB disease. We examined costs (measured in 2013 US dollars) and effects from the perspective of the Indian healthcare sector (including both public and private sectors), with future discounting of 3% per year. Outcomes included disability-adjusted life years (DALYs) averted (without age weighting), TB cases treated, and false-positive treatments (people without active TB who are inappropriately treated for active TB).

We took our reference (base-case) scenario to consist of the existing standard of care for TB diagnosis, but without the use of any microbiological tests. Thus, this scenario would consist of clinical evaluation plus any non-microbiological tests (e.g. chest X-ray) that might be routinely performed for TB diagnosis in a typical Indian setting. We compared this reference scenario against scenarios in which this standard of care was augmented by the addition of microbiological tests, namely sputum smear microscopy, IGRA, or Xpert MTB/RIF (a WHO-endorsed, sputum-based molecular test for TB) [18]. In making this comparison, we assumed that any individual who would be treated for TB in the reference scenario would also be treated for TB after performance of a microbiological test, even if that test result was negative. (For example, someone with a strong clinical suspicion of TB, but a negative smear, IGRA, or Xpert would still be treated as having TB.) We further assumed that negative microbiological test results

would not be taken as an indication to discontinue treatment among individuals started on anti-TB therapy.

In addition to smear, IGRA, and Xpert MTB/RIF, we also examined a scenario including mycobacterial culture. We do not present those findings in detail, however, as research has shown that culture results have limited impact on physician's treatment decisions in India [19]. We included the effects of multi-drug resistant TB (MDR-TB) on each these diagnostic scenarios, assuming an MDR-TB prevalence of 2.1% among all newly diagnosed Indian adult TB cases [20], and examined the costs and consequences of diagnosing and treating MDR-TB for the Xpert arm (as, unlike smear or IGRA, Xpert is capable of diagnosing resistance to rifampin, a proxy measure for MDR-TB). Though recommended by the RNTCP in certain situations, drug-sensitivity testing (DST) is not widely available in India [21], and therefore costs associated with DST were not included in the non-Xpert MTB/RIF arms. We took as our primary outcomes the incremental costs and consequences (including DALYs, secondary TB transmissions, false positive TB cases diagnosed, and TB cases treated) of diagnosis with either IGRA or Xpert MTB/RIF, compared to the reference scenario.

Parameters and Assumptions

Assumptions regarding the availability and turnaround time for sputum smear microscopy are as previously reported [17], and include a one week turnaround time for sputum smear microscopy with a loss to follow-up during this interval of 15% [22]. We assumed that IGRAs would be performed by private laboratories via send-out testing,

with a 1-week turnaround time and a loss-to-follow-up rate similar to that of sputum smear microscopy. To be conservative, Xpert MTB/RIF was assumed to have a delay between testing and treatment initiation of 7 days [23], and the same loss to follow-up as with IGRAs or sputum smear microscopy. Diagnostic testing cost estimates were based on published data, inflated to the year 2013 using the Indian GDP deflator [24], followed by conversion into US dollars at the 2013 exchange rate [25], where applicable.

We estimated the cost of sputum smear microscopy to be US$3 (range: US$1 – 5, for two smears) for each TB suspect tested [26]. Based on an internal survey (unpublished) of private laboratories [27], we estimated that IGRAs would cost US$30 (range: US$20 – 50) per test, while Xpert MTB/RIF was assumed to cost US$25 per test (range: US$20 – 57) [28,29]. After analysis overall costs were converted into 2013 Indian Rupees (INR) from 2013 US dollars using historical exchange rates [25], and cost outcomes are presented in both currencies.

Test accuracy estimates were obtained from the published literature, including meta-analyses where available. IGRA accuracy values were based on the QuantiFERON-TB Gold test, and obtained from studies performed in low- and middle-income country settings. While the T-SPOT.TB IGRA is unavailable in India, QuantiFERON-TB Gold In-Tube is available and commonly utilized, especially in the private sector [30] . For our analysis we used an IGRA sensitivity of 0.84 [4] (range: 0.56 – 0.96). For the purposes of illustrating the sensitivity of our model to a wider interval of possible sensitivities of IGRA tests, we used a wider range for sensitivity analysis around this variable than the published pooled confidence interval [4]. We used an IGRA specificity (for active TB, in individuals with

suspected TB in low and middle income countries) of 0.52 (range: 0.40 – 0.79) [4]. Additional parameter values are given in **Table 3.1**.

Sensitivity Analysis

We performed one-way sensitivity analyses on all model parameters, taking as the primary outcome the incremental costs and consequences of IGRA compared to the reference standard. Ranges for each model parameter are listed in **Table 3.1**. We performed additional two-way sensitivity analyses on those parameters with the greatest effects on model outcomes. Where data were lacking in regards to an appropriate range for the sensitivity analysis for a given parameter, we varied each parameter value by +/- 25% beyond its base value.

Finally, we performed a probabilistic sensitivity analysis (PSA) to incorporate uncertainty in all model parameters. In this analysis, we simultaneously varied all model parameters using Monte Carlo simulation (10,000 simulations), assuming that all parameters followed beta distributions with a mode equal to the most likely value (**in Table 3.1**) and an alpha (shape) parameter of four, with two exceptions. First, since it was unlikely that accuracy values (sensitivity and specificity) would approach zero, we varied these parameters using triangular distributions with minimum and maximum values based on the upper and lower estimates derived from systematic reviews where possible, and other published literature values where not. Second, some values (e.g., costs) do not have a natural upper bound; for these parameters, we assumed a gamma distribution with a mode at the most likely value and an alpha parameter of 100. The

full model used for the PSA can be seen in the Supplemental Material (**S2 File**). All analyses were conducted using TreeAge Pro 2013 (TreeAge Software, Inc., Williamstown, MA, USA).

RESULTS:

Our hypothetical cohort of one million people with TB symptoms included 143,000 individuals with active TB. When used alone, we estimated that clinical examination and reference scenario tests (such as X-ray) would detect 75,700 (53%) (95% Uncertainty Range, UR: 36,000 – 124,900) of these patients (**Figure 3.2**). Addition of sputum smear microscopy to this algorithm increased the overall yield to 108,400 (76%) (95% UR: 53,800 – 174,300) (**Figure 3.2**). Use of Xpert MTB/RIF instead of smear for all members of the cohort identified an additional 23,300 cases relative to smear (yield: 131,700, 92%) (95% UR: 64,100 – 206,100), while also identifying 55,000 fewer false-positive cases than smear microscopy (95% UR: 5,100 – 198,800). Use of mycobacterial culture methods (under the additional assumption that culture results could largely be translated into treatment decisions, with 10% additional loss to follow-up) resulted in qualitatively similar outcomes as those observed in the Xpert MTB/RIF arm (data not shown).

Use of IGRA rather than smear had a similar yield of true-positive diagnoses as Xpert (132,100 cases, 93%) (95% UR: 62,800 – 203,000), but at the expense of 438,200 false-positive diagnoses (95% UR: 345,600 – 552,400) – 3.3 false-positives diagnosed for

every true-positive – and 315,700 (95% UR: 118,300 – 388,400) more false-positives than sputum smear microscopy.

The cost of IGRA-based diagnosis, from the Indian healthcare perspective, was also high. For every million individuals tested by IGRA rather than sputum smear microscopy, the incremental cost of TB diagnosis and treatment was US$49.4 million ($67.3 million with IGRA vs. $18.0 million with sputum smear microscopy) (95% UR: $34.9 – 58.0 million) (**Figure 3.2**). The US$49 million (2.9 billion Indian Rupees, INR) in incremental costs reflected approximately US$27 million (1.6 billion INR) in additional diagnostic test costs, US$2 million (117 million INR) in the treatment of additional true-positive cases identified with IGRAs, and nearly US$21 million (1.2 billion INR) for the treatment of false-positive cases – people without active TB who nevertheless received six months of anti-TB drugs.

Similarly, although the cost of diagnosis with IGRA and Xpert MTB/RIF was similar, the total healthcare cost of IGRA was nearly US$15 million greater (95% UR: $-7.2 – 28.7 million) (854 million INR) than Xpert (US$67.3 million vs. $52.7 million) (3.9 billion vs. 3.1 billion INR), due to the large numbers of false-positive diagnoses triggering inappropriate treatment (**Figure 3.2**). Incorporating the possibility of MDR treatment for IGRA-diagnosed false positive cases would raise the total costs of the IGRA scenario even more. As a result of the poor specificity of IGRA, we estimated that Xpert MTB/RIF would avert more DALYs, and at lower cost, than IGRAs (as used for diagnosis of active TB), even after including the costs of treating drug-resistant TB in the Xpert MTB/RIF scenario. Compared to Xpert MTB/RIF, the use of IGRAs diagnosed only 400 additional

true TB cases (95% UR: -8,000 – 16,200), and made 370,600 more false-positive diagnoses (95% UR: 252,200 – 441,700). Relative to sputum smear microscopy alone, Xpert MTB/RIF cost US$345 (20,200 INR) per DALY averted, similar to prior analyses [28] , while the IGRA strategy was dominated by the Xpert strategy.

In one-way threshold analyses based on the pre-specified ranges of all variables in the model (**Figure 3.3**), the scenario using Xpert MTB/RIF averted more DALYs than IGRAs at IGRA sensitivities of 95.7% or less, very near the upper bound of 96%. When considering the cost of MDR treatment based on Xpert results, IGRA-based algorithms were more costly than Xpert-based ones unless the unit cost of Xpert exceeded US$39 (2,280 INR). Xpert MTB/RIF remained less costly than IGRA testing until the average cost of MDR treatment exceeded US$5100 (298,000 INR) per person, near the highest average cost of MDR treatment in India from 2008-2013 (US$5500) [31] (322,000 INR). In other scenarios tested, Xpert MTB/RIF (including MDR treatment) was both less expensive and more effective than IGRA testing.

In two-way sensitivity analyses, even with a specificity of 62% (the upper bound of IGRA specificities tested), IGRAs only averted more DALYs than Xpert MTB/RIF in situations in which the IGRA sensitivity was over 94% (**Figure 3.4**). In terms of overall costs, two-way sensitivity analysis found that even if IGRAs cost only US$20 (1,170 INR) per test (the lowest bound of IGRA costs tested), algorithms using Xpert MTB/RIF would still be less costly below a unit price of US$29 (1,700 INR) per Xpert test.

In probabilistic sensitivity analysis, IGRA was more costly than Xpert (without MDR treatment) in 100% of the simulations, and more costly than Xpert (including MDR

treatment) in 89% of simulations. Xpert averted more DALYs than IGRAs in 96% of simulations, and sputum smear microscopy averted more DALYs than IGRAs in 48%.

DISCUSSION:

More than 2 million individuals are diagnosed with active TB every year in India, leading to approximately 300,000 TB-attributed deaths [20] . Although diagnosis and treatment of LTBI is a valid TB control strategy in specific high-risk groups [32], given current resource constraints, national TB programs, including the Indian RNTCP, prioritize treatment of active TB over LTBI. A ban on antibody-based serodiagnostic tests and a provider preference for blood-based rather than sputum-based diagnostics [33] has expanded the market for IGRAs. Indeed, Indian physicians rarely treat LTBI in routine clinical practice [34], but tests for LTBI, including not only IGRAs but also TST, are commonly used [15]. Our analysis shows the likely adverse economic consequences to the healthcare system when IGRAs are utilized to diagnose active TB in areas with high background prevalence of LTBI. Given the growing popularity of IGRAs in other countries such as China, where evidence suggests the tests are also being used to diagnose active TB disease, these economic and healthcare system concerns likely extend to settings beyond India as well [11,12].

Based on the prevalence of LTBI in India's adult population [5] , IGRAs – even with perfect specificity for their designed indication (diagnosis of LTBI) – would be positive in more than 40% of all people without active TB, meaning that for every individual appropriately diagnosed with TB using IGRAs, about 3 individuals would be

falsely diagnosed and subjected to six months of treatment. Treating these individuals for active TB – even in a country with TB treatment costs among the lowest in the world – would cost US$36.1 million (2.1 billion INR) for every 1 million people with TB symptoms. By comparison, appropriate treatment for all individuals in the cohort with MDR-TB – an expense that has, in the past, been argued to be unsupportable by the Indian TB control program – would cost US$7.6 million (440 million INR), and even the use of commercial serology – now banned due to its poor performance – would cost less (US$31.7 million, 1.9 billion INR) and make fewer false-positive diagnoses (75,500 vs. 438,200) than IGRAs [17]. While we did not explicitly model the use of TST for active TB diagnosis in this analysis, these adverse consequences would be similar (though the cost of testing might be less), as neither IGRAs nor TST can distinguish LTBI from active TB disease.

While IGRAs are commercially available and commonly used in the Indian private healthcare sector, research has revealed substantial confusion and inconsistency in the interpretation of IGRAs on the part of healthcare practitioners [30] . A recent survey of Indian pulmonologists, ophthalmologists, and rheumatologists found that 91.9% of those surveyed reported using IGRAs “routinely” or “sometimes” in their practices. This same survey found that, despite the widespread use of IGRAs among those surveyed, more than 80% of those surveyed believed that the test was able to differentiate between latent and active TB, and only 13% believed that the test was mainly intended for diagnosing latent, and not active, TB infection . The main barrier to the use of IGRAs among those surveyed was the higher cost of the test [30]. As this analysis

demonstrates, however, the major cost to the health system of IGRA testing for active TB results from the treatment of the substantial number of false-positive TB patients identified by IGRAs.

In comparison, Xpert MTB/RIF identified a similar number of true positive TB cases as IGRAs (131,700 vs. 132,100), while making considerably fewer false-positive diagnoses (67,500 vs. 438,200). These additional false positive diagnoses by IGRAs represent a misallocation of financial and human-resources, as well as added health risks for individuals wrongly undergoing treatment for active TB. In addition to increased specificity and same-time drug sensitivity testing, Xpert MTB/RIF can provide TB results in as little as an hour, making same-day diagnosis and treatment initiation a possibility. Another significant advantage of Xpert MTB/RIF is the ability to rapidly perform drug susceptibility testing. While accounting for the expense associated with MDR treatment for drug resistant TB cases naturally increases the overall cost of the Xpert MTB/RIF scenario, appropriate, timely treatment of drug-resistant TB is likely cost-saving in the long term through the prevention of secondary MDR TB transmission and a reduction in MDR TB-associated morbidity and mortality. A recent model has explored the optimum implementation strategy to maximize the impact of Xpert MTB/RIF in India [35], and the price of this test has been reduced by nearly 50% in the private sector via an Initiative to Promote Affordable, Quality TB Tests (IPAQT), supported by the Clinton Health Access Initiative [36].

Our analysis has important limitations. By adopting a healthcare perspective, and thereby ignoring the costs of TB treatment borne by patients and their families, or the

erosion of trust in the healthcare system following misdiagnosis, we may underestimate the societal cost of false-positive TB diagnosis. Thus, our estimates of cost-effectiveness may actually be biased in favor of IGRAs compared to a societal analysis. Additionally, we used published data rather than empirical estimates for our parameter values, which often vary considerably and may not be fully generalizable to an Indian context. Nevertheless, our findings were robust to wide parameter variation in sensitivity analysis, and our estimates likely underestimate the cost of false-positive TB diagnosis in healthcare systems where treatment of TB is more costly than in India. Finally, we adopted a simplified model structure that, for example, assumed most people who tested positive for TB completed a full course of treatment, and that providers used IGRA results to diagnose active disease, rather than LTBI. This model therefore does not fully capture the complex dynamics of the system in which TB diagnosis is actually performed.

Improved diagnostics are a critical tool to control TB worldwide, and IGRAs have an important role to play in the diagnosis of LTBI, particularly in low--risk settings. The 2014 WHO guideline on management of LTBI suggests that either TST or an IGRA can be used to test for LTBI in high-income and upper middle-income countries with estimated TB incidence less than 100 per 100 000 [32]. The guideline recommends that IGRA should not replace TST in low-income and other middle-income countries [32]. However, in the setting of severely constrained resources for TB control, it is also important to deploy existing diagnostic tests in a manner that is both responsible and cost-effective. In such settings, tests for LTBI are likely to be most useful and cost-

effective if restricted to select high-risk groups (e.g. child contacts of active TB cases, immunosuppressed populations) in whom test results might feasibly be linked to LTBI treatment, and for whom such treatment offers the greatest clinical benefit [32]. This analysis quantitatively demonstrates that, due to the potential for massive misdiagnosis of individuals with LTBI as active disease, the use of IGRAs to diagnose active TB in high-burden settings is likely to result in tremendous wastage of vital resources, and at substantial loss of health, even relative to insensitive tools such as sputum smear microscopy. The Standards for TB Care in India explicitly discourage the use of IGRAs and TST for active TB diagnosis [13], but greater efforts are necessary to raise awareness about this recommendation among Indian clinicians and laboratorians, and to redirect TB control resources to microbiological tests with known validity for diagnosing active TB.

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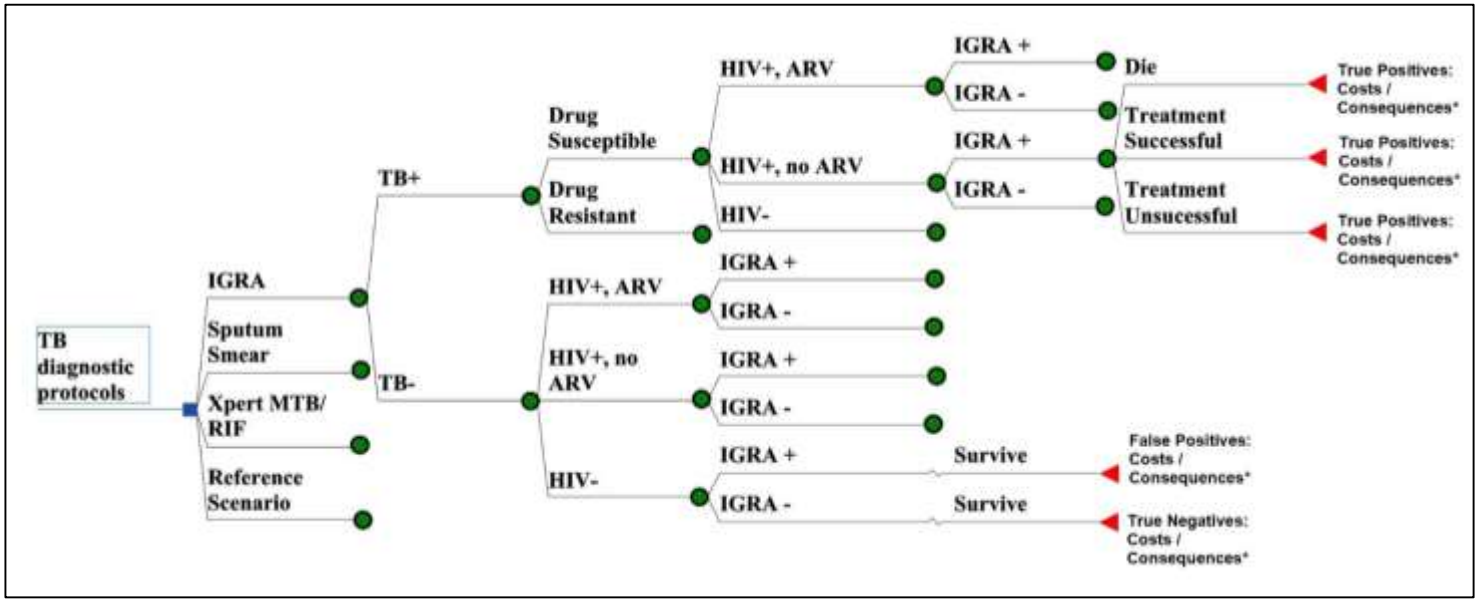
Figure 3.1: Decision Analytic Model for IGRA Testing for Active TB in India

A simplified schematic of the decision analytic model of one million TB suspects in India, with branches for the reference scenario (clinical exam only, no microbiological testing), reference scenario + testing with interferon-gamma release assays ("IGRA"), clinical exam + sputum smear microscopy ("Sputum Smear"), and clinical exam + testing with Xpert MTB/Rif with MDR treatment ("Xpert MTB/RIF"). Differential infectiousness (as denoted by smear status, in the event that a smear could be performed) is incorporated into the model, as are the reference set of tests, but these are not shown for simplicity.



* "Costs" includes the cost of empiric treatment and the cost of the reference test(s), as well as the cost of the microbiological testing and TB treatment (if applicable). The "Xpert MTB/RIF" also includes the cost of MDR-TB treatment. Consequences include deaths, DALYs, secondary cases, false-positives treated, and true positives treated.

Table 3.1: Estimates for Model Parameters

Parameter	Base Value	Range for Sensitivity Analysis	Source
TB Dynamics			
Probability of death, untreated smear-positive TB[1]	0.70	0.50-0.95	[37]
Probability of death, untreated smear-negative TB	0.20	0.15-0.25	[37]
Secondary TB infections per year, smear-positive TB	10	8-12	[38]
Relative infectiousness of smear-negative TB	0.22	0.16-0.28	[39]
Fraction of new TB cases that are smear-positive	0.53	0.40-0.66	[37]
Characteristics of TB diagnosis			
Prevalence of active TB among persons with suspected active TB	0.14	0.11-0.18	[40]
Sensitivity for TB			
Clinician diagnosis[2]	0.53	0.40-0.67	[31]
Sputum smear microscopy	0.53	0.34-0.65	[41]
IGRA[3] (QuantiFERON-TB Gold)	0.84	0.56-0.96	[4]
Xpert MTB/RIF[4] (smear-positive TB)	0.98	0.97-0.99	[18]
Xpert MTB/RIF (smear-negative TB)	0.67	0.58-0.74	[18]
Specificity for active TB[5]			
Clinician diagnosis	0.94	0.75-1.00	[42]
Sputum smear microscopy (two smears)	0.97	0.75-1.00	[43]
Xpert MTB/RIF	0.98	0.97-0.99	[18]
IGRA (QuantiFERON-TB Gold)	0.52	0.41-0.62	[4]
Xpert MTB/RIF Rif resistance			
Sensitivity	0.94	0.87-0.97	[18]
Specificity	0.98	0.97-0.99	[18]
Time to TB diagnosis (days)			
Sputum smear microscopy	7	2.92-14.05	[44,45]
GeneXpert MTB/RIF	7	0.50-14.05	
IGRA (QuantiFERON-TB Gold)	7	2.92-14.05	
Loss to follow-up			
Sputum smear microscopy	0.15	0.11-0.19	[46,47]
Xpert MTB/RIF	0.15	0.11-0.19	
IGRA (QuantiFERON-TB Gold)	0.15	0.11-0.19	[17]
Characteristics of TB treatment			
Proportion of treated TB patients who die	0.045	0.033-0.056	[31]
Proportion of treated HIV[6]/TB patients who die	0.090	0.068-0.114	[31]
Proportion of treated TB patients infections at 1 year	0.045	0.033-0.056	[31]
HIV/TB			
HIV prevalence, general population	0.3%	0.225-0.4%	[48]
HIV prevalence, patients with TB	5.3%	4.0-6.6%	[31]
Proportion of HIV-infected patients with ART[7] access	0.10	0.075-0.125	[48]
Costs and effectiveness, US Dollars (2013)			

Unit cost, independent laboratory			
Sputum smear microscopy (two smears)	$3.00	$1-$5	[24,49]
Xpert MTB/RIF	$25	$20-$57	[50]
IGRA (QuantiFERON®-TB Gold)	$30	$15-$50	[27,30]
Mean cost of treating one case of drug-susceptible TB	$66.00	$50-$75	[31]
Mean cost of treating one case of MDR[8] TB	$2600	$500-$5500	[31]
DALY[9] weights			
Active TB	0.264	0.198-0.330	[51]
TB treatment	0.132	0.099-0.165	[17]
Life expectancy after TB cure (years)	40	30-50	[52,53]

[1] TB, Tuberculosis

[2] In the absence of any TB-specific microbiological test

[3] IGRA, Interferon-Gamma Release Assay

[4] MTB/RIF, *Mycobacterium tuberculosis* and Rifampin Resistance Testing

[5] Excludes studies not performed in developing countries

[6] HIV, Human Immunodeficiency Virus

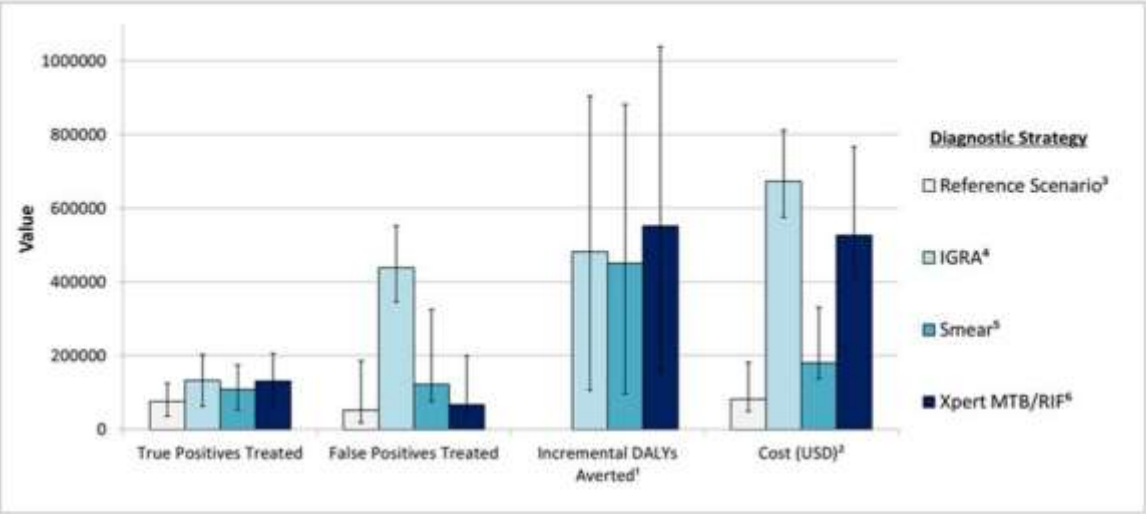
[7] ART, antiretroviral therapy

[8] MDR, Multi-drug resistant

[9] DALY, Disability-Adjusted Life Year

Figure 3.2: Economic and epidemiological outcomes among 1 million adults with TB symptoms in India

Model outcomes, including true positive TB cases treated, false positive cases treated, incremental DALYs averted, and costs (in 2013 US dollars) are presented below for each diagnostic strategy evaluated in the decision-analytic model.



Clinical Diagnosis	Incremental True TB Cases Treated	Incremental False-Positive Cases Treated	Incremental DALYs Averted	Incremental Cost (2013 USD)	Incremental Cost per DALY Averted	Incremental Secondary Cases Averted
Relative to Clinical Exam Only (Includes Chest X-Ray, Physical Exam, etc. No Microbiological Testing)						
Clinical Exam + Sputum Smear Microscopy	32,700	71,100	451,200	9,769,000	22	271,200
Clinical Exam + Gene Xpert	23,300	-55,000	100,600	34,721,100	59	106,900
Clinical Exam + IGRA	400	370,600	-70,400	14,625,000	Dominated	-33,900

[1] Compared to the reference scenario

[2] Costs are in 2013 US Dollars/100

[3] The reference scenario consists of clinical examination only, including chest X-Rays, physical exam, etc. No microbiological testing is considered in the reference scenario

[4] Interferon Gamma Release Assays

[5] Sputum smear microscopy

[6] Gene Xpert testing, including costs for treatment of drug-resistant tuberculosis

Figure 3.3: One-Way and Two-Way Sensitivity Analyses on Parameters Affecting Cost and DALYs Averted

Top) Tornado diagram examining model parameters with the largest impact on the cost of the IGRA testing strategy. Bottom) Tornado diagram examing model parameters with the highest impact on DALYs averted by IGRA testing.

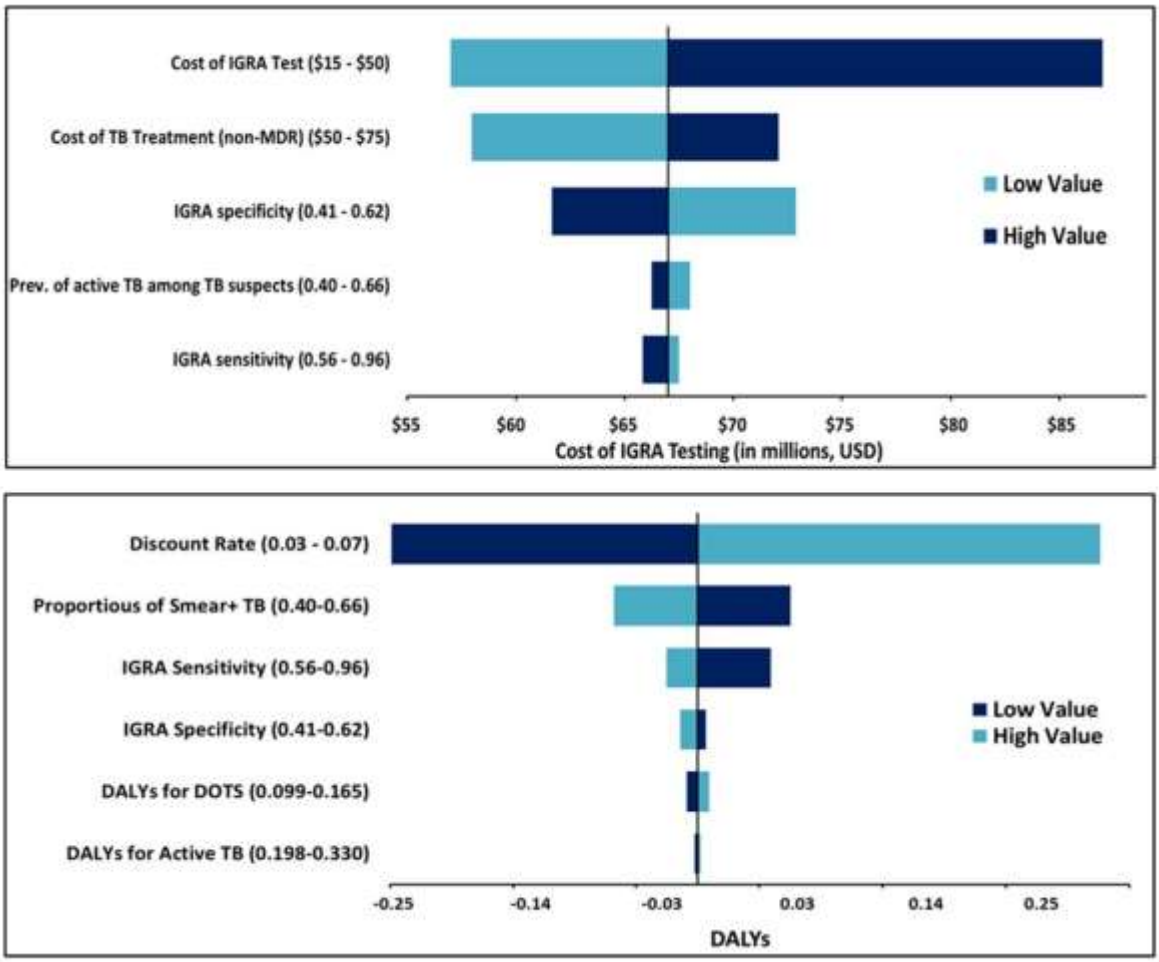
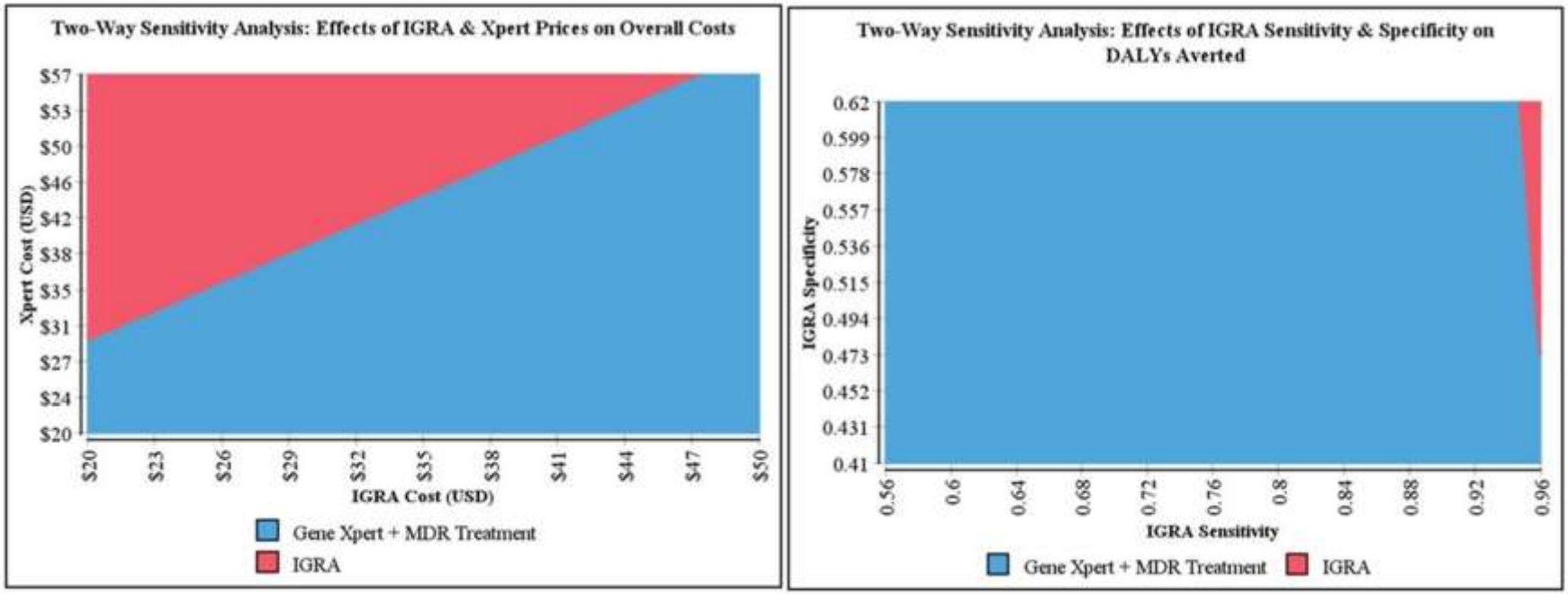


Figure 3.4: Select Two-Way Sensitivity Analyses

Left) Two-way sensitivity analysis of the effects of changes in IGRA sensitivity and specificity parameters within pre-specified ranges on DALYs averted, demostrating the most effective diagnostic strategy, irrespective of cost. Right) Two-way sensitivity analysis of the effects of changes in IGRA and Xpert MTB/Rif prices within pre-specified ranges on the cost of each diagnostic approach, demostrating the least costly diagnostic strategy, irrespective of effectiveness.



S1 File: TreeAge Decision-Analytic Model for IGRA Cost-Effectiveness Analysis in India
This TreeAge .trex file contains the full model and all parameters used for this analysis.

(Copies of this file can be obtained from the open-access journal PLOS ONE by visiting the following link:
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0124525)

S2 File: TreeAge Probabilistic Sensitivity Analysis for IGRA Cost-Effectiveness Analysis in India

This TreeAge .trex file contains the full model and all parameters used in the probabilistic sensitivity analysis.

(Copies of this file can be obtained from the open-access journal PLOS ONE by visiting the following link:
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0124525)

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CHAPTER 4:

PREDICTORS OF ISONIAZID PREVENTIVE THERAPY COMPLETION AMONG ADULTS NEWLY DIAGNOSED WITH HIV IN RURAL MALAWI

CHAPTER 4 INTRODUCTION

While **Chapters 2 and 3** explored TB case finding and the diagnosis or exclusion of TB disease through accurate diagnostics, respectively, TB can also prevented or treated through the use of appropriate therapy. **Chapter 4** explores the prevention portion of the TB case-finding and prevention pathway by looking at the use of isoniazid preventive therapy (IPT) in newly diagnosed HIV patients in rural Malawi. While IPT has been shown to effectively prevent TB reactivation in people living with HIV (PLHIV), preventive therapy has not been widely implemented. Even among those who receive IPT, the preventive therapy is only maximally effective for individuals who complete at least 6 months of treatment. Identification of high-risk individuals (who could benefit from additional support during the therapy period) may help to ensure that all PLHIV initiating IPT accrue the maximum value of the treatment. Boosting IPT completion rates among PLHIV may reduce TB-related morbidity and mortality. It may also benefit the larger community by preventing additional secondary disease transmission and reducing healthcare-associated spending. To inform potential interventions to encourage IPT completion, we sought to identify predictors of IPT-completion (and non-completion) in a cohort of newly diagnosed PLHIV in Malawi.

ABSTRACT

Background: To reduce the risk of TB among people living with HIV (PLHIV), WHO recommends receipt of at least 6 months of isoniazid preventive therapy (IPT) once tuberculosis (TB) disease has been excluded. However, completion of IPT remains a major challenge in resource-limited settings.

Methods: We evaluated predictors of IPT completion (defined as ≥150 daily doses) in newly diagnosed PLHIV recruited from eight rural primary clinics in Malawi, as part of a cluster-randomized trial of TB screening. Predictors of IPT completion were evaluated using a multilevel logistic regression model adjusted for patient characteristics, and random-effects term to account for clustering by clinic.

Results: 974 participants screened negative for active TB and were started on IPT. Overall, 732 (75%) completed ≥150 doses, although 8% of individuals experienced treatment interruptions of at least 2 months. After controlling for potential confounders, participants younger than 25 years (compared to those over 45 years, aOR: 0.33, 95% CI: 0.18-0.60) and males (compared to non-pregnant women, aOR: 0.57, 95% CI: 0.37-0.88) had significantly lower odds of IPT completion. Concomitant receipt of ART, alcohol use, or smoking status were not significantly associated with odds of IPT completion in this cohort.

Conclusions: We found that IPT screening and provision at the time of an initial HIV diagnosis was acceptable in rural Malawi. In our population of adults newly diagnosed with HIV, three-quarters of those who initiated preventive therapy successfully completed six months of IPT. We observed lower odds of completion among men and participants younger than the age of 25. Additional efforts may be needed to ensure IPT completion for men and young people who have been recently diagnosed with HIV.

BACKGROUND:

Tuberculosis (TB) remains a leading cause of death among people living with HIV (PLHIV) worldwide [1]. While antiretroviral therapy (ART) reduces the risk of developing TB disease among HIV-infected individuals through reconstitution of the immune system, the risk of TB activation is still higher among PLHIV than amongst their HIV-uninfected counterparts, especially in the first six months of ART [2]. Treatment with isoniazid preventive therapy (IPT) has been shown to prevent TB disease in PLHIV above and beyond the effects of ART alone, and has also demonstrated a synergistic effect when administered concomitantly with ART [3,4].

Despite longstanding recommendations from the World Health Organization (WHO) that 6 months of IPT should be offered to all PLHIV in which active TB disease is not suspected, global IPT coverage remains low [5]. It is estimated that only 25% of the IPT-eligible individuals in care for their HIV are currently receiving IPT [6]. The time of initial HIV diagnosis represents a frequently missed opportunity to screen individuals for TB and initiate IPT. Once IPT is initiated, PLHIV also face barriers to treatment completion, including stigma, fear of side effects, poor relationships with healthcare providers, transport costs for medication refills, and the challenge of taking medication in the absence of symptoms [7,8]. As global efforts to scale-up IPT coverage continue, strategies to increase treatment adherence and boost rates of IPT completion are simultaneously needed if the global burden of TB among PLHIV is to be reduced.

Providing IPT soon after an HIV diagnosis targets those individuals at highest risk of TB disease (who therefore stand to benefit the most from IPT) and is achievable in routine clinical settings. Identifying those individuals at greatest risk of non-adherence in this setting could inform targeted strategies to provide additional support during treatment, which in turn may boost completion rates and reduce incident TB in this population. While a small number of studies have evaluated predictors of IPT adherence in South Africa [7,9,10], few studies have looked at such predictors in a low-income setting, in the context of providing IPT soon after the first HIV diagnosis. In an effort to inform strategies to improve IPT adherence, we sought to identify predictors of IPT completion among a cohort of recently diagnosed HIV patients in Malawi, a high TB/HIV burden country where IPT scale-up has achieved relatively higher coverage [11].

METHODS:

Study Design

This analysis is nested in a larger randomized clinical trial of TB diagnosis among newly diagnosed PLHIV in rural Malawi (CHEPETSA, clinicaltrials.gov #NCT01450085). Twelve clinics were randomized in three phases (four clinics each) to one of two TB screening algorithms, namely symptom screening plus sputum smear microscopy and symptom screening plus Xpert MTB/RIF (Cepheid, Inc.; Sunnyvale, CA). Individuals in whom active TB disease was excluded were prescribed six months of IPT. Data for this analysis were limited to participants recruited and started on IPT on or before July 1,

2014, and comprise PLHIV from the eight clinics participating in the first two phases of the trial.

Participants were eligible for the study if they were ≥18 years of age, were not taking IPT, on TB treatment, or receiving antiretroviral therapy (ART) in the study clinic at enrollment. Participants were not eligible to participate if they were unable to speak English or Chichewa, had language and/or hearing impairments, were a prisoner, or were unwilling or unable to give informed consent. All participants underwent TB symptom screening, and those who reported one or more TB symptoms received microbiological testing at the point of care, on the day of diagnosis (performed by nurses or clinical staff), using either sputum smear microscopy with light-emitting diode (LED) fluorescence microscopy or Xpert MTB/RIF (Cepheid, Inc, Sunnyvale, CA, USA).

All participants in whom active TB disease had been excluded (either through symptom screening and/or microbiological testing) were screened for IPT eligibility according to routine program criteria [12]. Symptomatic participants in who tested negative for TB disease became eligible for IPT if/when their symptoms resolved, which was determined during subsequent monthly follow-up visits. Participants who had known liver disease, reported excessive alcohol consumption (2 or more times per week, or 3 or more drinks per typical drinking day), or had a history of epilepsy, kidney failure, or severe peripheral neuropathy were considered ineligible; all others were offered IPT. Eligible participants were prescribed six months of IPT, dispensed in monthly or semi-monthly intervals during routine clinic visits. The number of pills dispensed at each visit was documented in the participant's study file and used to track

adherence. ART was initiated after enrollment per the Malawian Ministry of Health's contemporary HIV guidelines [12]; eligibility for ART included WHO Stage 3 or 4 disease, CD4+ T-cell count <350 cells/mm3, or pregnancy/breastfeeding.

Study Procedures

Participants were followed-up during routine visits for HIV-related care every 1-3 months, until one year of follow-up was attained. Study participants who were eligible for IPT were offered 300 mg of isoniazid daily, as well as 25 mg of pyridoxine daily, for six months. Up to 180 doses of IPT in total were dispensed during routine clinical visits, the timing of which was determined by routine clinical guidelines and follow-up appointments, and was not dictated by the study.

Participants receiving IPT also underwent safety monitoring by study nurses to track potential hepatotoxicity, peripheral neuropathy, and other adverse reactions per local guidelines and practice [12]. Before initiating IPT, participants received routine counseling regarding the potential side effects of isoniazid, and were advised to seek treatment immediately if they experienced any of those symptoms. Individuals reporting symptoms of hepatotoxicity underwent blood draws to test bilirubin and transaminase levels.

Participants completed a demographic and clinical history questionnaire at baseline, as well as at each follow-up visit. Questionnaires were completed by trained study staff, and included questions about TB symptoms, possible IPT-related adverse events, ART status, pregnancy, and the number of isoniazid pills dispensed to date.

Tuberculosis symptoms included the presence of one or more of the following: cough, fever, night sweats, or weight loss. The presence of TB symptoms was assessed at enrollment and at each subsequent follow-up visit.

Statistical Methods

Our primary outcome was completion of IPT, which was defined as receipt of ≥ 150 doses of isoniazid, as documented in the participant's study file. Non-completion was defined receiving less than 150 doses of IPT, reasons for which included loss to follow-up, death, IPT cessation by healthcare provider, refusal to continue IPT, reported IPT side effects, incident TB diagnosis, or transfer to another clinic. We examined univariate associations with IPT completion using chi-square or Fisher's exact tests and Wilcoxon-Mann-Whitney tests. We constructed a multilevel logistic regression model to explore the relationship between IPT completion and individual-level and clinic-level predictors including concomitant receipt of ART, age, pregnancy status, IPT side-effects, and alcohol use. Concomitant ART exposure was defined as any self-reported receipt of ART drugs beginning either before, or within 7 days after, IPT initiation. We incorporated a random effects term to account for clustering at the clinic level. Variables that reached a significance of $p<0.1$ in the univariate analysis, or that were considered to be of epidemiological significance a priori, were considered for the multivariate model. Additionally we performed a time-to-non-completion survival analysis, stratified by key exposure variables identified in the analysis above. Time to non-completion was defined as days from IPT initiation to the date of the clinic visit

where the participant received his/her last IPT dosages. All analyses were performed in Stata 12 (Stata Corp., College Station, USA).

Ethical Considerations

This study was approved by the Malawi University College of Medicine Research Ethics Committee and the Johns Hopkins University School of Medicine Institutional Review Board. All study participants provided individual written informed consent before study participation.

RESULTS:

A total of 1,359 participants were enrolled (**Figure 4.1**) across 8 study clinics, for an average of 122 participants per clinic (range: 47-199) (data not shown). During screening, 504 (37%) participants reported one or more symptoms of TB (cough, fever, night sweats and/or weight loss) and received microbiological testing for active TB disease with either sputum smear microscopy or Xpert MTB/RIF. Of those tested, 27 (5%) had active TB and were thus ineligible for IPT. Of the 477 symptomatic individuals testing negative for TB disease, 253 (53%) returned for IPT eligibility screening. Altogether 1,106 participants were screened for IPT eligibility either at ART initiation or a subsequent visit (253 symptomatic TB-negative participants, and 853 asymptomatic participants). Of these, 95 (9%) failed to meet the IPT eligibility criteria, and 984 (89%) were started on preventive therapy by the pre-specified analysis close date. Only one

(0.09%) IPT-eligible individual in our study refused to initiate preventive therapy. Ten participants were subsequently excluded from this analysis because they were missing IPT outcome data.

Participants in our study were majority female (n=650, 67%) and had a median age of 33 (interquartile range [IQR]: 27-40) (**Table 4.1**). Male participants were significantly older than their female counterparts (38.1 vs. 32.4 years, p<0.001) (data not shown). Most participants reported being in "Good" or "Fair" health at enrollment (n=788, 81%), and were classified as WHO HIV Stage I or II (n=794, 82%) at the time of their HIV diagnosis. Individuals in our sample completed a median of 6 (IQR: 4-7) routine clinical follow-up visits during the study period. Concomitant ART exposure was relatively uncommon in our cohort (n=152, 16%), though the majority of participants reported initiating ART at some point during the IPT treatment period (n=670, 69%). Among those initiating IPT, the most (n=770, 79%) reported never drinking. Both smoking (39% vs. 4%, p<0.001) and alcohol use (51% versus 6%, p<0.001) were significantly more common among men than women in our study population (data not shown). IPT interruptions were relatively uncommon during the study; approximately 8% (n=82) of the sample experienced an interruption in treatment of 2 months or more.

The majority of participants initiating IPT completed treatment (n=732, 75%), though completion rates varied significantly across the 8 study sites (range: 57-90%, p < 0.001) (data not shown). Most non-completers stopped IPT due to treatment cessation/failure to return for follow-up (n=198, 82%), but other reasons for non-completion included transfer to another health facility for treatment (n=18, 7%), death

(n=10, 4%), refusal to continue treatment (n=7, 3%), side effects of treatment (n=6, 2%), incident TB disease (n=2, 1%), or a healthcare provider's decision to stop treatment (n=1, 0.4%). Individuals completing IPT received a median of 177 doses (IQR: 167-200), while non-completers stopped treatment after a median of 58 doses (IQR: 28-139).

Compared to non-completers, those who completed IPT were older (median age 34 vs. 31 years, p<0.001), had completed more follow-up visits (median 6 vs. 1, p<0.001), and were less likely to have experienced a prolonged treatment interruption (7% vs. 13%, p=0.01). IPT completers did not differ from non-completers in terms of self-reported general health, WHO HIV stage, or the presence of TB symptoms at enrollment. Rates of completion were highest among non-pregnant women above the age of 25 (82%, 95% CI: 78-86%), and lowest among young, non-pregnant women (63%, 95% CI: 53-73%) and young pregnant women (64%, 95% CI: 54-74%) (**Figure 4.2**).

Multilevel Model & Survival Analysis

After multivariate adjustment, age less than 25 (compared to age > 45, aOR: 0.33, 95% CI: 0.18-0.60) and male sex (compared to non-pregnant females: aOR: 0.57, 95% CI: 0.37-0.88) were significantly associated with worse IPT completion rates (**Table 4.2**). Though it did not reach statistical significance after adjustment, pregnant women had lower odds of IPT completion than non-pregnant women (aOR: 0.83, 95% CI: 0.55-1.27). Despite the fact that younger age appeared to reduce the rate of IPT completion among both pregnant and non-pregnant women more than it did among men, we did not find statistically significant evidence of an interaction between age and sex (data not

shown). Concomitant exposure to ART, self-reported alcohol use, being a current or former smoker, or reporting any TB symptoms at baseline were not significantly associated with IPT completion in our model. Survival analysis of time-to-IPT-non-completion illustrates the higher probability of treatment non-completion among participants younger than 25 years of age compared to their older counterparts (**Figure 4.3**), a difference that was statistically significant (Log-rank test p-value: 0.001).

DISCUSSION:

We found high rates of IPT completion in this cohort of newly diagnosed PLHIV in rural Malawi. Our results indicate that IPT completion among newly diagnosed PLHIV can be reasonably high even under operational conditions in rural, low-income settings. Given that over 99% of the IPT-eligible participants in our study initiated preventive therapy, it appears that IPT eligibility screening at the time of an initial HIV diagnosis is acceptable to patients in this setting. In our study population older age and being a non-pregnant female significantly increased the odds of IPT completion. While concomitant receipt of ART was not significantly associated with increased odds of IPT completion, most of our study participants did initiate ART during the preventive treatment period. Our findings suggest that point-of-HIV-diagnosis TB screening and IPT initiation may be an effective strategy to reduce the TB burden in newly diagnosed PLHIV, especially in the high-risk period immediately preceding and following ART initiation.

Our findings are supported by other findings from the published literature. Earlier studies conducted in high TB/HIV burden settings [13–17] have found similarly high rates of IPT completion. A previous meta-analysis on interventions to improve IPT adherence also suggests that TB/HIV integration may boost IPT completion rates [18]. These findings further support our conclusion that the initial HIV diagnosis represents an opportunity to screen HIV-infected individuals for TB and (for those who are eligible) to initiate IPT, as well as an effective strategy for further integration of HIV/TB programs.

While overall IPT completion was high in our study, several sub-groups had significantly lower rates. We found that individuals who were younger than 25 were significantly less likely to complete IPT than their older counterparts. Previous work from Tanzania [16] and Uganda [19] also found that younger age was associated with an increased risk of treatment non-completion among HIV-infected individuals on IPT, however, the reasons for this are unclear. Younger participants in our study tended to be healthier at baseline, and were less likely to have initiated ART during follow-up, potentially making it harder to adhere to IPT in the absence of any symptoms [7], or with the support of ongoing clinic visits to obtain antiretroviral drugs. A better understanding of the particular barriers to preventive treatment completion faced by young HIV-infected individuals is still needed, as are evidence-based interventions to address them.

While the IPT completion rates among pregnant women observed in this study were similar to rates observed in other studies conducted in low-resource settings [20], compared to their non-pregnant counterparts, women diagnosed with HIV through

antenatal care still had decreased odds of IPT completion (though this did not reach statistical significance after adjustment). WHO guidelines for the treatment of tuberculosis recommend the integration of TB prevention and treatment into existing antenatal care and prevention of mother-to-child HIV transmission programs [21]. However, integration remains a challenge in many settings, and results in low rates of IPT initiation among pregnant women [22,23]. Compared to non-pregnant women, men also had significantly lower rates of IPT completion in our study.

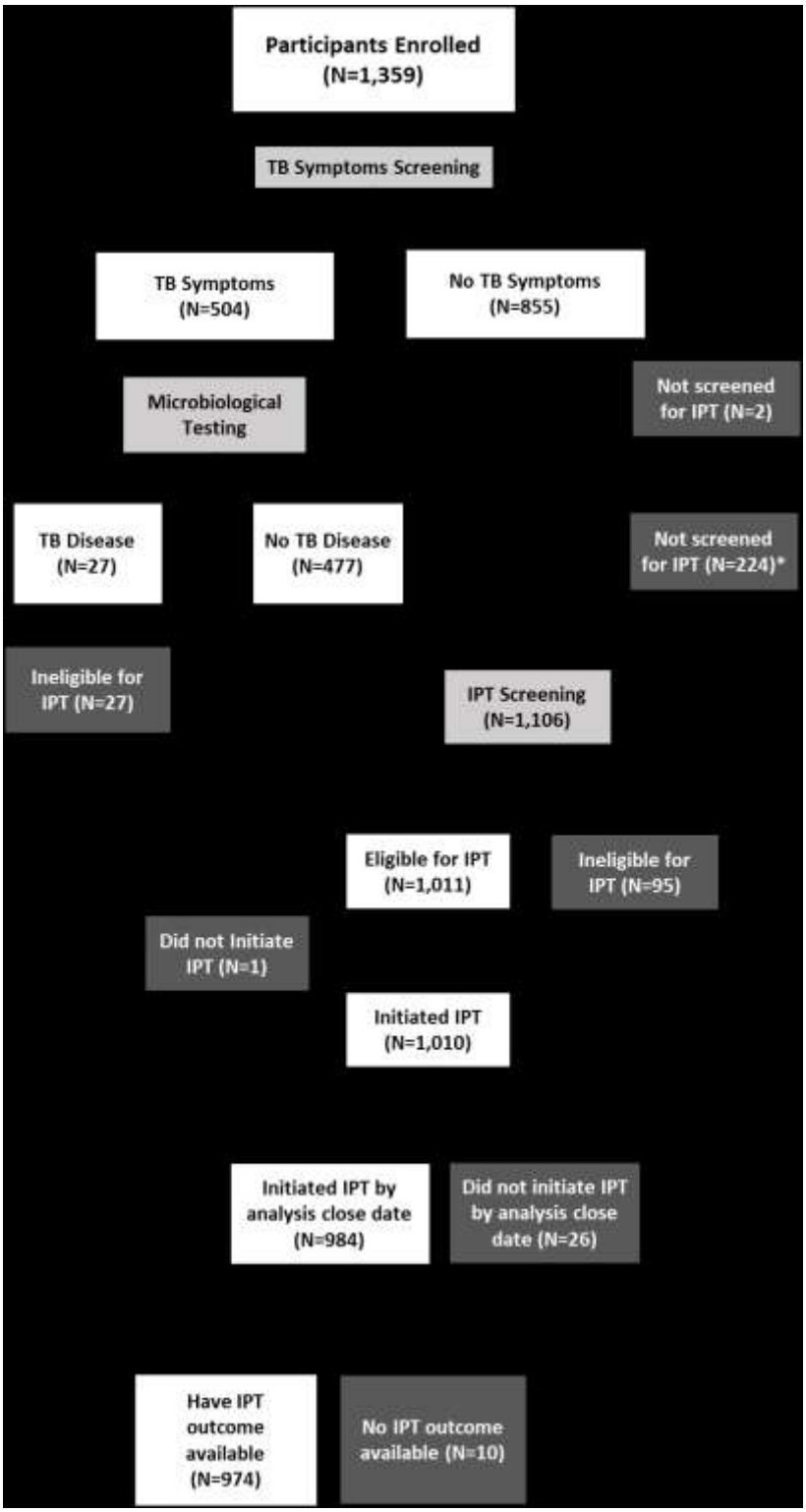
Unlike previous studies, we did not find a significant relationship between alcohol or tobacco use and IPT completion [14]. Both current/former smoking and any alcohol use were associated with small, non-significant reductions in the odds of IPT completion. It is possible that we did not observe a negative relationship between alcohol use and IPT completion given that moderate to heavy drinkers were not eligible for IPT in our study. Alternatively, alcohol and tobacco use may be weaker indicators of individuals who will have difficulty with treatment adherence in a rural, low income area than in other settings.

As with any observational study, this research has certain limitations. Measurement of IPT completion status was based on the number of IPT doses dispensed during routine study visits rather than any objective measure (e.g., urine metabolites). Nevertheless, self-reported and/or pill count adherence correlates reasonably well with other measures of adherence [25–27], and from a pragmatic perspective, it is unlikely that adherence will be measured in any other fashion in the field. While we captured the variables that are most likely to be programmatically

accessible, we were unable to measure all potential predictors of adherence, including clinic-level variables that appeared to have strong influence. Future research could more fully evaluate a wider range of associations with IPT adherence, and could also consider study of potential interventions to improve adherence in those at greatest risk of non-completion.

In conclusion, we found that – in this population of over 1,000 rural Malawian adults who were routinely screened for TB soon after a new HIV diagnosis – completion of preventive therapy for tuberculosis was high. These findings support the use of point-of-HIV-diagnosis screening for active TB, followed by immediate IPT initiation for eligible individuals. Our observed predictors of IPT non-completion highlight the importance of additional efforts to support younger patients and men. Ultimately, stronger systems to provide IPT at the point of HIV diagnosis, coupled with research to identify and overcome barriers faced by populations at high risk of non-completion, can help to expand the benefits of TB prevention among PLHIV in rural high-burden, low-income settings.

Figure 4.1: Screening and IPT Initiation



**224 individuals who had TB symptoms at enrollment and received microbiological testing for TB disease were not able to be screened for IPT eligibility, either because their TB symptoms did not resolve, or they did not present for additional follow-up*

Table 4.1: Patient-level clinical and demographic characteristics, by IPT completion status

Baseline Variables	Completed IPT (N=732)	Did Not Complete IPT (N=242)	Total (N=974)	P-value
	N (%)	N (%)	N (%)	
Age Category				
18-25	132 (18.0)	72 (29.8)	204 (20.9)	**0.001**
26-35	296 (40.4)	87 (36.0)	383 (39.3)	
36-45	204 (27.9)	58 (24.0)	262 (26.9)	
>45	100 (13.7)	25 (10.3)	125 (12.8)	
Sex/Pregnancy Status				
Pregnant female	151 (20.6)	60 (28.4)	211 (21.7)	0.133
Non-pregnant female	343 (46.9)	96 (39.7)	439 (45.1)	
Male	238 (32.5)	86 (35.5)	324 (33.3)	
Self-Reported Health				
Excellent	100 (13.7)	31 (12.8)	131 (13.5)	0.827
Good	368 (50.3)	125 (51.7)	493 (50.6)	
Fair	225 (30.7)	70 (28.9)	295 (30.3)	
Poor	39 (5.3)	16 (6.6)	55 (5.7)	
WHO HIV Stage*				
1 or 2	599 (82.4)	195 (81.3)	794 (82.1)	0.689
3 or 4	128 (17.6)	45 (18.8)	173 (17.9)	
Previous History of TB	10 (1.4)	3 (1.2)	13 (1.3)	1.0‡
Any TB Symptoms at Enrollment	164 (22.4)	40 (16.5)	204 (20.9)	0.052
Concurrent ART Exposure	122 (16.7)	30 (12.4)	152 (15.6)	0.113
Eligible for ART at Enrollment	355 (48.8)	117 (48.8)	472 (48.8)	0.983
Number of Follow-Up Visits (Median, IQR)	**6 (5-7)**	**1 (0-3)**	**6 (4-7)**	**<0.001**
Experienced IPT Side-Effects during Follow-Up	6 (0.8)	3 (1.7)	9 (1.0)	0.389‡
Hospitalized during Follow-Up	36 (4.9)	7 (3.9)	43 (4.7)	0.696‡
Experienced an IPT interruption of >2 months	**52 (7.1)**	**30 (12.5)**	**82 (8.4)**	**0.010**
Current/Former Smoker	112 (15.3)	42 (17.4)	154 (15.8)	0.448
Any Alcohol Use	147 (20.1)	57 (23.6)	204 (20.9)	0.250

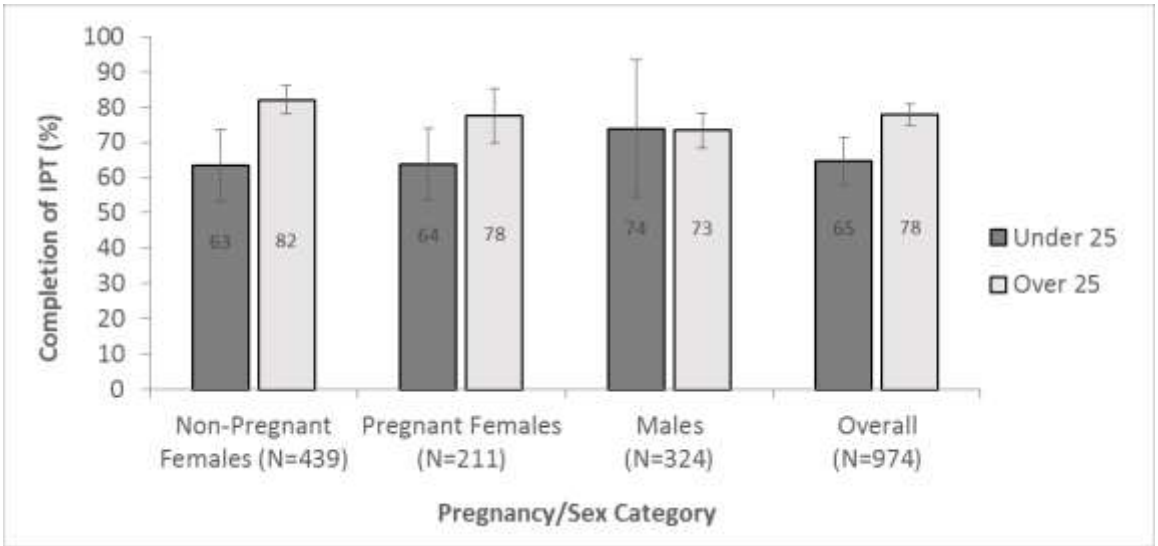
† P-value obtained from a two sample Wilcoxon rank-sum test

‡ P-value obtained from a Fisher's exact test

** 7 individuals were missing WHO stage classification*

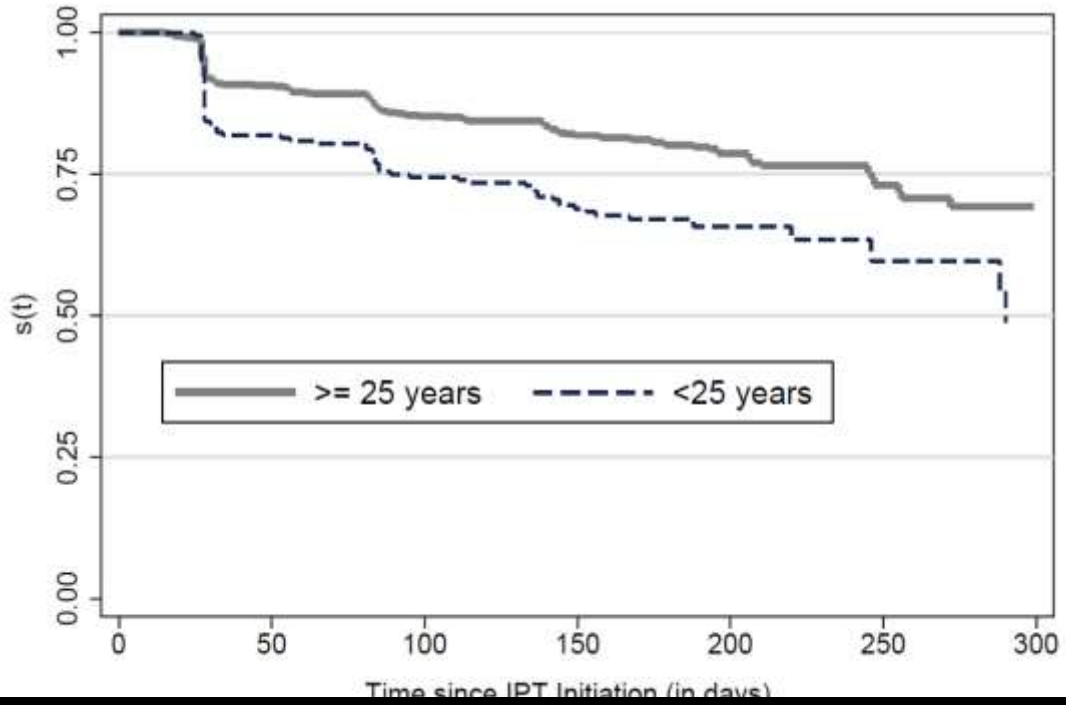
*** 5 individuals were missing ART eligibility because of missing CD4 cell counts and missing WHO stage*

Figure 4.2: IPT Completion Rates by Age Category and Sex/Pregnancy Status



Error bars indicate 95% Confidence Intervals around estimates. Isoniazid Preventive Therapy (IPT) completion was higher in the older age category, and lowest among young women, regardless of pregnancy status.

Figure 4.3: IPT Non-Completion Survival Curve, Time to non-completion of Isoniazid Preventive Therapy Stratified by Age



[redacted]

Shown are the Kaplan-Meier curves describing the time from IPT initiation to the date at which the participant either completed IPT (received the last dose), or was censored (due to treatment default, death , refusal of further treatment, IPT stopped by doctor, side effects, TB diagnosis, or transfer out of the clinic area), according to whether participants were older or younger than 25 years of age.

Table 4.2: Univariate and Multivariate Models for IPT Completion*

Baseline Variables	Unadjusted		Adjusted**	
	OR	**95% CI**	**aOR**	**95% CI**
Age Category				
18-25	**0.37**	**(0.21-0.64)**	**0.33**	**(0.18-0.60)**
26-35	0.80	(0.48-1.35)	0.78	(0.46-1.33)
36-45	0.84	(0.49-1.45)	0.85	(0.49-1.47)
>45	Ref	Ref	Ref	Ref
Sex/Pregnancy Status				
Female, not pregnant	Ref	Ref	Ref	Ref
Female, pregnant	**0.66**	**(0.44-0.98)**	0.86	(0.56-1.31)
Male	**0.69**	**(0.49-0.99)**	**0.57**	**(0.37-0.88)**
Any TB Symptoms at Enrollment	1.25	(0.82-1.89)	1.09	(0.55-2.19)
Concurrent ART Exposure	1.27	(0.80-2.00)	1.08	(0.70-1.72)
Experienced an IPT Interruption of >2 months	**0.53**	**(0.32-0.88)**	--	--
Any Alcohol Use	0.96	(0.67-1.39)	1.09	(0.70-1.72)
Current/Former Smoker	0.90	(0.60-1.36)	1.01	(0.62-1.63)

**Multilevel logistic models of IPT completion with clinic-level random intercept*
*** Model adjusted for age (over/under 25 years), sex/pregnancy status, the presence of TB symptoms at enrollment, concurrent ART exposure, any alcohol use, and current/former smoking status.*

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CHAPTER 5:

CONCLUSIONS

SUMMARY OF RESULTS:

Meeting ambitious global TB control goals, especially in high-burden settings, will require efficient, effective interventions targeting each stage of the TB case-finding and prevention pathway. The impact and relative cost-effectiveness of these interventions in a given location, however, will depend on a number of setting-specific factors including patient and community resources, awareness and concern over TB, underlying risk of TB acquisition and progression, transportation cost and availability, cost and availability of healthcare, TB/HIV-related stigma, among other factors. Research to identify context-specific barriers, and efficient TB-control interventions that take them into account, is vital to further reductions in TB related morbidity and mortality.

Our research found that active contact tracing—specifically household contact tracing—for TB was feasibly implemented in a rural South African setting. Our household contact tracing intervention found a high proportion of previously undiagnosed TB among household contacts (household prevalence: 3.9% (95% CI: 2.0-6.9%)) and a yield of 8.5 (95% CI: 4.2-15.1) new TB cases per 100 index cases traced. These findings were qualitatively comparable to the findings of a similarly-structured intervention carried out in Klerksdorp, an urban/peri-urban area in South Africa with a much higher population-level prevalence of TB [1].

The majority of household contacts with previously undiagnosed TB disease were smear negative, culture positive (10/11, 91%), and most (9/11, 82%) were

asymptomatic. In our multivariable, multilevel logistic regression model, factors significantly associated with active TB among household contacts included living in a female-headed household (aOR: 5.19, 95% CI: 1.06-25.44), and having more than a high school education (aOR: 6.88, 95% CI: 1.19-39.66). Female sex, age, household income, employment status, and symptom duration were not significantly associated with increased odds of previously undiagnosed TB among household contacts.

Accurate identification of TB cases through diagnostic testing of TB suspects is the next step on the TB case-finding and prevention pathway. For **Aim 2** we evaluated the incremental cost-effectiveness of a base-case scenario of empirical diagnosis (with no microbiological testing) to scenarios in which this base-case was augmented by the addition of either sputum smear microscopy, Xpert testing (with and without the additional cost of treating drug resistant TB cases identified by this test), and interferon-γ release assays (IGRAs). We evaluated the cost-effectiveness of IGRAs from the perspective of the Indian TB control sector in a hypothetical cohort of 1 million adult Indian TB suspects.

Because of IGRAs' poor specificity for active TB in settings with high background rates of latent TB infection (LTBI), the use of IGRAs in an Indian context would result in tremendous over-diagnosis of active TB. In fact, the use of IGRAs in a setting like India would result in approximately 3 additional false-positive active TB diagnoses for every additional individual correctly diagnosed. We estimated that, relative to sputum smear microscopy, the use of IGRAs this hypothetical cohort of Indian TB suspects would generate over 315,000 false-positive active TB diagnoses and result in nearly US$50

million in additional healthcare expenditures for every million patients tested in this fashion. Over 40% of the incremental cost of IGRAs compared to smear would be due to the expense of unnecessarily treating individuals with LTBI for active TB disease. This amount dwarfs the estimated US$7.6 million it would cost to treat all individuals in the cohort for multidrug resistant TB (MDR-TB), an expense that the Indian TB control program in the past has argued is unsupportable.

Once a diagnosis of active TB has been made or excluded, the next step of the pathway is appropriate preventive or curative treatment. For individuals at high risk of TB, such as people living with HIV (PLHIV), if active TB is not suspected, six months of treatment with isoniazid preventive therapy (IPT) is recommended [2]. While coverage rates remain low globally [3], IPT has been shown to reduce the risk of TB reactivation in PLHIV, above and beyond the effects of antiretroviral therapy (ART) alone, and can be effective in preventing TB disease in the high-risk months immediately before and after ART initiation [4,5]. For individuals who do begin IPT, treatment completion can be hindered by a number of factors, including distance to health facility, HIV and TB stigma, and transport costs (among others) [6–9].

For **Aim 3** we explored predictors of IPT completion among adults newly diagnosed with HIV in rural Malawi in the hopes of identifying sub-populations at risk of treatment non-completion who may benefit from added support during IPT. Of the 973 participants who started IPT (and in whom active TB disease had been excluded), just over 75% completed their course of treatment (732/973), defined as receipt of ≥150 doses. After adjusting for confounders and including a random effects term to adjust

for clinic-level clustering, male sex (compared to non-pregnant females, aOR: 0.57, 95% CI: 0.37-0.88) and age less than 25 (compared to age >45, aOR: 0.33, 95% CI: 0.18-0.60) were associated with reduced odds of IPT completion in this population of newly diagnosed adult PLHIV in rural Malawi. Though it was not statistically significant, pregnant women had lower odds of IPT completion than non-pregnant women in our study (aOR: 0.86, 95% CI: 0.56-1.31). Concomitant receipt of ART, the presence of self-reported TB symptoms, alcohol use, and smoking status were not significantly associated with IPT completion in our model.

STRENGTHS AND LIMITATIONS:

These analyses were subject to a number of important limitations. As a pilot study, the household contact tracing intervention (in **Aim 1**) included a relatively small sample size (130 households comprising 282 household contacts), which limited our power and ability to identify important differences between household contacts with and without active TB disease. Low clinic volumes, large distances between clinics, a small study team, and difficult road conditions meant that recruitment proceeded more slowly than expected. (Approximately 13 index cases and 28 household contacts were recruited per study month.) While this was an important finding in terms of the feasibility and challenges associated with implementing a similar intervention in this context, these barriers resulted in a smaller overall sample size than originally intended. Similarly, due to budget constraints, HIV status was ascertained via self-report, rather

than via rapid tests performed during the household visits. Self-reported HIV status likely underestimates the true prevalence of HIV among household contacts, which is problematic given the strong association between HIV status and TB disease. Future research will include point-of-contact HIV testing during household tracing visits to better assess the acceptability, yield, and cost-effectiveness of this approach.

Finally, for purposes of comparability to a similarly-designed contact tracing intervention conducted in a high TB burden urban/peri-urban in South Africa [1], we diagnosed individuals with active TB based on sputum smear microscopy and culture results. While the more sensitive culture testing proved necessary to identify smear-negative/culture-positive cases of TB in our study population, this TB diagnostic can take 4-6 weeks for results to be made available, does not provide same-time drug sensitivity results, and (at least in our setting) resulted in a relatively high number of non-tuberculosis mycobacterium infections that tested culture positive and required speciation. Future research will consider the cost-effectiveness of more rapid and sensitive diagnostic options such as Xpert MTB/RIF (a sputum-based molecular test for TB that can yield results in as little as two hours).

When comparing the cost-effectiveness of several microbiological tests for TB in a hypothetical cohort of Indian adult TB suspects (in **Aim 2**), we did so from the perspective of the Indian healthcare sector, rather than a societal perspective. Analysis from a societal perspective would have accounted for transport, TB testing, and TB treatment costs that are borne by patients and their families. This would include the excess costs generated by false-positive diagnoses, which may have biased our analysis

in favor of IGRAs by underestimating the societal costs of false-positive diagnoses. Because IGRAs are most commonly used in the Indian private sector, where patients (and not the TB control program) bear the testing and treatment costs, the use of an expensive diagnostic with a low specificity is particularly problematic. In performing this analysis we constructed a relatively simple model that did not include a number of factors that might influence the cost-effectiveness of TB diagnostics as used in the real world. For example, we did not explore the impact of LTBI, or the use of IGRAs to diagnosed LTBI, and we assumed that individuals who initiated treatment completed their treatment.

Additionally, the data used to inform our model were based on published estimates, which may not completely represent true parameter values in an Indian context. The model may be biased if the parameter values used to populate it are themselves biased, which is a known limitation of cost-effectiveness analysis more generally. Finally, because India's TB epidemic is not driven by a high prevalence of HIV infection, these results may not be generalizable to other high TB-burden settings (such as sub-Saharan Africa), where rates of HIV are higher, or the use of IGRAs may be less widespread.

When evaluating predictors of IPT completion among a cohort of newly diagnosed people living with HIV (PLHIV) in rural Malawi, our outcome (IPT completion) was defined as the receipt of ≥150 doses of IPT at the clinic. We were unable to include a more objective measure of adherence, such as isoniazid urine metabolites [10], and did not collect self-reported preventive treatment adherence in our questionnaire.

While previous studies have found reasonable correlation between the number of pills dispensed, patient self-report, and other objective measures of adherence [11–13], it is possible that we over-estimated the proportion of individuals completing IPT in our study. We collected information on a number of self-reported patient demographic and clinical characteristics, but we may have omitted important predictors of IPT completion. We did not have information on participant SES, distance from the health facility, cost of transport from their home to the health facility, knowledge and beliefs about TB, TB/HIV stigma, or perceived barriers to treatment completion. These factors (and others) may play important roles in the likelihood of treatment completion for PLHIV in this setting, and should be explored further in future research. Clinic level factors, such as size, patient volume, wait times, staff/patient relations, and facility qualities, may also impact IPT completion and deserve further exploration.

PUBLIC HEALTH IMPORTANCE:

Analysis of the impact and potential cost-effectiveness of interventions targeting three different stages of the TB case-finding and prevention pathway may provide additional data for decision makers in rural, high TB burden settings. For **Aim 1**, our findings suggest that high yields may be obtained from contact tracing, even in settings of moderate background TB transmission, and that household may be an important site of TB acquisition and exposure in these contexts. The majority of household contacts

diagnosed with TB disease in our study were culture positive/smear negative, suggesting that household contact tracing can be an effective approach to identifying additional TB cases (assuming that the diagnostic test used is of sufficient sensitivity). If successful in identifying cases, systematic screening could also lead to initiating treatment earlier in the disease course than passive case detection methods alone. Given that care-seeking delays averaging a year more have been documented globally [14], preventing further household and community-level TB transmission by reducing the time between symptom onset and treatment initiation through ACF interventions could be important.

While identification of undiagnosed TB cases among household members is a crucial first step, diagnosis without treatment represents a substantial waste of scarce TB control resources (while also failing to prevent ongoing TB transmission in the community as well as TB-related morbidity and mortality). Encouragingly, 100% (11/11) of household contacts who were diagnosed with TB disease in our study presented to health facilities to receive TB treatment within 30 days of their diagnosis. Though these numbers are small, they represent a proof of concept that household-based TB diagnoses can be effectively translated into TB treatment initiation under real-world conditions.

Despite the number of household contacts diagnosed with TB and linked to care, the relative cost-effectiveness of household contact tracing in rural, high-burden settings remains to be seen. Our results indicate that less expensive diagnostic options such as sputum smear microscopy, which cost approximately $2 per test in South Africa [15], were not sensitive enough to identify TB cases in this population. Given that only 1

individual was smear positive in our study, the use of smear microscopy alone, though less costly than diagnostic options such as culture or Xpert MTB/RIF, would have resulted in our missing over 90% of the active TB cases found among household contacts. Other studies have also reduced expenses and testing burden by performing symptom screening to identify the household contacts at highest risk of TB disease [16], and therefore most likely to benefit from microbiological testing. However, had we performed even the most general symptom screening (the presence of any cough, fever, or night sweats) before performing diagnostic testing, we would have only identified 2 new (culture positive) TB cases (18% of all true cases), while still testing an additional 120 individuals without active TB. While larger studies should be performed to confirm this, our findings suggest that symptom screening before diagnostic testing may miss a substantial portion of TB cases among household contacts, especially those early in the disease course who may be smear negative, but culture positive. Further analysis of our outcome and cost data will help to answer the incremental cost-effectiveness of each of these approaches to household contact tracing. Future research will also explore the cost-effectiveness of sensitive diagnostic methods such as Xpert compared to smear and/or culture. Though more research is needed, our results suggest that active case-finding interventions should be seriously considered in high burden settings, including in rural areas, in an effort to control TB. Our findings are also consistent with the limited number of other active case-finding interventions conducted in rural areas [16,17], which found high rates of previously undiagnosed TB and HIV, and had good success with the integration of TB and HIV testing in this high-risk population.

While household contact tracing in this setting found a high prevalence of previously undiagnosed TB among household contacts of newly diagnosed TB patients, the intervention was not without its challenges. Transportation infrastructure, including roads and household addresses, was limited in many parts of Vhembe District (Limpopo Province) where our study took place. Unpaved roads, of which there were many, became nearly impassable during the rainy season, frequently requiring the study team to reschedule visits or walk long distances to reach index case homes. Long distances between health facilities and households also presented a challenge, and meant that the study team could only visit a small number of homes each day. Together these factors likely contributed substantially to the slow rate of recruitment (Roughly 13 households visited per month) and relatively higher costs than were observed in the Klerksdorp study (data not shown). These findings are also important for policy makers and implementers to consider when setting budgets and planning interventions, and may have substantial impact on the reach and cost-effectiveness of contact tracing in rural areas.

In **Aim 2** we found that the use of IGRAs in India as a diagnostic for active TB disease would be substantially less cost-effective than more appropriate diagnostic options such as Xpert MTB/RIF or sputum smear microscopy. This was due primarily to IGRAs poor specificity for active TB in a setting with high background rates of latent TB, as the test cannot distinguish between LTBI and active TB disease. While the WHO does not recommend IGRAs as a test for active TB disease, or recommend the use of IGRAs as a tuberculin skin test replacement in low- and middle-income countries [18], evidence

suggests these tests are being used increasingly in countries such as China and India [19]. This is especially true in the private sector, where awareness of guidelines for TB diagnosis and treatment may be lower, and training/oversight more limited.

In 2012 India banned the use serological tests for TB, another TB diagnostic that was widely—though incorrectly—used in the private sector to diagnose active TB disease [20]. Though the ban prevents serological test kits from being imported into India, several companies continue to manufacture the tests within India, and evidence suggests that the tests are still routinely recommended by private sector healthcare providers [21]. Concerns are mounting that IGRAs are also being routinely used by private sector providers to diagnose active TB disease, especially among children who may have difficulty producing the sputum necessary for tests such as smear microscopy or Xpert MTB/RIF. There is worry that the use of IGRAs have increased in the wake of the ban on serological tests in India.

In addition to raising concerns that IGRAs have filled the void created by bans on serological tests for TB, our findings also raise concerns about the quality of TB diagnosis and treatment available in the Indian private sector, where 80% of all TB cases receive testing and as many as 50% receive treatment for their TB [22]. Our analysis indicates that widespread use of IGRAs in India would result in considerable wastage of healthcare resources, in addition to negative impacts on the health and safety of TB suspects wrongly diagnosed and treated for active TB. Better guidance and training (as well as oversight) may be necessary to ensure proper TB diagnostic and treatment algorithms are followed in the private sector. This is especially true for IGRAs, which

continue to be used incorrectly as a test for active TB. Additional efforts to educate practitioners on TB care standards—including the appropriate use of IGRAs in this context—should be carried out.

Our results provide quantitative data to better illustrate the deleterious effects of continued use of IGRAs for the diagnosis of active TB in India and other settings with high rates of LTBI, and may help bolster outreach and educational efforts to discourage off-label IGRA usage. Providing cost-effectiveness data on IGRA usage may also help to highlight the potential human and financial costs of ignoring this issue in India and other similar settings.

For **Aim 3** we looked at predictors of IPT completion among a cohort of newly diagnosed PLHIV in rural Malawi. Newly diagnosed individuals were immediately screened for TB using a combination of symptom screening and (if TB symptoms were present) microbiological testing. Those individuals with no indication of active TB were then screened for IPT eligibility. Though the cost-effectiveness of this approach has not yet been assessed, our findings indicate high levels of acceptability of this approach among participants. The vast majority of IPT-eligible individuals initiated treatment, suggesting that the first HIV diagnosis is an ideal time in which to screen for TB and assess IPT eligibility. This strategy is relatively simple to implement, and would be a further step towards fully integrating TB and HIV care in high dual-burden settings.

As IPT initiation rates continue to increase under WHO's scale up of the "Three Is for TB/HIV" initiative, ensuring treatment adherence will become increasingly

important. Our study found high treatment adherence among study participants initiating IPT soon after their first HIV diagnosis. Though adherence was based on self-report, and not direct observation or other objective measurement (and therefore may be an over-estimation), these rates were observed when IPT was administered in a routine clinical setting. These conditions are similar to real-world scenarios in which individuals are diagnosed with HIV in a clinical setting, assessed for active TB, and (if eligible) started on IPT immediately. Our findings indicate that this may be a feasible and effective strategy for providing IPT to newly diagnosed PLHIV.

Though completion rates differed between older and younger participants, the majority of all study participants—regardless of age—received a full course of treatment. While barriers for non-completers should continue to be explored further, our findings indicate that a substantial portion of newly diagnosed PLHIV are willing to make monthly (or bi-monthly) visits to the clinic to receive preventive therapy for TB. Given the clear benefits of IPT for PLHIV, especially those who are newly diagnosed and ARV-naïve, clinic-based provision of IPT for newly diagnosed HIV patients should be routinely conducted.

Our research identified several sub-populations that may benefit from additional support while receiving IPT to ensure treatment completion. Younger participants (who may be healthier than older participants) had lower rates of completion than older participants, and pregnant women and men had lower rates of treatment completion than non-pregnant women. Additional research on the specific barriers faced by these sub-populations is needed. Future implementation science research may also evaluate

interventions to boost completion rates among newly diagnosed PLHIV under operational conditions. By identifying sub-populations at risk for treatment non-adherence, this research may provide a starting point for future work on IPT initiation and treatment completion in high TB/HIV burden areas.

CONCLUSIONS:

While TB incidence continues to decline globally, the TB burden in sub-Saharan Africa and Southeast Asia remains high. Ambitious global TB control targets have been set as a part of the WHO's "End TB Strategy", but if a global TB incidence rate of 10/100,000 population per year is to be achieved by 2035 new strategies need to be deployed in high burden settings. Research on the cost and potential impact of potential TB control interventions, especially as deployed in particular contexts, will be vital to inform policy decisions and ensure the efficient deployment of scarce TB control resources. This analysis has evaluated potential interventions that span the TB case-finding and prevention pathway, from identification of new TB cases to the deployment of proper diagnostic tests and identification of factors associated with preventive treatment completion in high-risk populations. Our results have the potential to better inform regional and local policy decisions around TB control. This kind of focused operational research is crucial to evidence-based decision-making, and ensuring that the TB control interventions deployed will help us to achieve the vision of a "TB free world" by 2035.

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CHAPTER 6:

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DePauw University, Greencastle, IN
Study Abroad: University of Auckland, Auckland, New Zealand (Spring 2006)

PROFESSIONAL EXPERIENCE

Jun 2014 – Present **Research Assistant for CHEPETSA Study**
PI: Dr. Richard Chaisson, Johns Hopkins School of Medicine, Baltimore, MD
• Provided training and review of STATA cleaning files in conjunction with study data manager
• Performed data cleaning and data quality assurance functions
• Conducted data analysis and manuscript writing and presentation of results at conferences

Aug 2014 – Apr 2015 **Consultant, TB Prioritization under New Funding Model**
Global Fund for TB, HIV, and Malaria
• Designed an interview guide and conducted qualitative interviews with in-country representatives and Global Fund staff
• Analyzed qualitative data and performed desk review of grant applications
• Presented results at Global Fund meetings and prepared a report of the findings

Aug 2013 – Present **Research Consultant, Thol'impilo Study**
Aurum Institute, Johannesburg, South Africa

• Planned and coordinated the costing data collection for the Thol'impilo HIV-linkage to care study in Ekurhuleni and Limpopo Provinces, South Africa
• Performed the cost-effectiveness analysis of multiple linkage-to-care interventions compared to the standard of care in South Africa in increasing three month initiation into HIV care
• Building a Monte Carlo simulation model exploring the cost and consequences of linkage-to-care interventions on reducing secondary HIV transmission and HIV mortality

Jun 2013 – Present **Data Analyst, Kids Active Case-Finding Study**
Perinatal HIV Research Unit, Johannesburg, South Africa
• Performed data management, cleaning, and analysis in STATA and R for multiple longitudinal and cross-sectional tuberculosis case-finding studies
• Provided statistical support for protocol writing, study planning, and data analysis projects

Jun 2013 – Present **Research Coordinator, "Coldspots" Active Case-Finding Study**
Epidemiology Department, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
• Drafted study protocol and completed IRB approval process for a tuberculosis household contact tracing study to be carried out in Limpopo Province, South Africa
• Created survey instruments, data collection forms, and built study database
• Travelled to South Africa to hire and train study staff, and to supervise data collection and management
• Collected costing data, and performed cost-effectiveness analysis in TreeAge
• Collaborated with a diverse team including researchers, clinic staff, study personnel, and research participants

Jan 2013-Present **Research Assistant for Dr. David Dowdy, Epidemiology Department**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
• Performed cost-effectiveness analysis on the use of Interferon Gamma Release Assays for the diagnosis of active tuberculosis in India using TreeAge software
• Described the results in an article for scientific publication

Sep 2012-Sep 2014 **Guest Researcher, Parasitic Diseases Branch, Center for Global Health**
Centers for Disease Control and Prevention, Atlanta, GA
• Performed data analysis of projects pertaining to parasitic and neglected tropical diseases
• Wrote and edited manuscripts for scientific publication

Sep 2011 - Sep 2012 **ORISE Fellow, Parasitic Diseases Branch, Center for Global Health**
Centers for Disease Control and Prevention, Atlanta, GA
• Performed complex statistical analysis on large Demographic and Health Survey data from 36 countries in sub-Saharan Africa using SAS

to evaluate the feasibility of including preventative interventions into routine healthcare visits
• Analyzed data from a morbidity census in India on risk factors for lymphedema, and mapped disease prevalence by village using ArcGIS 10.1
• Collected data for an economic analysis of a lymphedema management program for patients with lymphatic filariasis in Orissa, India
• Compared community-based survey data with facility-based surveillance data for estimating community-level prevalence of soil-transmitted helminth infection
• Presented findings at scientific conferences and published articles in peer-reviewed journals

May 2011 – Sep 2011 **Fellow, Parasitic Diseases and Malaria Branches, Center for Global Health**
Centers for Disease Control and Prevention, Atlanta, GA
• Cleaned and analyzed longitudinal data from a lymphedema management program in India and collaborated in the writing of articles for publication
• Wrote a manual designed to assist NGOs in launching or scaling up lymphedema management programs in resource-limited settings
• Collaborated in the design and editing of continuing medical education modules for malaria and Eosinophilia, while also completing the accreditation process in conjunction with supervisor
• Performed an exhaustive literature review and constructed prophylaxis, treatment, and adverse event tables for a CDC "Expert Paper" on Chloroquine use

Apr 2009 – May 2011 **Research Assistant for Senior Associate Professor Patrick Kilgo**
Biostatistics & Bioinformatics Department, Rollins School of Public Health, Atlanta, GA
• Cleaned and analyzed data on pre-operative risk factors for pulmonary complications in a cohort of patients following coronary artery bypass surgery
• In conjunction with the principle investigator and biostatistician, wrote and edited an abstract for a scientific conference

Aug 2009 – May 2011 **Epidemiology Assistant, NCHHSTP, Perinatal HIV Prevention Team**
Centers for Disease Control and Prevention, Atlanta, GA
• Created presentations for team, supervisors, and Branch Chief on topics pertaining to the prevention of mother-to-child transmission of HIV
• Data cleaning and analysis in SAS
• Synthesized findings and prepare manuscripts for scholarly publication
• Prepared, managed, and compiled documents for Clearance, IRB, as well as Paperwork Reduction Act and Office of Management and Budget approval processes for publications and studies

TEACHING EXPERIENCE

Teaching Assistant, Johns Hopkins Bloomgerg School of Public Health

2014	Principles of Epidemiology, Lechaim Naggan
2014	Emerging Infectious Diseases, Kenrad Nelson
2014	Epidemiology Methods III, David Dowdy, Shruti Mehta, Keri Althoff
2012	Infectious Disease Epidemiology, Kenrad Nelson

Teaching Assistant, Emory University Rollins School of Public Health

2011	Health in Complex Humanitarian Emergencies, Fiona Long
2011	Monitoring and Evaluating Global Health Programs, Clair Null
2011	Statistical Methods I, Patrick Kilgo

ADDITIONAL EXPERIENCE

Aug 2008 – Jun 2009 **Admissions Representative**
Oakland City University, Oakland City, Indiana

Jun 2008 – Sep 2008 **Adjunct Faculty Member**
Ivy Tech Community College, Terre Haute, Indiana

Jul 2007 – Jun 2008 **English as a Second Language Instructor**
WorldTeach, Ulien, Arno Atoll, Marshall Islands

ACTIVITIES

Aug 2014 – May 2015 **Co-President**
Epidemiology Student Organization, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Aug 2014 – Dec 2014 **Member**
Student Outbreak and Response Team, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Mar 2011 – May 2011 **Volunteer, International Emergency and Refugee Health Branch**
Centers for Disease Control and Prevention, Atlanta, GA

Aug 2009 – Feb 2011 **President & Member**
Student Outbreak and Response Team, Rollins School of Public Health, Atlanta, GA

Nov 2010 **Conference Recorder**
Innovations in Global Health, Development, and Climate Change Adaptation: A Symposium, Atlanta, GA

Jul 2009 **Volunteer Research Assistant**
FutureGenerations/Perú, Cusco, Perú

May 2010 – Sep 2012 **Member & Amateur Whitewater Kayaker**
Georgia Canoe Association, Atlanta, GA

Aug 2009 – May 2011 **Member**
Emory Global Health Organization, Atlanta, GA

2008 – Present **Interviewer**
WorldTeach, Boston, MA

May – Aug 2009 **Health volunteer and Spanish student**
FairPlay Perú, Cusco Perú

2008 – 2009 **Volunteer (Big Sister)**
Big Brothers Big Sisters, Evansville, IN
Jun 2008 **Volunteer**
AMPATH, Eldoret, Kenya

PUBLICATIONS

• **Little KM**, Pai M, Dowdy DW (2015). "Costs and Consequences of Using Interferon γ Release Assays for the Diagnosis of Active Tuberculosis in India". *PLoS ONE* 10(4):e0124525. DOI:10.1371/journal.pone.0124525.

• **Little KM**, Budge PJ, Mues KE, Kennedy ED, Prakash A, Rout J, Fox LM (2013). "Impact of Community-Based Lymphedema Management on Perceived Disability and Quality of Life among Patients with Lymphatic Filariasis in Orissa State, India". *PLoS Negl Trop Dis* 7(3): e2100. doi: 10.1371/journal.pntd.0002100.

• **Little KM**, Taylor AW, Rose C, Bohannon B, Dominguez K. *HIV, SIDS, and Breastfeeding in the Pediatric Spectrum of HIV Disease Cohort*. (Manuscript in consideration at *Pediatrics*)

• **Little KM**, Taylor AW, Borkowf CB, Whitmore KS, Weidle PJ, Nesheim SR. *Perinatal Antiretroviral Exposure and Prevented Mother-to-Child HIV Infections in the era of Antiretroviral Prophylaxis*. (Manuscript in consideration at the *Journal of Acquired Immune Deficiency Syndrome*)

• **Little KM,** Hu DJ, Dominguez K. (2012). "HIV and Breastfeeding in the United States." Human Immunodeficiency Virus-1 and Breastfeeding: Biology, Research Advances, and Policy. Kourtis AP and Bulterys M. New York, New York, Springer.

• **Little KM**, Kilmarx PH, Taylor AW, Rivadeneira ED, Nesheim SR. *A review of evidence for transmission of HIV from children to breastfeeding women and implications for prevention.* Pediatr Infect Dis J 2012;31:938-942.

•Lampe MA, Nesheim S, Shouse RL, Borkowf CB, Minasandram V, **Little K**, Kilmarx PH, et al (2010). "Racial/Ethnic Disparities Among Children with Diagnoses of Perinatal HIV Infection—34 States, 2004—2007" *MMWR*, 59(04). 97-101.

PRESENTATIONS

•**K Little**, R Msandiwa, N Martinson, J Golub, R Chaisson, D Dowdy. *Yield of Household Contact Tracing for Tuberculosis in Rural South Africa*. Poster Discussion Session. Union World Conference on Lung Health. Barcelona, Spain, October 2014.

•**K Little,** B Lopez, P Juliao, F Muñoz, J McCracken, G Derado, V Cuéllar, A Thornton, J C Patel, G Lopez, L Reyes, K Lindblade, S L. Roy. *Comparison of Health Facility and Community-Based Estimates of Soil Transmitted Helminth Infection in Nueva Santa Rosa, Guatemala—2010.* Oral presentation. American Society of Tropical Medicine and Hygiene Conference. Atlanta, GA, November 2012.

•**K Little,** DH Hamer. *Global Health: Child Health Session*. Co-Chair. American Society of Tropical Medicine and Hygiene Conference. Atlanta, GA, November 2012.

•**K Little**, A Miller, & M Deming. *Using current and extended routine prevention visits to health facilities to achieve higher coverage with child-survival interventions in sub-Saharan Africa*. Oral presentation. American Society of Tropical Medicine and Hygiene Conference. Atlanta, GA, November 2012. 1355 & 1478.

• **K Little**, B Lopez, P Juliao, F Muñoz, G Derado, V Cuéllar, A Thornton, JC Patel, G Lopez, L Reyes, W Arvelo, K Lindblade, S Roy. *Health-Seeking Behaviors and Treatment for Soil-Transmitted Helminth Infection in Nueva Santa Rosa, Guatemala—2010.* Poster presentation. American Society of Tropical Medicine and Hygiene Conference. Atlanta, GA, November 2012.

• **K Little**, AJ Blackstock, P Juliao, B Lopez, G Derado, V Cuéllar, A Thornton, JC Patel, F Muñoz, G Lopez, W Arvelo, L Reyes, K Lindblade, S Roy. *Comparison of the Fecal Parasite Concentrator and Kato-Katz Methods for the Diagnosis of Soil-Transmitted Helminths.* Poster presentation. American Society of Tropical Medicine and Hygiene Conference. Atlanta, GA, November 2012.

• A Taylor, **K Little**, X Zhang, C Borkowf, S Whitmore, P Weidle, M Lampe, & S Nesheim. *Estimated Perinatal Antiretroviral Exposures, Cases Prevented, and Infected Infants in the Era of Antiretroviral Prophylaxis in the US*. Conference on Retroviruses and Opportunistic Infections. Seattle, WA. T-103 and T-107.

• **Little KM**, Rout J, Budge PJ, Prakash A, Michyari A, Fox LM. *Quantifying the Economic Benefits of a Community-based Lymphedema Management Program—Orissa State, India*. Poster presentation at the American Society of Tropical Medicine Conference. Pittsburg, PA, December 2011.

• Budge PJ, **Little KM**, Mues KE, Kennedy ED, Prakash A, Rout J, Fox LM. *Impact of Community-Based Lymphedema Management on Perceived Disability and Quality of Life among Patients with Lymphatic Filariasis in Orissa State, India*. Oral presentation at the American Society of Tropical Medicine Conference. Pittsburg, PA, December 2011.

• **Little K**, Harrison C, et al, *Extra Hands in Emergencies: Emory's Student Outbreak and Response Team and Mutually Beneficial Collaborations with Public Health Partners.* Poster Presentation, Public Health Preparedness Summit. 2011: Atlanta, GA.

• Leshnower BG, Puskas J, Kilgo P, **Little K**, Leeper K, Cooper W, et al. *STS Criteria for Severity of COPD is Not a Strong Predictor of Common Pulmonary Complications in CABG Patients.* Abstract, Society of Thoracic Surgeons (STS) Meeting. January 2011

MEMBERSHIPS

2011 – Present **American Society of Tropical Medicine and Hygiene**

HONORS & AWARDS

2012 – Present	**Mary B. Meyer Memorial Scholarship**, Johns Hopkins Bloomberg School of Public Health
May 2013 – Jan 2014	**Global Health Established Site Field Placement Award,** JHSPH
May 2007	**Phi Beta Kappa Honor Society**, DePauw University
May 2007	**Summa Cum Laude graduate**, DePauw University
May 2007	**Theodore Englehart Prize** (Top Student in the History Department), DePauw University
April 2007	**Phi Alpha Theta** (History Honor Society), DePauw University
2005 - 2007	**National Society of Collegiate Scholars**
2003 – 2007	**Braden Scholarship** (100% tuition plus room and board), DePauw University

SKILLS

- SAS, STATA, R, ArcGIS, TreeAge, and Epi Info, SUDAAN and SPSS
- Basic speaking and listening competence of Marshallese
- Intermediate reading, writing, listening, and speaking competence of Spanish

CERTIFICATIONS

2009 – Present	CITI certified in HIPAA, GCA, and Human Subjects Research
2011	Complex humanitarian emergencies, Emory University
2010	Centers for Disease Control Emergency Operations Center: EOC 101
2009 – 2010	Red Cross Trainings (Fulfilling our Mission, Mass Care Overview)
2009	DeKalb County Board of Health Volunteer Certified
2009 – 2011	• NIMS Certified (100, 200, 700, 800)