Using Time and Motion Studies to Determine the Human Resource Needs Associated with Improving the Latent Tuberculosis Infection Cascade of Care

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Abstract

It is estimated that almost one quarter of the world's population, or 2 billion people, have latent tuberculosis infection (LTBI). Of those latently infected with TB, between 5-15% will go on to develop active TB. In 2015, the World Health Organization (WHO) outlined the End TB Strategy aimed at ending the TB epidemic globally, including a specific target to increase provision of preventive therapy to household contacts (HHC) of confirmed, pulmonary TB to over 90% by 2025. Despite the WHO's focus on improving access to LTBI preventive therapy, there has been little data reported on the human resource needs to provide such services.

In the **first manuscript** of my doctoral thesis, I present the systematic review and meta-analysis of the literature we conducted to determine the proportion of persons completing each step in the patient journey for HHC: from initial investigation and screening for LTBI through to completion of LTBI preventive therapy, also known as the LTBI Cascade of Care. This review demonstrated that fewer than 20% of eligible HHC completed preventive therapy. And interventions aimed at reducing losses at the early steps in the LTBI Cascade showed greater public health impact than interventions focused on improving patient completion of treatment.

The ACT4 trial is a cluster-randomized controlled trial conducted in 24 health facilities in 5 countries (Benin, Canada, Ghana, Indonesia, and Vietnam) to address the gaps in LTBI services identified in the first manuscript. The **second manuscript** in this thesis quantifies the precise healthcare worker (HCW) time required to perform clinical work activities at each step in the LTBI Cascade of Care, using a time and motion (TAM) study of consenting HCW in all ACT4 health facilities. This TAM data was also used in the **third manuscript** which quantifies the change in proportion of HCW time dedicated to LTBI activities resulting from the ACT4 intervention of

LTBI program evaluation and strengthening. Results from a linear mixed model demonstrate that there was a 10% increase in HCW time spent on LTBI services due to the ACT4 intervention. The negative costs of the intervention show that HCW time was taken away from active TB patient care, justification for additional staffing needs to improve LTBI services.

The fourth manuscript in this thesis aims to validate the use of a daily, HCW self-reported time-estimation questionnaire (TEQ) to replace the TAMs as a tool to capture HCW time in four main categories: 1) total time worked; 2) time on direct patient care; 3) time on active TB patient care; and 4) time on LTBI patient care. Although the TAMs are the most accurate method to estimate time, they are time-consuming and costly, thus we aimed to validate a simpler tool for measuring time that can be applied in other program settings. For my doctoral research, I piloted and tested the initial TEQ performance compared to the TAMs then refined the TEQ tool to better capture HCW time in those four main categories.

The work I conducted for my doctoral thesis fills an important gap of quantifying the human resource needs for improving the LTBI Cascade of Care. My thesis provides estimates of HCW time requirements for expanded LTBI services, in both high- and low-and middle-income counties, from prospectively collected primary data as part of the ACT4 trial. These human resource needs are key to addressing the WHO End TB Strategy Goals of expanding access to LTBI services to the millions of household contacts of pulmonary TB patients around the world.

Résumé

On estime que près d'un quart de la population mondiale, soit 2 milliards de personnes, sont infectée avec la tuberculose latente (ITL). Parmi eux, entre 5-15% vont continuer à développer la tuberculose active. En 2015, l'organisation mondiale de la santé (OMS) a défini la stratégie de la lutte contre la tuberculose visant à mettre fin l'épidémie de tuberculose dans le monde, notamment un objective spécifique consistant à augmenter l'approvisionnement d'un traitement préventif aux contacts étroits de la tuberculose pulmonaire confirmé a plus de 90% d'ici 2025. Malgré la stratégie de l'OMS, pour améliorer l'accès au traitement préventif pour les gens avec l'ITL, peu d'informations ou des données ont été rapportées par rapport aux implications pour les ressources humaines qui seront nécessaire pour faire ce travail.

Pour le **premier manuscrit** qui fait partie de ma thèse de doctorat, je présente le revue systématique et méta-analyse de la littérature que nous avons fait pour déterminer la proportion des personnes qui ont complétées chaque étape dans le parcours patient des contacts étroits. Ce trajet inclus les étapes depuis l'investigation initiale et dépistage pour l'ITL jusqu'à la fin du traitement préventif, aussi appelé « La Cascade de Soins de l'ITL ». Cette revue systématique a démontré que moins de 20% des contacts étroits éligibles ont complétés le traitement préventif. Des interventions qui se concentre sur la diminution de la pertes des contacts étroits aux premières étapes dans la Cascade de l'ITL ont démontrées un plus grand impact sur la santé publique que les interventions qui avait l'objectif d'améliorer les nombres des contacts qui complètent le traitement préventif.

ACT4 est un essai clinique randomisée en grappes conduit dans 24 établissements de santé de cinq pays (Bénin, Canada, Ghana, Indonésie et Vietnam) pour combler les lacunes dans les services de l'ITL identifiées dans le premier manuscrit. Le **deuxième manuscrit** qui fait partie de ma thèse à

quantifier le temps précises requis par les travailleurs de la santé pour effectuer des travaux cliniques à chaque étape dans la Cascade de l'ITL, en utilisant la méthode du « temps et motion (TAM) » avec les travailleurs de la santé de toutes les cliniques d'ACT4 qui ont donnés leur accord. Les mêmes données de l'essai TAM ont été utilisées pour le **troisième manuscrit** qui a quantifié le changement de proportion du temps que les travailleurs de la santé ont dédies aux soins reliés à l'ITL résultant de l'intervention d'ACT4 pour évaluer et renforcer du service de l'ITL. Les résultats d'un model mixte linéaire ont démontrés qu'il y avait une augmentation du 10% chez les des travailleurs de la santé temps sur le service de l'ITL après l'intervention d'ACT4. Les coûts négatifs de l'intervention montrent le changement du temps des travailleurs de la santé était enlevé du temps avec les patients qui avait la tuberculose active. Ce changement justifie le besoin de personnel supplémentaire pour améliorer les services de l'ITL.

Le **quatrième manuscrit** qui fait partie de ma thèse doctorale avait l'objectif de valider l'utilisation d'un questionnaire quotidien d'estimation de temps (TEQ) auto-déclarée par les travailleurs de la santé Le but était que le TEQ puisse remplacer les TAMs en tant qu'outil pour capturer le temps que les travailleurs de la santé travaillaient en quatre catégories principales : 1) temps travaillé pendant toute la journée ; 2) temps totaux pour faire des soins directs aux patients ; 3) temps pour faire des soins des patients de la tuberculose active ; et 4) temps pour faire des soins des patients de l'ITL. Bien que les TAMs soient la méthode la plus précise pour estimer le temps, ils sont longs et couteux, nous avons donc cherché à valider un outil plus simple pour mesurer le temps et qui pourrait être appliqué dans les autres programmes de la santé. Pour ma recherche doctorale, j'ai piloté et testé la performance initiale du TEQ par rapport aux TAMs puis raffiné l'outil TEQ afin de mieux capturer le temps des travailleurs de la santé dans les quatre catégories principales.

Le travail que j'ai fait pour ma thèse de doctorat comble un vide important en termes de quantification des besoins de ressources humaines pour améliorer la Cascade de l'ITL. Ma thèse fournit une estimation des besoins en temps des travailleurs de la santé pour les services d'ITL élargis, à la fois dans les pays à revenus élevé et faible, à partir de données primaires collectées de manière prospective dans le cadre de l'essai ACT4. Ces besoins en ressources humaines sont essentiels pour atteindre les objectifs de la stratégie de lutte contre la tuberculose de l'OMS visant à élargir l'accès aux services d'ITL aux millions de contacts étroits des patients atteint de tuberculose pulmonaire dans le monde.

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I am humbled by this opportunity to pursue my dream. I am eternally grateful to my supervisor, Dr. Dick Menzies, for providing me with the funds and support to be part of such meaningful research. I would not have been able to complete my doctoral research without his constant questions, insights and push for me to work harder – while somehow always being able to make me laugh.

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Contribution of Authors

Each manuscript that comprises this thesis is listed separately below, and I am first author for all four manuscripts. I developed the research questions for all manuscripts with the support of my supervisor, Dr. Menzies.

For the first manuscript, I was one of the two reviewers for this systematic review and meta-analysis, was involved in all stages from study design, data extraction, collection, analysis, interpretation of the results and writing of the manuscript.

I was involved in all aspects of the time and motion (TAM) study (manuscripts #2-4) including: study design and defining the objectives, creating all data collection forms, piloting and revising the TAM forms, training study personnel for data collection in all five countries, and analysis of all TAM data. I conducted on-site personnel trainings for the TAMs in Benin, Ghana and Montreal, and conducted trainings and refresher trainings for all other study sites (Indonesia, Vietnam, Edmonton, Calgary and Vancouver) via Skype.

I also designed the time-estimation questionnaire (TEQ), oversaw the pilot of the TEQ and conducted trainings on the TEQ for each site via Skype. I performed the analysis of the pilot TEQ data, then revised the TEQ form for the final study based on pilot study results and feedback from the sites. I performed all data analysis for the TEQ study presented in manuscript #4 and was responsible for all management and communication aspects of the TAM and TEQ studies. Once the data was finalized at each site, I performed data cleaning, coding and analysis.

Dr. Menzies provided me with critical input throughout the entire process of my doctoral research and asked poignant questions as I presented my research in an on-going manner. Dr. Menzies helped shape the direction and cohesiveness of my thesis and reviewed all manuscripts in detail, providing me with timely, insightful feedback.

My committee members (Dr. Andrea Benedetti, Dr. Kevin Schwartzman, and Dr. Erin Strumpf) also provided support and feedback based on their areas of expertise. Dr. Benedetti was instrumental in helping with my data analysis, ensuring I was answering the questions I set out to address using the proper methods. Dr. Benedetti provided exceptional support and was particularly insightful in suggesting additional methods to validate the TEQ tool. Dr. Schwartzman provided useful feedback on the substantive components of my protocol and thesis. Dr. Schwartzman encouraged me to present my results on human resource needs in manuscripts 2 and 3 in terms of full-time equivalents rather than a traditional cost-analysis or dollar value, a more pragmatic metric in the public health setting. In addition, Dr. Schwartzman's substantive knowledge of tuberculosis (TB) was apparent in the nuanced comments and feedback he provided for me throughout all my doctoral research which offered me an opportunity to learn more substantively about TB disease. Dr. Strumpf provided a useful, critical eye and review as someone who is not immersed in the TB field. Dr. Strumpf gave useful feedback on how to ensure the epidemiologic concepts of my research were clearly presented and communicated. Dr. Strumpf also helped me to better communicate the significance of my findings to a broader public health audience.

Manuscript 1: **Alsdurf H**, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2016;**16**(11):1269-78.

Manuscript 2: **Alsdurf H**, Oxlade O, Adjobimey M, Bastos M, Bedingfield N, Benedetti A, Boafo D, Buu T, Chiang L, Cook V, Fisher D, Fox GJ, Fregonese F, Hadisoemarto P, Johnston J, Kassa F, Khan F, Long R, Moayedi Nia S, Nguyen TA, Obeng J, Paulsen C, Romanowski K, Ruslami R, Schwartzman K, Sohn H, Strumpf E, Trajman A, Valiquette C, Yaha L, Menzies D. How much healthcare worker time does it take to complete the latent tuberculosis cascade of care? A time and motion study in five countries. Submitted to *WHO Bulletin* for review.

Manuscript 3: **Alsdurf H**, Benedetti A, Adjobimey M, Cook V, Fisher D, Fox G, Fregonese F, Hadisoemarto P, Johnston J, Long R, Obeng J, Oxlade O, Ruslami R, Schwartzman K, Strumpf E, Menzies D. How labour intensive is latent tuberculosis management? Using time and motion studies to estimate labour needs for scale-up. Currently being prepared for submission to *Health Services Research*.

Manuscript 4: **Alsdurf H**, Benedetti A, Adjobimey M, Cook V, Fisher D, Fox G, Fregonese F, Hadisoemarto P, Johnston J, Long R, Obeng J, Oxlade O, Ruslami R, Schwartzman K, Strumpf E, Menzies D. How well do healthcare workers estimate their time spent on tuberculosis patient care activities? A validation study. Currently being prepared for submission to *Journal of Epidemiology and Community Health*.

Statement of Originality

I attest that the work presented herein is my own and the manuscripts are considered original scholarship. I declare that this doctoral thesis and each manuscript therein to be of my own authorship. I received guidance throughout the process from my supervisor, as well as my doctoral thesis committee, but the design, analyses and manuscripts were of my own design.

My doctoral thesis aims to make significant contributions to the knowledge and literature in the area of health system needs for improved tuberculosis (TB) care. My research set out to address the gap in the literature by generating data to quantify the personnel time requirements for performing all the necessary work tasks for providing quality care for close household contacts (HHC) of patients with active, pulmonary tuberculosis. And from there, I focused on capturing the additional human resources needed (i.e. time) for improving care for patients with latent tuberculosis infection (LTBI). The data gathered for the human resources needed to provide these services was meant to address the lack of data and information in the literature on these components of care, which will also be useful to inform costing analyses of TB programs and scale-up of LTBI services in other countries. Thus, by providing quality data my research will inform estimates of time and cost used for program expansion and policy development. I attest that I developed all materials for the time and motion (TAM) study and the time-estimation questionnaires (TEQ) on my own.

List of Abbreviations

ACT4	Enhancing the Public Health Impact of Latent Tuberculosis Infection Diagnosis and Treatment: A Pragmatic Cluster Randomized Trial (ACT4)
ATB	Active Tuberculosis
CEA	Cost Effectiveness Analysis
CHW	Community Health Worker
CI	Confidence Interval
CIHR	Canadian Institutes of Health Research
DOTS	Directly Observed Treatment – Short Course
FTE	Full Time Equivalent
HCW	Health Care Worker
HHC	Household Contact
HHRP	Health Human Resource Planning
HIC	High Income Country
HIV	Human Immune-deficiency Virus
ICC	Intra-Class Correlation Coefficient
IGRA	Interferon-Gamma Release Assay
INH	Isoniazid
IPT	Isoniazid Preventive Therapy
ITL	Infectée avec la Tuberculose Latente
LMM	Linear Mixed Model
LTBI	Latent Tuberculosis Infection
LMIC	Low- and Middle-Income Countries
OMS	Organisation Mondiale de la Santé

R	Rifampin
RCT	Randomized Controlled Trial
SDG	Sustainable Development Goals
SME	Subject Matter Experts
SOP	Standard Operating Procedures
TAM	Time and Motion Study
TB	Tuberculosis
TEQ	Time Estimation Questionnaire
TST	Tuberculin Skin Test
UHC	Universal Health Coverage
UNHLM	United Nations' High-Level Meeting
WHO	World Health Organization

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Chapter 1 - Research Objectives

1.1 Objectives

Overall Aim: This doctoral thesis aims to determine the human resource requirements for health systems to deliver quality, patient-centered latent tuberculosis infection (LTBI) care and to develop and examine a simple, cheap tool for quantifying healthcare worker (HCW) time providing this patient care.

Specific Objectives:

1. To systematically review the published literature and determine the pooled cumulative proportion of persons completing each step in the LTBI Cascade of Care, from initial investigation and screening for LTBI through to completion of LTBI therapy (Manuscript 1).
2. To quantify the time it takes HCWs to perform the work tasks associated with each step along the LTBI cascade of care for household contacts (HHC) in Canada (a high-income country), and in four low- and middle-income countries (LMIC); and to estimate the annual human resource needs to provide LTBI care to all HHC of new, confirmed, pulmonary TB patients in each of the participating countries (Manuscript 2).
3. To estimate, using a time and motion (TAM) study, the overall change in HCWs time devoted to patient care activities for LTBI resulting from a standardized intervention to increase diagnosis and treatment of HHC with LTBI. And to determine the associated changes in HCWs time devoted to other patient care activities (i.e. negative impacts to active TB or non-TB patient care) following the LTBI program evaluation and strengthening intervention (Manuscript 3).

4. To assess the criterion validity of a time-estimation questionnaire (TEQ) compared to a TAM study, which will be considered the reference standard for measuring time dedicated to three pre-specified categories of clinical work; and to assess the day-to-day variability of HCWs time as measured by the TEQ (Manuscript 4).

1.2 Thesis Overview

The chapters that follow include the background and literature that serve as the substantive and methodologic foundations of this study (Chapters 2 and 3); the four main manuscripts that comprise my doctoral thesis (Chapters 4-7); and lastly, a discussion of the significance of my doctoral research (Chapter 8).

Overview:

- **Chapter 2** describes the background of latent tuberculosis infection, healthcare worker task-shifting and time allocation and time and motion (TAM) studies. This chapter also briefly describes the pragmatic trial and setting in which my doctoral research took place.
- **Chapter 3** describes the study design and methods used to conduct my doctoral research, namely the TAM and TEQ methodologies.
- **Chapter 4** includes the manuscript entitled "The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis"(1). This systematic review was published in the *Lancet Infectious Diseases* (2016) and provides the background and context of the LTBI cascade of care, and the importance of evaluating where patient losses occur in the cascade (manuscript 1).
- **Chapter 5** includes the manuscript entitled "Resource implications of the latent tuberculosis cascade of care. A time and motion study" which has been submitted to the *Lancet Global Health* for review. This manuscript presents my original doctoral research which designed and implemented a TAM study to quantify HCWs time spent on care at each step in the

LTBI Cascade of Care at local health facilities in the five participating countries. Results from this study provide estimates of HCWs time requirements for work tasks at each step in the LTBI cascade that are then used to extrapolate the number of additional HCWs needed for expansion of LTBI services in each country (manuscript 2).

- **Chapter 6** includes the manuscript entitled "Human resource implications of latent tuberculosis program strengthening". This chapter examines the changes in allocation of HCW time devoted to LTBI patient care following the intervention to evaluate and strengthen LTBI services at health facilities participating in the larger pragmatic trial (manuscript 3).
- **Chapter 7** includes the manuscript entitled "How well do healthcare workers estimate their time spent on latent tuberculosis management activities? A validation study". This chapter presents a second study performed for my doctoral thesis to pilot and then validate the use of an interviewer-administered, short questionnaire (TEQ) to replace the use of the TAMs for assessing HCWs time allocation on various work activities (manuscript 4).
- **Chapter 8** provides a summary and discussion of research presented in this doctoral thesis. The discussion highlights the significance and contributions of the findings presented here, as well as the usefulness of these results and tools globally.

A consolidated reference list is provided at the end of this document (pages 192-195). Appendices include all relevant tools developed for the TAM and TEQ studies, as well as any other supporting documentation.

Chapter 2 Background and Literature Review

2.1 Tuberculosis Disease

2.1.1 Pathogenesis and Transmission of Tuberculosis

Tuberculosis (TB) is an airborne infectious disease, caused by the bacillus *Mycobacterium tuberculosis,* which is spread from person to person(2). Tuberculosis infection occurs when someone inhales aerosolized droplets containing *M. tuberculosis* that become lodged in the lung tissue(3). After being exposed to someone with active contagious and untreated pulmonary TB, the risk of progressing to active TB disease is highest within the first two years following infection, but only 5% of healthy people with new infection will progress to active TB disease (Figure 2.1)(4). People with a compromised immune response, due to illnesses such as human immune-deficiency virus (HIV), progress to active TB disease at a faster rate once they have acquired infection(3). Infants and young children are also at a higher risk of progressing from infection to active disease, but the rate of progression wanes in children aged 5-15 years old as their immune systems mature(3).

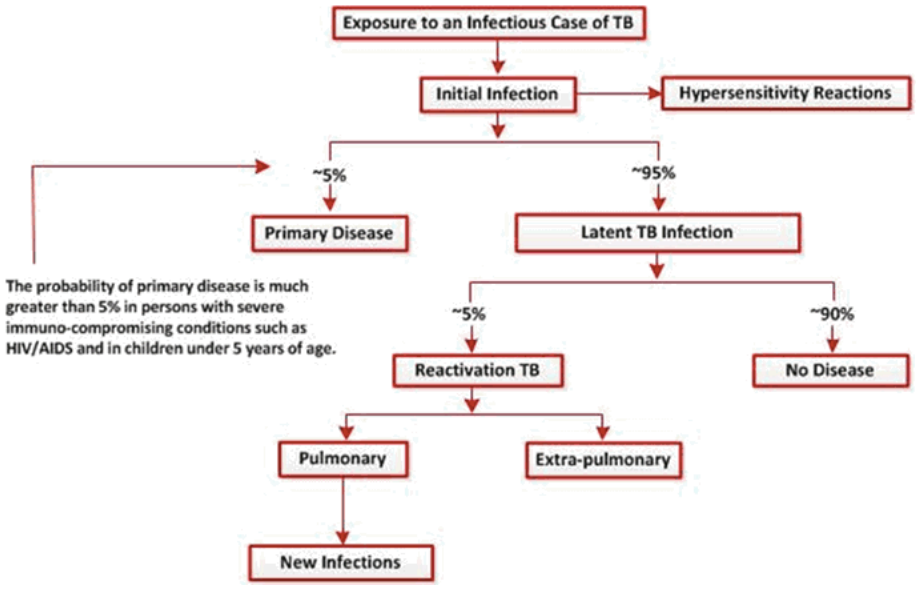


Figure 2.1 The Pathogenesis of Tuberculosis in the Infected Host
(Source: Adapted from the 6th Edition of the Canadian TB Standards)

2.1.2 Latent Tuberculosis Infection (LTBI)

Although TB disease is a continuum from infection with *M. tuberculosis* to active infectious disease, patients are typically categorized as having either latent tuberculosis infection (LTBI) or active TB disease for simplicity in the clinical setting(2). LTBI occurs after transmission and acquisition of infection, when the TB bacteria lie dormant in a person. Despite the fact that people with LTBI are not sick or contagious, they are at risk of developing active TB disease(see Figure 2.2, p.25)(5).

Between 5-15% of people with LTBI will go on to develop active TB disease over the course of their lifetimes (6). Patient, pathogen and environmental factors all determine whether transmission of TB occurs(4).The risk of transition from LTBI to active TB disease is primarily dependent on the immune system of the individual host, and a growing body of evidence which suggests that host genetic factors may also play an important role in susceptibility and progression to active disease(4). A number of proximate risk factors have been identified for TB disease such as: HIV, lung disease, diabetes or malnutrition, air pollution, increasing age and genetic factors(7).

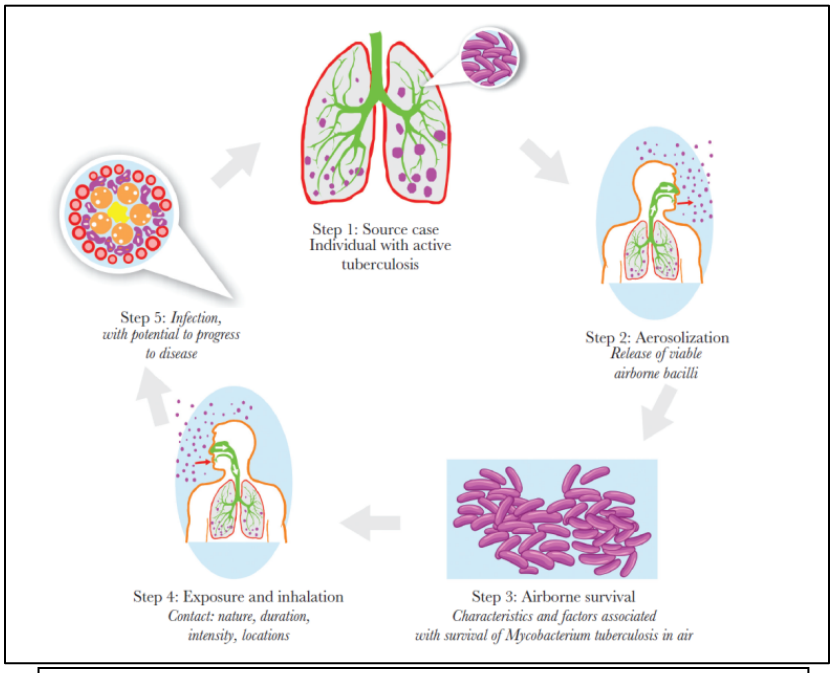


Figure 2.2 Cascade of tuberculosis transmission
(Source: The Aurum Institute)

Close household contacts (HHC) of those with active TB disease and children under 5 years old are at much higher risk of developing active TB disease following acquisition of infection due to high-level contact with infectious droplets and weakened immune defense(6). Compounding these risk factors, a number of social determinants have also been identified as upstream influences to TB disease progression such as poverty, low education and low socio-economic status(7).

2.1.3 Household Contacts

Close household contacts (HHC) are defined as someone who spent extended periods of time at the home of the index case during the three months prior to diagnosis of active TB disease(8). According to a systematic review, the prevalence of active TB disease ranged from 1-5% among HHC(9). Another recent systematic review and meta-analysis found the pooled prevalence of LTBI among contacts in low- and middle-income countries (LMIC) to be 51.5%, compared to 28.1% in high-income countries(10). The goal of testing for LTBI is to identify individuals who are more likely to progress to active TB disease and therefore would benefit from treatment of LTBI. Those with active TB are more likely to pass along TB to close contacts, thus an important component to prevention is identifying persons who spend the most amount of time with someone who has active TB disease and are at highest risk for infection, and ultimately developing active TB disease.

A contact investigation refers to the process of the health system identifying close contacts of recently diagnosed active TB patients (i.e. index case) and screening those contacts for both active and latent TB infection(8). However, this can be a time-consuming process for healthcare workers (HCWs) since it often requires a visit to the home of the person with active TB in order to identify everyone who spends time there. Contact investigation is a recommended component of all TB

programmes but is performed less consistently in high TB-burden areas, partially because the workload of treating and caring for persons with active TB disease takes precedence(9).

2.1.4 Clinical Aspects of LTBI

No gold standard method for diagnosing LTBI exists, but two available tests – the tuberculin skin test (TST) and interferon-gamma release assay (IGRA) – both require a competent immune response in order to identify persons infected with TB (11). The 2018 World Health Organization (WHO) updated guidelines for programmatic management of LTBI strongly recommended the use of either test for LTBI, based on affordability and availability in the local setting(11).

Fortunately, treatment is available to prevent those who test positive for LTBI from developing active TB disease. The standard LTBI treatment is nine months of the antibiotic isoniazid (INH) taken daily, with strong evidence that six months of INH (6INH) monotherapy can be used for all LTBI patients(11). However, recent evidence from a randomized-controlled trial (RCT) found that a shortened regimen of four months of rifampin (4R) was not inferior to the standard 6 or 9 months of INH treatment for the prevention of confirmed, active TB and significantly safer(12). Advances in preventive therapy, to reduce the time required for patients to take medication, have made important contributions to improving the quality of care for LTBI patients. Providing treatment to persons with LTBI means that individuals: 1) avoid developing active disease with resultant morbidity and mortality; 2) avoid transmitting the TB bacterium; and 3) need fewer medications and experience fewer side effects. Despite less toxic, shorter treatment regimens, there are numerous other barriers for close HHC to be identified and complete LTBI treatment. HHC of persons with active TB disease are often inhibited from screening and treatment due to: individual healthcare-

seeking behavior, structural barriers to accessing healthcare, and health system issues such as delays in diagnosis and treatment initiation(13).

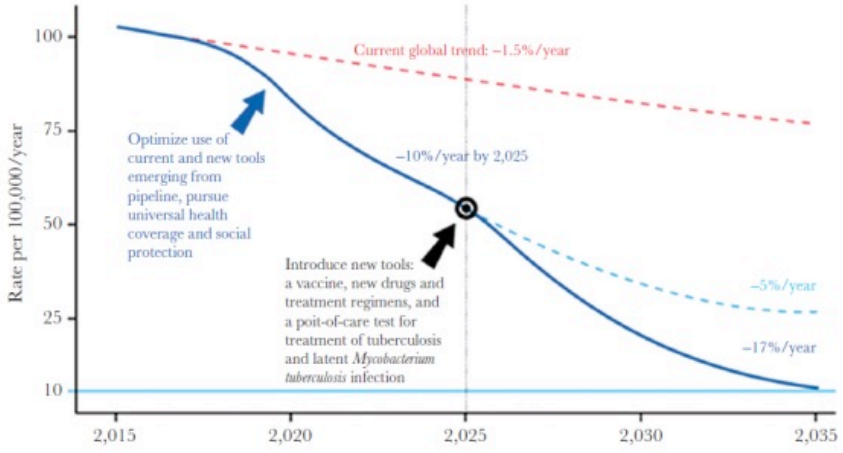
2.2 Global Epidemiology of Tuberculosis

Globally, it is estimated that 10 million people developed TB disease and 1.3 million people died from TB in 2017 alone, making TB the leading cause of death due to an infectious disease(6), particularly due to high morbidity and mortality rates in LMIC(2). It is further estimated that almost 2 billion people, or approximately 25% of the world's population, have latent LTBI(6). The 30 countries on the WHO list with the highest burden of TB disease account for almost 90% of the cases worldwide(6). Persons with active TB disease in these countries will go on to infect many of their close contacts, thereby increasing the reservoir of LTBI.

The analogy of "turning off the tap" is commonly used in TB because it will be necessary to halt the progression from LTBI to active TB in order to significantly decrease the number of new cases of TB each year(14). Preventing transmission of active TB will have other downstream benefits to the public health system, since TB is the leading cause of HIV-related deaths worldwide(11). Patients with active TB often have severe symptoms including: fever, fatigue, lack of appetite and weight loss, and people with pulmonary disease may have a persistent cough(2). Treatment for active TB is much longer and more difficult for patients than treatment for LTBI, thus preventing active disease is an advantage for patients. By working to prevent progression from LTBI to active TB, health systems will also spend fewer resources on diagnosis and treatment services for active TB patients(14). In 2015, the WHO announced the End TB Strategy which envisions "*a world free of tuberculosis by 2035*"(15). A critical component to achieving this goal is providing LTBI preventive treatment to halt the progression to active TB(11).

2.2.1 End TB Strategy

Tuberculosis has been called "one of the world's most neglected health crises" as far back as 1994, when the World Health Organization (WHO) first declared TB to be a global emergency(16). Yet 25 years after this declaration, TB remains the leading infectious disease killer(6). In 2015, to align with the Sustainable Development Goals (SDG), the WHO outlined the End TB Strategy which is aimed at ending the TB epidemic globally by 2035(15). Although global rates of TB have been decreasing annually, TB incidence is only falling at a rate of about 2% per year, and this pace does not currently put TB programs on track to reach the End TB Strategy goal to eliminate TB (i.e. incidence of less than 10/100,000)(6). Modelling projections show that in order to meet these goals, a rate of decline of 10% in TB incidence annually would be required. Such a drop will only be achievable if TB programs include a prioritization of LTBI screening and preventive therapy (see Figure 2.3, black arrow)(15).



Projected acceleration in the decline of global tuberculosis incidence rates to target levels. From WHO END TB Strategy [3].

Figure 2.3

2.2.2 Challenges for LTBI Scale-up and Implementation

Since HCWs in high TB-burden settings, such as LMIC, typically prioritize providing care for active TB patients, the WHO's increased emphasis on LTBI services will require changes in HCW time

allocations to provide such services, particularly an initial investment of time and energy to systematically increase contact investigations. LTBI services are often given low priority, in both high and low TB-burden settings, a key impediment to the patient care journey. First, time dedicated to LTBI is seen as taking away from care for patients with active TB disease, considered the priority in high TB-burden countries. In low-burden countries, such as Canada and the United States, LTBI services are primarily for screening of new immigrant populations and not always given high-priority(17). Thus, in both settings there are system-level barriers to LTBI treatment that de-incentivize healthcare providers from putting time and energy into LTBI services.

Within the context of the push by the WHO and United Nations (UN) to expand LTBI services in order to meet the ambitious End TB Strategy goals, little data exists on how increased LTBI services will impact and change workload and time management of HCWs. The End TB Strategy includes an indicator for the percentage of eligible people living with HIV and children under 5 who are contacts of TB patients being treated for LTBI; however, no health systems indicator to measure the impact of increased screening and treatment efforts on the part of HCWs(15).

2.2.3 Improved LTBI Services

The 2018 WHO guidelines include a new recommendation that people age 5 or older who are household contacts of a confirmed, pulmonary TB case be tested and treated(6). This recommendation would significantly increase those who are eligible for treatment globally. Based on this recommendation, the WHO and UN estimated that at least 20 million HHC would be eligible for treatment globally by 2022(6). In order to address these recommendations, health facilities treating active TB patients will need to expand the focus of their programmes to provide significantly more human and financial resources for LTBI-related services.

2.3 High-quality Healthcare

In 2018, the United Nations convened the first High Level Meeting on TB (UNHLM-TB). After this meeting, a declaration was announced reaffirming the commitment made in the SDGs to end TB by 2035, which also included support to increase the healthcare workforce providing TB services(18). Both the WHO and UNHLM declarations to increase TB care globally have also centered around a shift from a healthcare delivery model requiring HCWs to directly observe patients taking their medications (i.e. directly observed therapy, short course (DOTS)) to a new model emphasizing the need to provide person-centered, high-quality TB care(6, 18, 19). Coupled with the conversation about universal health coverage (UHC) taking place in many high TB-burden countries around the world, the impact of TB care on healthcare delivery systems is sure to be significant. In 2018, the Lancet Global Health established a Commission on High Quality Health Systems to assess the quality of healthcare in LMIC, and to develop a framework for measuring quality improvements to healthcare delivery in LMIC (20). As shown in Figure 2.4 below, the framework outlined key foundational components for delivering high quality health services for all health conditions (i.e. cancer, cardiovascular diseases, diabetes, infectious diseases, etc.). One of the five primary components emphasized was the strengthening of the healthcare workforce (highlighted in red in Figure 2.4 below)(20).

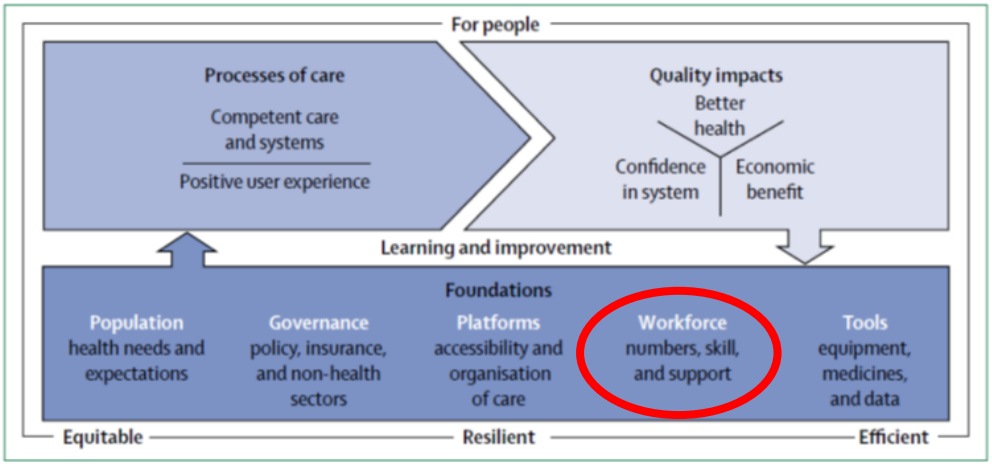


Figure 2.4 High quality health system framework
(Source: Lancet Commission on High Quality Health Systems)

A variety of things must be done to improve the healthcare workforce and its delivery of quality care, such as competency-based clinical education, trainings on ethics and respectful care, as well as empowering patients to hold health systems accountable for providing high-quality care(20).

2.4 Quantifying Human Resource Needs

To anticipate human resource needs for LTBI scale-up and avoid any negative impacts to other patient care activities, it will be critical for health systems and TB programmes to have accurate estimates of the staffing needs at the local and national levels. Health human resource planning (HHRP) is a framework, primarily used in high-income countries, for forecasting staffing needs to enable policymakers to anticipate cycles of shortages and abundances in the healthcare workforce(21). However, the HHRP framework includes various forecasting methods ranging from supply/utilization-based approaches (i.e. determining number of needed personnel based on current population needs for health service delivery), demand-based approaches (i.e. setting targets for the delivery of health services based on estimated future population needs) and econometric approaches (i.e. health system components are evaluated in the context of economic systems)(21). These approaches to HHRP involve the use of simulation models or staffing projections in some form. In a review of the HHRP literature O'Brien-Pallas et al. noted the need for better data, particularly on services required per patient and the amount of personnel time associated, to inform projections of healthcare workforce needs(21).

Many approaches to quantify time spent on work tasks have been developed. Among the most common are work-sampling, time efficiency questionnaires, task inventory (i.e. daily logs) and time and motion studies(9, 22, 23). Of these, time and motion studies are generally considered the most reliable method for quantifying the allocation of HCWs time on work tasks(23).

2.5 Study Methods

2.5.1 Time and Motion Studies

Frederick Taylor was one of the first researchers to use time studies in the early 20th century to measure the amount of time workers spent performing tasks on assembly lines in order to improve efficiencies in the manufacturing process(24). Taylor found that inefficiencies in human resources (i.e. "wasted" time) resulted in significant profit loss for manufacturers. Time studies in manufacturing described the details of each worker's time to determine how long it ought to take a worker to perform a specific task(24). In 1914, Frank and Lillian Gilbreth added the component of motion to determine if reducing the movement ("motion") of a specific activity would result in that task becoming more efficient and less costly(24). The Gilbreths were the first to apply this method to the healthcare industry, developing what become known as time motion studies (now referred to as "time and motion studies"). In the modern era, TAM studies have been used in the healthcare context to document workflow-related factors, inefficiencies in healthcare delivery, laboratory procedures, and to support decision-making on implementation of new health technologies(24).

As highlighted in a systematic review by Tipping et al., TAM studies are the best tool for capturing the activities HCWs perform; this method relies on clearly defined categories of activity to enable proper classification, as well as comparison to other TAM studies(25). However, only a limited number of TAM studies have been conducted on HCWs, and the majority of those only observed HCWs for short periods of time (i.e. 1, 3, 5 or 10-minute intervals) performing a set of pre-specified work tasks (i.e. work-sampling) rather than continuous TAM measurements throughout an entire workday. These findings are consistent with Lopetegui et al. found that fewer than 30% of the 212 TAM studies on HCWs retrieved in their literature review involved continuous observations(24). A PubMed search conducted on April 30, 2019 identified 524 articles, 51 of which included TAM

studies of HCWs, although 23 were not continuous TAM measurements. A total of 28 articles were identified of TAM studies of HCWs, but none were of HCWs time on LTBI(22, 23, 25-33). Of the studies identified from LMIC, the TAM studies were performed on HCWs providing HIV or maternal and child care services(34-38).

2.5.2 Self-reported Measures of Time Allocation

Because TAM studies are a costly measurement technique, they are not often performed, particularly in LMIC. Although the TAM method eliminates potential self-reporting bias and captures more precise details of time spent on each category of work activity(31), they are labor intensive, requiring an external observer to be present throughout the TAM day. Consequently, researchers often limit the number of HCWs being observed to minimize the cost of performing a study(29).

Self-reported measures of work activities are often used to capture allocation of time; this method is commonly performed with nursing staff to help evaluate the appropriate allocation of nursing personnel needs(29). Advantages of self-reported data cited in the literature include: 1) avoiding direct observation of HCWs since many professionals do not like to be observed throughout their work day; 2) minimizing misinterpretation of work categories (i.e. it may be more difficult for an observer to classify work tasks than the HCW performing those tasks); 3) eliminating observer bias; 4) alleviating the potential for Hawthorne bias; and 5) allowing HCWs to report activities being performed in situations that are not observable (i.e. capturing private, complex patient interactions generally unavailable to outside observers)(26).

However, self-reporting by HCWs can results in discrepancies if HCWs have different perceptions about how to categorize work activities(31). And concerns about social-desirability bias arise in self-

reported measures of time allocation since HCW responses may reflect self-perceived, rather than actual, job performance(29). Furthermore, few studies compare self-reported categorization of work activities to work-sampling or TAM studies among HCWs(26, 39).

2.5.3 Task-shifting for HCWs

Task-shifting is defined as the transfer of a work task typically performed by a more qualified health professional, such as a doctor, to another HCW with less training and/or experience (e.g. nurse or community health worker (CHW))(40). The concept of task-shifting has been used since the 19th century in France, when "*officiers de sante*" were recognized as a non-physician level of HCW(41).

Since that time, various iterations of task-shifting are discussed in the literature, with much of the focus centered on moving certain tasks from physicians to nurses or CHWs as a more efficient way to reorganize the healthcare workforce, especially in LMIC with limited personnel or human resources(40). Three recent systematic reviews found that task-shifting can be cost-saving and cost-effective for providing HIV care in LMIC(40, 42, 43). Much of the literature on task-shifting in LMIC has centered on HIV care and services, and only a few studies have examined TB care (44-47). Thus, another gap in understanding of the importance of HCWs time allocation and impacts of task-shifting specific to TB and LTBI-related services.

2.6 Summary of Thesis Rationale

The primary goal of my doctoral research was to conduct a TAM study on LTBI services in both high-income countries and LMIC. A second goal was to validate the use of self-reported measures of HCW time in order to provide TB programmes with a simple, inexpensive tool for capturing human resource needs at the local- and country-level. My research aims to provide health systems

and TB programmes with standardized measurement tools to determine the anticipated number of HCWs needed in each cadre (i.e. doctors, nurses, other HCWs) to address the local burden of LTBI.

The recent push from the WHO and the UNHLM-TB to increase LTBI care globally reinforces the need for more data about the impact of increased LTBI services on the healthcare work force time allocation. My doctoral research addresses this gap in the literature and aims to provide important data to health systems and TB programmes for strategically planning scale-up of LTBI services(20).

Chapter 3 Methods

3.1 Overview of methods

All data analyses in this dissertation were conducted using SAS version 9.4 (SAS Institute, Cary, USA). Methods are described for each manuscript individually below. The TAM study, which I led as part of my doctoral research, is described under the section for manuscript 2 but was the method and data source for manuscripts 2-4.

3.2 Manuscript 1

Manuscript 1 was a systematic review of the literature on the reported primary data for diagnosis and treatment of latent tuberculosis infection (LTBI). The specific outcomes of interest for the systematic review included: the number of people eligible for testing for LTBI; the number who initiated and completed screening with IGRA or TST; and the number with positive tests who had chest radiographic and medical evaluation; and who were prescribed, started and completed treatment for LTBI. Details of the methods used in this objective are found in the manuscript.

3.3 Manuscripts 2-4

Manuscripts 2-4 involved the development of standard operating procedures (SOPs) and standardized data collection forms for the TAM study as part of my thesis. The TAM data was collected and used for the analyses presented in manuscripts 2-4. The TAM methodology is described here for all three manuscripts.

3.3.1 Aim and Objectives

The overall goal of the TAM study was to measure HCW time spent on all non-clinical activities as well as clinical activities for patients with active TB, LTBI and non-TB health problems, within a cluster randomized public health intervention trial.

3.3.2 Setting - The Parent Trial

The parent trial for the TAM study was a CIHR-funded pragmatic, cluster-randomized controlled trial (RCT) entitled "*Enhancing the public health impact of latent TB infection diagnosis and treatment 'ACT4.'*" The ACT4 trial consisted of 24 randomisation units (health facilities) in five countries (Benin, Canada, Ghana, Indonesia, and Vietnam)(48). The aim of the ACT4 trial was to evaluate and strengthen the LTBI cascade of care in these settings(48). The primary ACT4 objective was to estimate the increase in the number of HHCs initiating LTBI treatment per newly diagnosed active TB patient (index case) within three months of diagnosis. The secondary objective for the trial was to assess the costs and cost-effectiveness of the LTBI programme evaluation and strengthening(48).

Health facilities randomised to the intervention group received a 20-month public health intervention which consisted of an initial phase of standardized LTBI programme evaluation (Evaluation phase), followed by a locally driven process of selecting solutions to improve the LTBI cascade of care. Tools created as part of the LTBI programme strengthening process included a registry-based system for periodic evaluation of the LTBI cascade of care that corresponds to WHO TB reporting criteria(48). Then the locally chosen solutions were implemented in all intervention sites (Implementation phase). Control sites did not participate in either the Evaluation or Implementation phases, but continued programmes as usual with no explicit LTBI strengthening activities(48).

3.3.3 Time and Motion (TAM) Methodology

The rationale for the use of a TAM study is described in detail in section 2.5.1 above. In brief, TAM studies began in the manufacturing industry(24) but they have been used in other settings, such as health care, to capture time spent on different work tasks. TAMs require an external observer to record a HCWs time and activities continuously throughout an entire workday and classify their work activities based on pre-specified categories (28). TAM studies are considered the most precise method for measuring the amount of time that is required to perform specific work tasks(24). For our study, TAMs were used to capture the daily work activities of HCWs participating in the parent trial (see section 3.3.2 above) on a typical day. Using the TAMs, we aimed to estimate the impacts of an intervention to improve LTBI services on HCWs' time allocation, by conducting prospective TAM measurements before and after a standardized public health intervention during the parent trial.

3.3.4 TAM Sampling

TAM measurements were taken for consenting HCWs at each of the 24 participating health facilities. The sample size for the initial TAM (Evaluation phase) was based on the numbers of HCWs that it was feasible to study at each health facility. Since the African sites had fewer personnel in each health facility, the sample size included all eligible staff. At the other sites, the aim was to recruit a minimum of ten HCWs, with at least three of each HCW cadre (i.e. doctor, nurse, other HCW). Using the baseline proportion of time on LTBI activities from the TAMs in the Evaluation phase (mean = 14%) while accounting for clustering using a design effect, a total of 143 TAMs were needed per study arm to have 80% power (alpha 5%) to detect a 15% change in the proportion of time spent on LTBI-related patient care activities between the Evaluation and the Implementation phases (see **Appendix 4**).

3.3.5 HCW Recruitment

At each participating health facility (site), an initial informational meeting was held to describe the TAM study and allow HCWs to ask questions. Following this meeting, HCWs were asked if they agreed to participate, and if they consented then their names and contact information were added to the roster for the TAMs at that health facility.

3.3.6 TAM Study Training

To ensure standardized measurements, I provided training to all research staff performing the TAMs on how to observe and record HCWs time using standard data collection forms and properly classify and code each observation (see **Appendix 2**). I conducted the TAM training for research assistants in-person at the sites in Benin, Ghana and Montreal, and via Skype for all other sites. Training consisted of a power-point presentation with detailed review of all classification categories, example scenarios and instruction on how to properly complete the TAM forms. Refresher trainings were provided before each phase in the parent trial at all sites.

3.3.7 Data Collection

Data collection for the TAMs occurred at three time points: 1) Evaluation phase: January – March 2017; 2) Implementation phase: January – March 2018; and 3) Crossover phase: January – March 2019. A total of 140 and 143 HCWs completed the TAMs in the Evaluation and Implementation phases, respectively, and 132 HCWs completed TAMs in the Crossover phase of the parent trial. Since the TAM study aimed to determine the proportion of HCWs total time worked throughout the day spent on direct patient encounters, before and after the intervention, continuous TAMs were needed to capture complete data on their entire workday(28).

3.3.8 Measurement Instruments

The work tasks performed by HCWs were categorized into three main types of activities, and recorded on the TAM data collection forms: 1) Direct patient care (i.e. any face-to-face encounter or phone call with a patient); 2) Other clinical activities (i.e. charting, dictations, reviewing laboratory results or x-rays); and 3) Training or administrative tasks (i.e. supervising trainees, being trained, meetings or emails). Time spent on breaks (i.e. restroom, meals or personal phone calls) was recorded on the TAMs but removed from analyses. Direct patient care was sub-categorized according to the patients' medical conditions which were categorized as: 1) LTBI; 2) active or suspected TB; and 3) non-TB, meaning any other medical condition.

A key advantage of the TAM methodology of data gathering is that the TAMs provide a precise measurement of the time spent on tasks being observed. We revised the data collection forms following completion of the first set of TAMs in the Evaluation phase by adding codes to capture details on each of the steps in the LTBI cascade of care. These steps were: 1) Identification of contacts; 2) Placing TST or drawing blood samples for IGRA; 3) Reading TST; 4) Conducting medical evaluation; 5) Recommending and discussing LTBI treatment; and 6) LTBI treatment follow-up visits.

3.4 Manuscript 2

Manuscript 2 focused on the use of the TAM methodology to estimate human resource needs for scale-up of LTBI services along the cascade of care.

3.4.1 Aim and Objectives

The aim of this study was to estimate the annual human resource needs to provide LTBI care to all HHC of new, confirmed, pulmonary TB patients in each of the countries participating in the parent trial. The objective of the study was to quantify the time it takes HCWs to perform the work tasks associated with each step along the LTBI cascade of care for all HHC in Canada (a high-income country) and in four LMIC.

3.4.2 TAM Study

The methodology for the TAM study is described in detail above (see section 3.3). Additional categories of work activities were added to the TAM forms, during the Implementation phase of the parent study, to capture each of the specific steps of the LTBI cascade of care (see section 3.3.8). Adding these detailed categories enabled me to capture the precise time spent on each step, which had previously not been done in a systematic way. Other studies, particularly costing and cost-effectiveness studies, have estimated HCWs time to perform certain steps such as placing or reading a TST, but not using the TAM methodology to precisely measure time(49-56). Data from our TAM study was aggregated for each individual HCW at each step during the TAM day. This data was used to inform the linear mixed models used to determine the average HCW time at each step (see section 3.4.3).

3.4.3 Linear Mixed Models (LMM)

Cluster randomized trials are used when it is not possible to randomize at the individual level due to logistic, financial or ethical reasons and so randomization occurs at the group level (i.e. community, hospital ward, institution)(57). The parent trial (ACT4) was a pragmatic, cluster RCT design, and the intervention was at the group level of each health facility. But a concern with cluster RCTs is that

individual units within a cluster are correlated which needs to be considered for sample size calculations (see section 3.3.4) and analyses(57). Multilevel modeling is a methodology for analyzing data with complex patterns of nested sources of variability(58). There were two-levels of variability in the TAM study: 1) between different health facilities (site); and 2) between individual HCWs. Mixed effects models are a statistical method of regression analysis that assumes some coefficients are random and others are fixed in order to avoid drawing incorrect conclusions by not accounting for the different sources of variability(58).

Random effects are used to model the correlation between individuals within the same cluster(57). In our analysis, clustering was accounted for at the health facility (site) level [i] and random effects for the individual HCWs level [j]. Some statisticians argue that many observations are needed for reliable estimates (i.e. 50 groups of at least 20 observations)(59) but others have found that it is only when there are fewer than 10 groups that estimates become problematic due to issues with consistency and efficacy of estimates(58). Despite the lack of agreement in the literature on the minimum number of clusters required, the 24 health facilities in our TAM study provide sufficiently large numbers for analysis using linear mixed models (LMM).

LMMs were fit for each step in the LTBI cascade of care (i.e. steps #1-6, see section 3.4.2) in order to estimate the effect of the following covariates on HCWs time: 1) HCW cadre (i.e. doctor, nurse, other HCW); 2) TB-specific job role; 3) type of setting (i.e. high-income vs. LMIC). A total of 108 models were run; one model for each covariate for all six steps of the LTBI cascade of care (see example for step #1 below).

Example: $\mathbf{Y_{ij} = \beta_0 + \beta_1*(LMIC) + u_j + e_{ij}}$

- where: **Yij** = HCW time spent on work-related tasks for identification of HHC (step #1); **LMIC** = dichotomous variable (LMIC = 1, Canada =0); **site** = i; **HCW (individual)** = j

In this model, β_0 is the intercept which represents the average time HCWs spent identifying all HHC (step#1) for all HCWs in all sites; β_1 is the additional HCWs time on that step in LMIC. Each health facility (site) had a random effect [u(i)] which was added to β_0 to determine the average HCWs time spent on that step at that specific health facility (site). Final estimates of total HCWs time required at each step in the LTBI cascade presented in the manuscript were based on statistically significant models.

3.5 Manuscript 3

Manuscript 3 focused on quantifying overall changes in the amount of time HCWs spent delivering LTBI-related patient care activities following the intervention from the parent study to strengthen LTBI-services.

3.5.1 Aim and Objectives

The aim of this study was to estimate, using a TAM study, the overall changes in HCWs time devoted to patient care activities relating to LTBI in the context of a standardized intervention designed to increase diagnosis and treatment of HHC with LTBI. This study further aimed to determine if there were any changes in HCWs time on other patient care activities (i.e. negative impacts to active TB or non-TB patient care) following the strengthening intervention.

3.5.2 TAM Study

The TAM study (see section 3.3.3) conducted in the Evaluation and Implementation phases of the parent study (ACT4) served as the data for analysis presented in manuscript 3. The primary outcome for this study was the change in HCWs proportion of total hours worked on the TAM day spent on LTBI-related activities (i.e. aggregated time on all steps of the LTBI cascade of care discussed in manuscript 2 above).

3.5.3 HCWs Time Allocation

HCWs time was calculated by aggregating total time spent in each category of activities (see section 3.3.8 above). Proportion of total time spent on the three categories of activities (other clinical activity, direct patient care, and training/administrative tasks) was calculated as time (hours) in each category divided by total time worked (hours) on the TAM day. Proportion of time spent on subtypes of direct patient care was calculated as: time on a specific type of patient care (i.e. active TB, LTBI, non-TB) divided by total time (hours) on direct patient care for each individual HCW. Then, time (hours) on other clinical activities was apportioned to the three reasons for patient care based on the proportion of direct patient care time calculated above. Total patient care time was calculated as observed time (hours) on direct patient care plus the apportioned time (hours) on other clinical activities. Finally, the proportion of total time by reason for care was calculated as the category-specific total patient care time (hours) divided by total time on all direct patient care (i.e. all three reasons for care plus other clinical activity). Formulas for the calculations are shown below:

> **Equation 1**: Proportion of direct patient care on LTBI = Time (hrs) on LTBI / total time (hrs) on direct patient care (Active TB + LTBI + Non-TB)
>
> **Equation 2**: Total LTBI patient care time = Total hours on LTBI + (Proportion of time on LTBI (equation 1 above) x (time on other clinical activities (hrs))

Equation 3: Proportion of total LTBI patient care time = Total LTBI patient care time (equation 2) / (total hours on direct patient care + total time on other clinical activities (Active TB + LTBI + Non-TB))

For these calculations, all HCW time spent on other clinical activities on the TAM day was assumed to pertain to the same mixture of time as the type of patients that presented in the clinic on the same TAM day. Thus, any error should be non-differential as there is no reason for a HCW to systematically perform other clinical activities on one patient group more than another.

3.5.4 Linear Mixed Models

LMMs were fit for each type of patient care using the adjusted proportions (i.e. attributing proportion of time on other clinical activities to direct patient care) of time calculated above. The dependent variable for the LMMs was the proportion of hours worked in each category. Each model included a term for phase, intervention and their interaction (see example for LTBI below).

Example: $\mathbf{Y_{ij} = \beta_0 + \beta_1*(Phase) + \beta_2*(Intervention) + \beta_3*(Phase\ x\ Intervention) + u_j + e_{ij}}$

- where: **Yij** = Total LTBI patient care time; **Phase** = dichotomous variable (Evaluation = 0, Implementation =1); **Intervention** = dichotomous variable (Control sites = 0, Intervention sites = 1); **site** = i; **HCW (individual)** = j

In this model, β_0 is the intercept which represents the average time HCWs spent on LTBI-related patient care activities for all HCWs in all sites; β_1 is the additional HCWs time after Implementation of the intervention; β_2 is the additional HCWs time on LTBI-related patient care at intervention sites; and β_3 is the additional time for HCWs after Implementation phase among HCWs who received the intervention. A random intercept for health facility (site) was included to account for

correlation between HCWs in the same facility, and a random intercept for HCW (individual) was included to account for correlation between observations in the same HCW.

3.5.5 Sensitivity Analyses

Two types of sensitivity analyses performed: 1) adjusting for covariates; and 2) including only the HCWs who participated in TAMs in both the Evaluation and Implementation phases (i.e. had two TAM measurements). The second sensitivity analysis is described in the manuscript (see Chapter 6) and therefore not outlined in further detail here.

In sensitivity analyses, we considered adjusting for the following covariates: 1) sex; 2) TB-specific job position; 3) HCW cadre (i.e. doctor, nurse or other HCWs); 4) country; and 5) type of setting (i.e. Canada vs. LMIC). Interactions, defined *a priori*, were considered between receiving the intervention and type of setting, sex, cadre and TB-specific job. These sensitivity analyses did not include: 1) a large number of covariates; 2) multiple outcomes; 3) numerous subgroups; or 4) multiple definitions of exposure or outcome. Therefore, no adjustment was made for multiple hypothesis testing particularly since the analyses were exploratory in nature.

An example of the LMM for an interaction with type of setting is shown below but were performed for all interactions of interest:

Example: $\mathbf{Y_{ij} = \beta_0 + \beta_1*(Phase) + \beta_2*(Intervention) + \beta_3*(Phase\ x\ Intervention) + \beta_4*(LMIC) + \beta_5*(LMIC\ x\ Phase) + \beta_6*(LMIC\ x\ Intervention) + \beta_7*(LMIC\ x\ Intervention\ x\ Phase) + u_j + e_{ij}}$

- where: **Yij** = Total LTBI patient care time; **Phase** = dichotomous variable (Evaluation = 0, Implementation =1); **Intervention** = dichotomous variable (Control sites = 0,

Intervention sites =1); **LMIC** = dichotomous variable (Canada = 0, LMIC = 1); **site** = i; **HCW (individual)** = j

The β coefficients are interpreted as explained in the example LMMs above (section 3.5.4). In the interaction models, our main interest for the sensitivity analyses was to determine if there was a significant effect of the interaction (β_7) for HCWs working in LMIC at intervention sites following the Implementation of the intervention to improve LTBI services.

3.6 Manuscript 4

Manuscript 4 involved the development of an interviewer administered TEQ as a simpler, affordable tool to be validated to replace TAMs in the programmatic setting.

3.6.1 Aim and Objectives

The aim of this study was to assess the criterion validity of the TEQ compared to the TAMs, considered the reference standard, for measuring time on three pre-specified categories of clinical work: 1) total hours worked; 2) time (hours) on active TB patient care; 3) time (hours) on LTBI patient care. This study also aimed to assess the day-to-day variability of HCWs time on the same three pre-specified categories of clinical work, across a period of two work weeks (i.e. 10 consecutive workdays).

3.6.2 Questionnaire Development

Despite the precision that TAMs provide for a single measurement day, a key disadvantage of TAMs is the inability to capture the day-to-day variability of work tasks(29). Questionnaires are a method of capturing data on a wide range of health outcomes(60). But health questionnaires typically use either categorical or dimensional forms of assessment(61). Categorical assessment is aligned with

more traditional medical distinctions of diagnosing a patient as having (or not having) a certain medical condition, often based on a pre-determined threshold at which point a person is considered to need a certain intervention (i.e. diastolic blood pressure over 90 mmHg is considered hypertensive)(61). Dimensional models are credited to S. Smith Stevens who introduced the idea of 'levels of measurement' based on the theory that the more finely something is measured, the better(62).

However, TAM studies do not measure the presence (or absence) of a disease state or assess the level of health. Standard measures of agreement, such as Cronbach's alpha or kappa statistic are not appropriate for measuring the validity and reliability of the TEQ compared to the TAMs because the data were not categorized into scores or other classifications to enable such categorical comparisons. Rather, TAMs are a continuous measure of time. The continuous reporting in the TAM makes it more complicated to determine agreement with self-reported measures (i.e. TEQ) since it requires HCWs to keep track of their time throughout the entire day (i.e. requires longer recall period) to enable comparisons of the two method. But since the TEQ requires recall for a block of activities (i.e. all LTBI patient care throughout the day) it is not a truly continuous measure of time. This may introduce some form of cognitive bias if HCW have difficulty recalling certain patient encounters or other work activities performed throughout the day.

3.6.3 Questionnaire Measurement Properties

Terwee et al. outlined eight key measurement properties that should be assessed for development and evaluation of health status questionnaires: 1) content validity, 2) internal consistency, 3) criterion validity, 4) construct validity, 5) reproducibility, 6) responsiveness, 7) floor and ceiling effects, and 8)

interpretability(60). Not all eight of these measurement properties are relevant to the development of every questionnaire but their relevance should be considered in the process.

To develop the interviewer administered TEQ used in my doctoral research, I focused on three of the measurement properties outlined above: 1) content validity, 2) criterion validity, and 3) reproducibility. I chose to limit it to these as they are the three most commonly discussed measurement properties in the literature(60) and were applicable, measurable and comparable between the two tools (i.e. TAM and TEQ) for my study data.

Pearson's correlation coefficient (*r*) is one of the most frequently used measures of agreement for continuous variables but is also one of the least appropriate(63). Although commonly used, Pearson's *r* is a measure of linear association and not of agreement(63). For the TAM and TEQ measurements, the goal of our study was to demonstrate the validity of the TEQ as a tool to assess HCWs time allocation, but we did not expect a perfectly linear association between the two measures, thus Pearson's *r* was not considered an appropriate measure to use for this study.

3.6.4 Content Validity

Content validity refers to whether the concepts of interest are comprehensively represented by the items, or domains, in a questionnaire(60). Key components to content validity include: measurement aim of the questionnaire, target population, concepts the questionnaire intends to measure, item selection and interpretability of the items(60). A standard method to asses content validity is through the use of subject matter experts that have expertise in the content of the test or domain on the questionnaire(64). Subject matter experts are often used to ensure that questions address key content areas and to lessen interpretational ambiguity(64). Our study consulted principal investigators at the

local health facilities as the subject matter experts, since they are clinicians responsible for providing TB care and managing TB clinical services. These principal investigators were consulted to ensure that the categories for the TEQs included the necessary content items, or domains, and that they were well-aligned with the TAMs to enable validation of the TEQ.

3.6.5 Criterion Validity

Criterion validity is the correlation of a new or different measurement method with some other measure of the item (i.e. work task) under study, ideally a reference standard which has been accepted in the field(61). There are two types of criterion validity: concurrent and predictive validation. The TEQ aimed to demonstrate ***concurrent validation*** which is possible when the new measurement method is given at the same time as the reference standard to enable correlation of the two measures(61). One advantage of criterion validity is that it is often cost-saving since it requires administering the questionnaire to fewer people who are selected as participants for both measures, and thus reduces the time for data collection (i.e. only performed once for both tools)(64). However, one disadvantage with concurrent validation is that since participants are selected there is potential for selection bias if the motivation of participants is linked to their performance in some way (i.e. if only HCWs who keep detailed notes of their time allocation participated in the TEQs)(64).

Fortunately, there is no potential for selection bias in our TEQ study, since almost all HCWs (95%) who participated in the TAMs completed the TEQs as well. For continuous criterion variables, the appropriate measure of effect size is correlation(64). Thus, criterion validity was assessed in our study via correlation to determine how well correlated the two measurement tools (i.e. TAM and TEQ) were to one another among the same individuals (i.e. HCWs participating in the TAMs)(61) based on the accepted correlation threshold of at least 0.70 or higher(60).

3.6.6 Reproducibility

Reproducibility is the stability between repeated measures (i.e. test-re-test) within an individual(60). Unfortunately, reproducibility was not a measure that could be assessed by the TAMs and TEQs since the nature of clinical work is that there is high variability, both between HCWs on the same day and within the same HCW on multiple workdays. Reliability is linked closely with reproducibility and is defined as 'the degree to which the measurement is free from measurement error(65, 66). For continuous measures, such as time estimates for the TEQs, the intra-class correlation coefficient (ICC) is the most commonly used parameter to asses reliability(60). The ICC is similar to the kappa statistic for continuous variables and has the advantage over Pearson's *r* (or Spearman's correlation coefficient) of being a true measure of agreement because it combines information on both the correlation and systematic differences between measurements(63). The McGraw and Wong convention is a two-way, mixed effects model for absolute agreement with a single measure and is the preferred measurement for agreement using the ICC and was used for the purpose of our study(60, 67).

3.6.7 Pilot of the time-estimation questionnaire (TEQ)

The initial stage of the TEQ aimed to develop a simple measurement tool (i.e. questionnaire) to assess HCW time spent on all TB, active TB and LTBI activities on the same day as the TAM. As previously discussed, the additional personnel (i.e. external observer) and associated costs, along with feasibility issues, are key limitations of the TAMs. My doctoral research aimed to assess the use of a different instrument (TEQ) that could be completed at the end of the same day to quantify HCWs time in clear, broad categories of work to enable HCWs to recall their time without difficulty. The TAMs provide a detailed breakdown of HCWs time allocation but are not feasible as a measurement tool in the real-world, programmatic setting. My goal was to develop and validate a

standardized tool that was simple, affordable and could be used in programmatic settings to gather data on HCWs time allocation for staffing and planning purposes, particularly in the context of LTBI service scale-up. The items on the initial TEQ were limited to TB-related patient care activities and did not include any questions related to other work activities (see **Appendix 3A**).

After piloting the TEQ and assessing the agreement of the TAM and TEQ measures, the TEQ was not performing sufficiently well (i.e. did not meet the 0.70 threshold for agreement)(60). Using item selection methods, we decided to add questions to be aligned with the TAM categories of time. Traditional content validity techniques tend to apply item reduction following review of pilot results, however we added questions to the TEQ(60). Adding questions was a means to mimic the TAM categories to enable clearer understanding for HCWs since they were already familiar with those activity categories. The revised TEQ was piloted in four HCWs in Ghana to ensure the additional questions and table format of the tool was straightforward for the interviewers and HCWs. There was good correlation between the TAM and TEQ in those four HCWs, and positive feedback from the research assistants conducting this mini-pilot of the final TEQ forms, thus we decided to use this final version of the TEQ.

3.6.8 TEQ Following Pilot and Revision

The final, revised TEQ was presented in a table format with boxes for seven categories of HCW time (in hours) for each day in the week: 1) Total hours worked; 2) Direct patient care; 3) Other clinical activities; 4) Training/administrative tasks; 5) active or suspected TB; 6) LTBI; and 7) non-TB (see **Appendix 3B**).

3.6.9 Training

The investigator (HA) conducted a training via Skype on the final TEQ instrument for the research assistants in each country. Research assistants were provided written instructions with the TEQ forms on how to administer the questionnaire at the end of each TAM day, and then to follow-up with each HCW at the end of the day for 10 consecutive working days, either in-person or via phone calls. The first two TEQs from each health facility were sent to the investigator (HA) to verify that the time estimations were entered properly and provided research assistants with any feedback.

3.6.10 Data Collection

The TEQ was developed to be a tool to replace the TAMs in the programmatic setting. As such, the main goal of piloting and refining the TEQ was to ensure that its construct and criterion validity could be assessed compared to the TAMs. Data collection took place in conjunction with the TAM study at health facilities among the same HCWs who participated in the TAM study. At the end of the TAM day, research assistants asked each HCW to estimate the number of hours they worked that day in the four main categories corresponding to the TAMs: 1) Total hours worked; 2) Direct Patient Care; 3) Other Clinical Activities; 4) Training/Administrative tasks. It was explained to HCWs that categories #2-4 should equal the total number of hours worked that day (category #1). Then, HCWs were asked to estimate the number of hours they worked on three main reasons for direct patient care: 1) Active TB; 2) LTBI; and 3) Non-TB. The time in those three categories of patient care should have added up to the time reported for direct patient care (main category #2, above). The final TEQ form was in a simple table format that included a box for each of the seven categories and a column for each day of one full work week. After reviewing the TEQ form in-person at the end of the TAM day to ensure each HCW clearly understood the categories of work

tasks, the research assistant called the HCW to complete the TEQ form at the end of every day for two full weeks (i.e. 10 consecutive days of work) (see **Appendix 3B**).

Final data collection for the TAMs and TEQs occurred between January – March 2019. A total of 132 HCWs participated in the TAMs and 125 HCWs participated in both the TAMs and TEQs (i.e. 7 HCWs participated in the TAMs but did not complete the TEQs).

3.6.11 Testing Agreement

Scatterplots and Bland-Altman plots are two of the most common methods to visually assess agreement for two continuous measurement instruments(63). Scatterplots are a simple, visual method to assess strength of the relationship based on cluster of data points and proximity to a straight line(68). Data points that are clustered closely together for the two measurement tools, TAM and TEQ, indicate a strong relationship for the tools. A linear relationship between the two measurements of HCW time would be shown if the data points lie close to a straight line(68). Bland-Altman plots are a graphical method to compare two measurement techniques by plotting the difference between the two measurements (i.e. TAM minus TEQ measurement) against the reference standard (i.e. TAMs)(69). Using this method allows for the comparison of the time on each category of activity between two measurement instruments (i.e. TAM and TEQ) in the same individual HCW.

Furthermore, the limits of agreement method examines the average difference between the two methods across all participating HCWs, while accounting for the variability in the differences across individuals(69). It should be noted that there is an assumption with the limits of agreement approach, that the difference between the two methods is relatively stable across the range of

measurements(69), which holds true for the TAM and TEQ study since we did not transform the data in anyway. If there was perfect agreement between the two measurements, then the x-axis for the Bland-Altman would be at zero, indicating no difference between the time reported on the TEQ from the TAM measurement (i.e. perfect agreement) and no data points outside of the dashed lines for the limits of agreement (i.e. no bias).

3.6.12 Intra-class correlation coefficient (ICC)

The intra-class correlation coefficient (ICC) was used to measure the degree of correlation and agreement between the TAM and TEQ measurements(67, 70, 71). Using the McGraw and Wong convention, a two-way, mixed effect for absolute-agreement with a single-measurement was used to calculate the ICC for the TAM and TEQ measurements(67). Correlation of the TEQ with the TAMs (i.e. reference standard) above the threshold of 0.70 was considered to meet the requirements to achieve criterion validity(60).

We used a linear mixed model (LMM) to account for clustering at the health facility (site) level for the primary analysis comparing the TAM and TEQ measurements on the same day. The ICCs from the LMMs express the similarity between HCWs in the same health facility, compared to those at other health facilities. The general formula for ICC is the following(63):

$$\text{ICC} = \frac{V_b}{Vb+Ve}$$

- where v_b = variance between individuals and v_e = unwanted variance ("error").

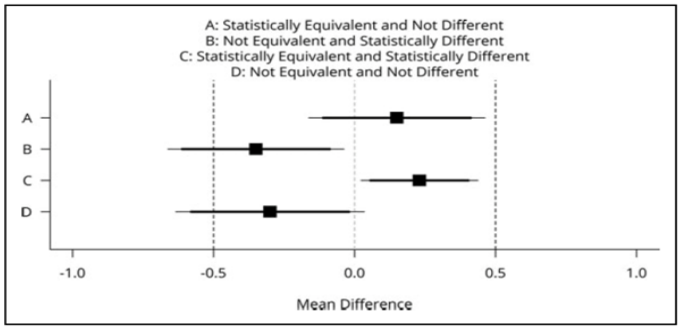
ICCs provide an estimate of how much variability was due to each level of clustering(58). ICCs are similar to a kappa statistic for continuous variables, and ranges from 0 – 1(63). The ICC has the advantage over a Pearson's (r) or Spearman's correlation coefficient because it is a true measure of agreement(63). The ICC is interpreted as measuring how similar HCWs in the same health facility

are with one another, thereby measuring the effect of being a HCW working at a specific facility on the average time spent on LTBI due to working at that health facility. ICC levels above 0.5 for ICC indicate that more of the variability was due to between-health facility differences than to differences of HCWs within the same facility(58). In the TEQ study, the ICC had an additional level of clustering at the individual HCW level since there were repeated measures for each HCW(i.e. 10 days of TEQ values for each individual HCW)(58).

3.6.13 Equivalence Testing

In a frequentist framework, it is statistically impossible to test the hypothesis that the true difference in effect between two measures is zero(72). When comparing two treatments, or two measurements (i.e. TAM and TEQ), an alternative hypothesis is to test a finite but clinically meaningful interval of "equivalence" between the two measurements known as equivalence testing(73). In equivalence testing, the hypothesis is that the two measurement tools are not equivalent, thus we reject the test hypothesis when the confidence interval (CI) falls completely within the equivalence interval(73). The values of the upper and lower threshold that would be considered a clinically small enough difference between two measurement tools (i.e. TAM and TEQ) in order to be considered equivalent are set *a priori* (72). To conclude equivalence, the 95% CIs around the observed mean difference should exclude these upper and lower bounds(72). If the estimated difference, and its 95% CI is entirely within the limits, we may conclude that the TAM and TEQ are statistically equivalent (see figure 3.1, at right)(72).

Figure 3.1



. Mean differences (black squares) and 90% confidence intervals (CIs; thick horizontal lines) and 95% CIs (thin horizontal lines) with equivalence bounds $\Delta_L = -.5$ and $\Delta_U = .5$ for four combinations of test results that are statistically equivalent or not and statistically different from zero or not.

Chapter 4 The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis

4.1 *Preface: Manuscript 1*

Prior to our systematic review and meta-analysis, literature reviews existed of treatment outcomes for patients with latent tuberculosis infection. However, there had not previously been a synthesis of studies collecting data for each of the steps of the patient journey for identification, screening and treatment for latent tuberculosis infection. The manuscript presented here filled that gap in the literature to summarize the evidence of the proportions of eligible contacts who completed each step.

The two main outcomes of interest for this systematic review and meta-analysis were: number identified and screened for LTBI and the number of those eligible who completed preventive treatment. Since I knew that not all studies would report on each step in the LTBI cascade of care, the goal was to provide estimates of completion rates at each step based on all available data. And I aimed to formally apply the cascade of care framework to tuberculosis as a means of clarifying the discrete steps in the patient journey required for latent tuberculosis care.

The following manuscript is entitled "**The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis**." This work was peer-reviewed and published in the *Lancet Infectious Diseases*.

4.2 *Manuscript 1*

The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis

Abstract:

Background: The WHO has estimated that one-third of the world's population has latent tuberculosis infection (LTBI), and that less than 5% are diagnosed and treated to prevent tuberculosis (TB). We conducted a systematic review of studies reporting the steps in the process from initial TB screening through to LTBI treatment, which we termed the LTBI Cascade of Care.

Methods: Studies were included if they reported primary data from a cohort investigated and treated for LTBI. The search was conducted using key words related to LTBI in three electronic databases. Meta-analysis was performed using random and fixed effects analyses in SAS.

Results: The review included 58 studies, describing 70 distinct cohorts, comprised of a total of 748,572 persons. Steps in the Cascade associated with greater losses included: 72% of those intended for screening completed testing, 66% of those with a positive LTBI test completed medical evaluation, of which only 66% were recommended therapy, and 69% completed treatment if started. Steps with fewer losses included: TST reading or receiving an IGRA result, referral for evaluation if test positive, and accepting to start therapy if recommended. Overall, of those estimated to have LTBI, less than 20% completed LTBI treatment. Factors associated with fewer losses were an immune-compromising medical indication, being part of contact investigations and use of rifamycin-based regimens.

Conclusions: This review identified major losses at several steps in the LTBI Cascade of Care. Improving management of LTBI will require programmatic approaches to address the losses at each step in the Cascade.

Keywords: Tuberculosis, Latent tuberculosis, Cascade of Care, Systematic Review

Research in context panel

Evidence before this study

Latent tuberculosis infection is estimated to affect more than a third of the world's population. Although methods exist to diagnose and effectively treat latent tuberculosis infection, they are slow and imprecise. This scarcity leads to difficulties in the identification and treatment of this vast pool of infected people, which has been identified as a key barrier to global tuberculosis control. There are multiple steps in the care process from initial identification of people with latent tuberculosis infection who could potentially benefit from therapy, until treatment completion. Patients can, and do, drop-out or are lost at each of these steps. We searched three electronic databases, for studies that were published between 1948 and June 20, 2016, describing the full procedures of diagnosis, evaluation and treatment of latent tuberculosis. There have been multiple studies of the problems leading to non-completion of therapy once it has been started: one systematic review identified 68 studies from North America alone. This systematic review showed inconsistent associations between adherence and patient factors or treatment characteristics. Far fewer studies have estimated the losses and drop-outs at earlier steps, largely because these patients are not seen by health-care personnel, and so it is unknown how often and why these problems occur. We undertook this systematic review to understand the extent, and reasons for patient losses, during the entire latent tuberculosis cascade of care.

Added value of this study

To our knowledge, our study is the first to conceptualise the latent tuberculosis cascade of care and develop an explicit framework of analysis to account for the losses during each individual step in this cascade, from initial identification of risk of infection, through to completion of treatment. We show estimated losses at each step and identify the patient and health system factors associated with those

losses. Notably, losses before starting therapy accounted for greater net reduction of the public health benefit of latent tuberculosis infection management than did patient non-adherence with therapy once started.

Implications of all the available evidence

Interventions that aim to reduce losses at the early steps of the latent tuberculosis cascade of care should enhance the public health impact of diagnosis and treatment of infection more than will interventions that focus on improving patients' completion of treatment. To achieve the goals of the new WHO End TB Strategy of reducing the tuberculosis incidence rate to less than ten infections per 100 000 by 2035, latent tuberculosis management needs to be substantially scaled up. Our findings suggest that every step in the entire cascade of latent tuberculosis care will need improvement to achieve that goal. And, although we clearly demonstrated the extent of the problem and some health-system factors associated, very little published evidence was found of successful interventions to reduce the losses at every step.

Introduction:

In many high-income countries, reactivation of latent tuberculosis infection is estimated to account for more than 80% of all incident cases of tuberculosis, and prevalence of latent tuberculosis might exceed 50% in certain populations(1). There is no gold-standard test to diagnose latent tuberculosis, but based on currently available immune-based tests, a third of the world's population has presumptive latent tuberculosis(2, 3). Although an updated estimate of the global burden of latent tuberculosis would be very helpful(4), it is accepted that there is a vast reservoir of latent infection, from which it is estimated that approximately 100 million people will develop active, contagious tuberculosis over their lifetimes(5).

Management of latent tuberculosis is considered to be one of the core interventions for tuberculosis elimination. In the 1960s and 1970s several studies showed that isoniazid for 6-12 months could significantly reduce the risk of reactivation of active tuberculosis in people with a positive tuberculin skin test (TST)(6, 7). However the length of therapy, need for close follow-up, and risk of potentially fatal hepato-toxicity(8) reduced uptake, acceptance, and completion of therapy(9). These problems substantially reduce the cost-effectiveness(10) and the population-level epidemiological impact of this approach(11, 12). As a result, in the past two decades, randomised trials have aimed to identify shorter regimens that are as effective as, yet safer and more acceptable, than isoniazid(13). These trials have identified several alternative rifamycin-based regimens that have recently been recommended for treatment of latent tuberculosis infection(14-16).

Factors associated with non-completion of treatment of latent tuberculosis have received considerable attention: a recent systematic review identified 68 studies investigating non-completion from North American centres alone. The authors noted the importance of strategies to improve treatment adherence that are specific to the context and populations being served, and that a one-size-fits-all approach was unlikely to be successful(12). However, there has been very little

recognition for the impact of losses during the many steps in patients' trajectories before therapy is begun. People with latent tuberculosis might not be identified for screening, and even if they are, might not be tested, or a TST might be done but not read, or an interferon-gamma release assay (IGRA) result might not be received by providers. Individuals with a positive TST or IGRA might not complete medical evaluation (eg. symptom check, physical exam and chest radiography)(17-21), and providers might not recommend therapy or treatment might not be started or completed. Given the lack of recognition of this problem, it is not surprising there have been very few studies of interventions to prevent the losses and drop-outs at these steps. With the new End TB Strategy to eliminate tuberculosis by 2035, there has been increased recognition of the importance of addressing latent tuberculosis infection. This systematic review offers evidence for the importance of addressing the losses along the cascade of care, if efforts to eliminate tuberculosis are going to be successful.

We aimed to systematically review the published research about the so-called cascade of care in latent tuberculosis diagnosis and treatment. Specific outcomes of interest included: the number of people eligible for testing for latent tuberculosis infection; the number who initiated and completed screening with IGRA or TST; and the number with positive tests who had chest radiographic and medical evaluation; and who were prescribed, started, and completed treatment for latent tuberculosis infection.

Methods:

Search strategy and selection criteria

We did a systematic review and meta-analysis of study-level observational data. We searched MEDLINE (via OVID), Embase, and Health Star for cohort reports of diagnosis and treatment of latent tuberculosis infection published between 1946 and April 12, 2015. To identify additional relevant articles, we searched the Cochrane Database of Systematic Reviews and used reference lists

of identified reviews from this search, original articles, other recent reviews, and recent treatment guidelines(22). Search terms were: "latent TB OR latent tuberc* OR tuberc* infection or inactive tuber*" OR "screening OR contact OR investigation OR finding OR tuberc* screening" OR "adherence OR completion OR compliance OR yield".

We used MOOSE guidelines for reporting of observational studies(23). We included studies published in English, French, Italian or Spanish that reported primary data. We excluded randomised trials, case-control studies, reviews, editorials, and letters, in addition to surveillance or other studies that reported aggregate data and not outcomes at the level of individuals. We included studies that reported, at a minimum, the number of people intended for latent tuberculosis infection screening and the number completing latent tuberculosis infection treatment (ie, the two ends of the cascade). Studies that reported contact investigations without reporting the number intended to be screened were included if the number of index cases with pulmonary tuberculosis was given. In these studies, we extrapolated the number of contacts from the number of index cases, using the average number of close contacts identified per index case reported in two recent systematic reviews(7, 24). We included studies that did not report the number of patients completing therapy for latent tuberculosis infection if the number starting therapy was given. In this circumstance, we extrapolated the number completing therapy based on the number starting and indication for testing, using data from a recent systematic review on treatment completion that was stratified by indication(12).

Data analysis

Data were abstracted by two reviewers (HA and DM) using a standardised data abstraction form. Both authors in duplicate extracted data for 14 studies and then findings were checked for concordance. Data from the remaining studies was abstracted by a single reviewer. Data collected included: author, years, country (using World Bank classifications as low-middle income country

[LMIC] or high income), population screened and risks for latent tuberculosis infection, type of screening test (TST or IGRA), characteristics of population studied (age, sex, etc), and treatment given (isoniazid or rifamycin based). Programmes were labeled outbreaks or pilots if characterised as such by the authors of the source paper; otherwise the program was considered routine. Numbers extracted were the reported numbers of patients who: were intended to be screened (1), tested (2), TST read or IGRA result obtained (3), completed medical evaluation (4), recommended therapy (5), accepted or started therapy (6), and completed therapy (7). Data for risk factors for losses at these steps were also recorded.

The pooled proportion of participants with latent tuberculosis infection completing each step in the cascade was estimated using random effects meta-analyses with PROC Nlmixed in SAS version 9.3. These pooled proportions were also estimated in subgroups stratified by different characteristics of interest. The key outcome was the proportion who completed therapy for latent tuberculosis infection of all those estimated to have latent tuberculosis in the population being screened. This was calculated by dividing the number of people who completed therapy by those estimated to have latent tuberculosis (total number intended to be screened multiplied by the proportion with a positive test), and was used to generate forest plots of the estimated impact on the full range of the cascade. Extrapolated values for number intended to screen and completing therapy were not used for the analysis of factors associated with losses at each step. To estimate the cumulative losses at each step, the proportion remaining at that step was multiplied by the proportion remaining after the preceding step; we estimated these pooled proportions and 95% CI using fixed meta-analyses (using Proc Glimmix in SAS version 9.3). We estimated heterogeneity with the I^2 statistic (25). Sensitivity analyses were done by repeating analyses without key groups for which services might be organised very differently: prison populations, HIV-infected populations, and the general population.

Role of the funding source

The funder had no role in study design, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

We identified 110 full-text articles for review, of which 58 studies were considered eligible and included in the systematic review (figure 1) (10, 17-21, 26-77). All studies were published after 1990, and 50 were published since 2000. These studies described 70 distinct study populations (henceforth referred to as cohorts; n=748 572), of which 59 (n=741 540) were from high-income countries and 11 (n=7032) from LMIC (studies summarised in appendix pp 2-3). 36 cohorts (n=418 367) received care as part of routine programmes, whereas 25 (n=327 533) received pilot interventions and 9 (n=2672) were part of outbreak investigations (appendix p 4). TST was the method of testing for 60 cohorts (n=731 032), whereas six (n=16 059) were tested with IGRA (two used IGRA only if TST was positive) and four (n=1481) did not have details reported for which test was used.

The most important losses in the cascade occurred at four steps: initial testing of those intended for screening, completing medical evaluation if test was positive, provider recommendation of treatment, and completing therapy if started (figure 2).

The most important predictive factor for completion of the first step of screening was the indication (table 1). Of people estimated to have latent tuberculosis infection, 86% with immune-compromising medical indication (eg, patients with HIV or diabetes mellitus or those being treated with tumour-necrosis factor antagonists) completed screening and received a result, as did 83% of marginalized groups (eg, homeless people) and 79% of people had been in contact with someone with tuberculosis for more than 5 h per week (ie, contacts) compared to 62% of those from the

general population samples and 43% of migrants (table 1). The proportion completing this step in the cascade, as well as all subsequent steps, was highly heterogeneous with I^2 values exceeding 95% for most strata. Of those who had a TST, 94% returned for reading, and 98% of those tested with IGRA had valid results (appendix p 5).

The pooled prevalence of positive results for latent tuberculosis infection was 61% for populations in LMIC versus 25% for populations in high-income countries (appendix p 6). The intermediate steps from positive test to starting therapy were reported in fewer cohorts: referral for evaluation (18 cohorts), completing medical evaluation (29 cohorts), treatment recommended (26 cohorts), and therapy accepted (25 cohorts; appendix pp 7-10). Over 90% of participants with latent tuberculosis infection who received positive tests were referred for further evaluation, medical evaluation was completed by 90% of those referred, providers recommended LTBI treatment to 70%, and 90% started if they were recommended treatment (appendix pp 7-10).

The cumulative results of these steps are summarised in table 2. Treatment acceptance and initiation of isoniazid therapy was lower than for that of rifamycin-containing regimens (62% *vs* 83% of people with positive tests). Higher proportions of people with medical indications (85%) and contacts (75%) started treatment, as compared with marginalised groups (56%), migrants (55%) or the general population (51%, table 2). Of people who started therapy, only 62% completed overall (appendix p 11); in LMIC only 52% of those who started completed treatment compared to 70% in high-income countries.

As a result of all the losses in the cascade, of all people estimated to have latent tuberculosis infection, only 50% of people with medical indications completed latent tuberculosis infection treatment, compared with 14% of migrants, and 10% of the general population cohorts (table 3). This estimate of overall impact was very heterogeneous, with wide variation in different settings and populations (appendix pp 13-14). In three sensitivity analyses, exclusion of HIV-infected

populations (three cohorts), prison populations (six cohorts, including one very large study), and the general population (ten cohorts) resulted in findings very similar to the results with all cohorts (appendix p 12).

Reasons for not completing screening were put into two main categories: social situations impeding the completion of screening and health-system issues (panel). Barriers to the referral and recommendation of treatment included: being considered too old (older than 35 years), low health-provider knowledge about the benefits and risks for latent tuberculosis infection, and social situations. Barriers to treatment completion included side-effects to drugs, health-systems issues and social situations (panel).

On June 20, 2016 we repeated our search using the same search strategy and inclusion criteria to check whether any additional papers had been published since our analysis. Two additional articles would have met our study inclusion criteria. In one study(78), 43 (29%) of 149 refugees arriving in Philadelphia (PA, USA) with "non-communicable tuberculosis conditions" completed latent tuberculosis infection therapy, and in the other study(79), 35% of all close contacts with latent tuberculosis infection in the USA in 2012 completed treatment. Although the completion rate was higher than the pooled estimates in our findings, both studies identified drop-outs and losses at each stage of the cascade, similar to the major findings of this Article.

Discussion

Findings from our systematic review and meta-analysis show that important losses occurred at the steps of initial screening, completing medical evaluation, and starting and completing therapy in all settings and study populations for latent tuberculosis infection.

We used the HIV cascade of care as a model. First recognised in 2009 to quantify the importance and cumulative impact of losses at each stage of care(80,81), this framework identified the five points along the continuum of care where HIV patients are commonly lost to follow-up.

These pre-treatment losses accounted for much greater reduction in effective HIV care than non-adherence to antiretroviral therapy(26, 50, 80). Applying this care framework to latent tuberculosis infection could help to identify problems and help develop strategies to improve diagnosis, management and treatment completion(80). By focusing on better patient retention and referral, particularly in high-risk groups, a substantial portion of patients with latent tuberculosis will be kept in care, initiated on appropriate regimens and ultimately complete treatment, thereby reducing the reservoir of latent tuberculosis from which active tuberculosis develops(82).

Although some steps of the cascade were associated with major losses, other steps were consistently done much better. Of those tested with TST, about 94% received their results. Additionally, more than 90% of patients with positive tests were referred for further evaluation, and of those who were recommended therapy, more than 90% agreed to start. The negative findings suggest important areas for improvement, whereas the positive findings suggest where training and motivation appear to have been successful. We speculate that the fewer overall losses in high-risk populations, such as close contacts(48, 57) or patients with serious medical conditions(49), might be due to their high-risk status, as a result of which they may have received more intensive health care. This finding suggests that better outcomes might be seen in other groups of patients if they receive a similar intensity of care(18, 50, 63, 83).

There has been a major investment in the past two decades to complete more than a dozen major trials of shorter courses of therapy for latent tuberculosis infection with rifamycin-containing regimens(8, 55). Our findings show that these shorter regimens were associated with a 20% greater treatment completion. However, in a hypothetical cohort of 1000 people with latent tuberculosis infection, improving the proportion screened from 70% to 90%, the proportion evaluated from 79% to 90%, and the proportion starting treatment from 74% to 90%, but keeping isoniazid as the therapy regimen (assumed 61% treatment completion) will result in 445 completing effective latent

tuberculosis infection therapy. On the other hand, without changing the losses at the earlier steps, only 336 would complete effective therapy if a rifamycin-containing regimen was introduced (completion 82%). Therefore treatment losses earlier on can result in greater overall reduction in public health benefit of latent tuberculosis infection management.

The primary focus of other reviews of latent tuberculosis infection management have been the prevalence of latent tuberculosis in contact investigations(7) or adherence to treatment once started(12, 24). To our knowledge, this is the first systematic review to evaluate the full cascade of care for latent tuberculosis infection through all steps of the diagnostic and treatment process. We included 46 studies that reported on factors affecting the losses at each step, allowing tabulation of potentially actionable items to improve the cascade. Although screening and treatment for latent tuberculosis infection might be more difficult in high-burden countries due to the financial constraints and need to prioritise limited resources for detection and treatment of active tuberculosis cases, WHO recommends latent tuberculosis treatment(16) only for the highest risk groups in LMIC. These high-risk groups include people living with HIV and children younger than 5 years old who are household contacts of newly diagnosed active tuberculosis cases. Our findings highlight the need to carefully evaluate the public health impact of this approach, given the potential reduction in the benefits due to losses and drop-outs at different steps in the cascade.

This systematic review and meta-analysis has several limitations. Most papers included did not completely report on the different steps in the cascade; only ten publications reported on all steps. Only 18 studies reported data on referrals, medical evaluation, and recommendations to start treatment, and all of these were from high-income countries, thus limiting the generalisability of findings related to these steps. The type of test used was missing in four cohorts, and treatment regimen was not reported in ten studies, somewhat limiting analysis of these factors. Heterogeneity was high for most analyses, even within many of the stratified analyses, suggesting substantial

unexplained variation in the results. Our study similar to other meta-analyses of observational studies was subject to potential selection bias, as well as differences in individual study measurements(23, 24). The relatively large numbers of studies allowed a number of stratified analyses to help address heterogeneity, which might have helped limit these problems. Finally, only 11 cohorts from LMIC were included in this review, compared to 59 cohorts from high-income countries, and only three cohorts reported data from HIV-positive subpopulations. Since the largest global burden of latent tuberculosis infection occurs in LMIC, and many of these countries have high HIV coinfection rates, there is a need for more information regarding the cascade of care in these high-burden settings and high-risk populations.

We believe that our findings provide important insights to inform the ongoing global efforts to enhance the programmatic management of latent tuberculosis infection. Improving the cascade of care for latent tuberculosis infection will require systematic investigation of the extent and risk factors of the losses at each step, including trials to identify cost-effective and feasible interventions that can be adopted by tuberculosis control programmes. In resource-limited settings, the diagnosis and adequate treatment of all people with active tuberculosis must remain the priority. However, in order to maximise the public health impact of expanded diagnosis and treatment, programmes must plan strategies to correct the problems identified in the cascade of care for latent tuberculosis infection.

Contributors: HA and DM conceived of the study and did the literature review, data collection, and data analysis for the paper. All authors evaluated the data. All authors reviewed the draft, had critical input, and reviewed the final submission

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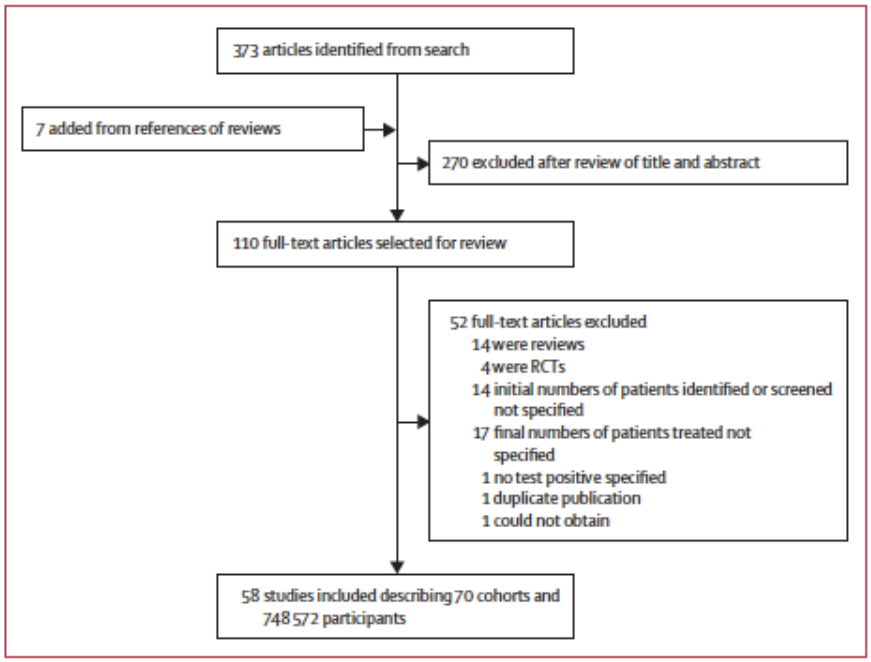
Figures

Figure 4.1: Study selection



RCT = randomised controlled trial

Figure 4.2: Losses and drop-outs at each stage of the cascade of care in latent tuberculosis

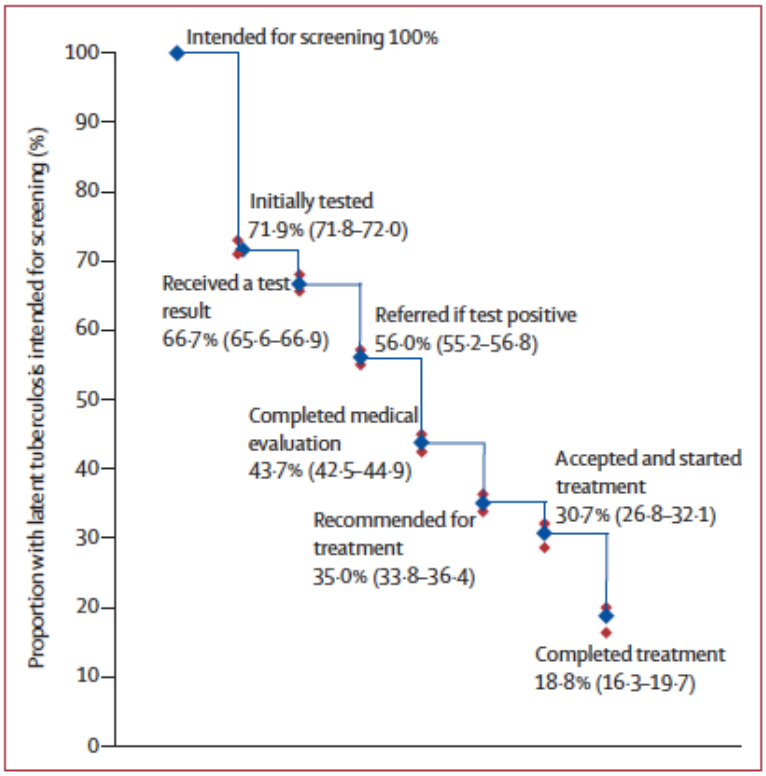


***Figure 2*: Losses and drop-outs at each stage of the cascade of care in latent tuberculosis**

Numbers in parentheses are 95% CIs. The value for each level is calculated as the product of the value from the preceding step, multiplied by the pooled estimate for that step (from fixed-effects analysis).

Panel: Risk factors and reasons associated with losses at different steps of the cascade

Panel: Risk factors and reasons associated with losses at different steps of the cascade, identified in the studies included in the Article

Initial identification

- Health authorities unable to contact (invalid addresses)[32]
- Immigration examination is reason for consult (fear of not being allowed entry into the country based on tuberculosis status)[26]

Testing of intended for screening

- Health-care workers hired before pre-employment TST mandated[42]
- Not offered TST by health-care worker or physician due to:
  - medical contraindications (ie, previous treatment for latent or active tuberculosis, skin conditions, or recent measles injection)[17,23,26,27,29,31,50]
  - language barriers[27]
- No interest in being tested[28]
- Self-perceived low risk of tuberculosis infection (had not been in contact with tuberculosis in the past)[26]

Completing screening and testing

- Did not perceive tuberculosis to be a serious disease[26]
- Health systems issues:
  - hard to access the clinic or long wait times[17,28,29]
  - does not like needles (for the interferon-gamma release assay)[28]
  - stigma, mistrust, or unwillingness to visit tuberculosis centre[28,28]
  - difficulties with health insurance[30,31]
  - end of local health awareness campaigns[29]
- Social situations impeding screening completion:
  - language or cultural barriers[26,27]
  - feels too ill[28]
- No administrative enforcement of mandated post-exposure testing[42]

Referral for medical evaluation

- Older age (35 years of age or older)[17,32–34]
- Low perceived risk of tuberculosis infection[23,25]
- Less parental supervision for attending tuberculosis clinic appointments (eg, high-school students)[49]
- Termination of financial compensation[35]

Recommending treatment

- Low health-care worker knowledge about the need for therapy for latent tuberculosis infection[25,26,32,38,39,40,41,42,71]
- Medically contraindicated (ie, previous treatment for latent or active tuberculosis or elevation of liver enzymes)[17,20,26,32,68]
- Social situations impeding treatment:
  - substance abuse[17,20,28,72]
  - recent release from jail or prison[43,45,47]
  - no transportation[40,44]
  - fear of deportation or immigration status[30,46]

Starting treatment

- Refusal to start due to immigrant status[25,53,58]
- Older age (35 years of age or older)[43]
- Low perceived risk of active tuberculosis (for themselves or their children)[10,18,20,28,38,52,58,60]
- Poor linkages between the tuberculosis programme and general health services (ie, delays between TST and clinic visit)[44,58]
- Not receiving a chest radiograph[65]
- Previous latent tuberculosis treatment in their country of origin[65]
- HIV infection[65]

Completing treatment

- Development of adverse effects after medication (ie, hepatotoxicity, neurological, psychiatric, or gastrointestinal symptoms)[17,20,25,28,32,34,40,43,48–56]
- Long duration of treatment course[42]
- Health systems issues:
  - mistrust of the health-care system[28]
  - patient did not know when to come back for treatment refills[37]
  - physicians did not consider adherence to therapy to be part of their responsibility[37]
- Treated elsewhere[20,37,70]
- Social situations impeding treatment completion:
  - relocation or moving[30,32,33,45,54,55,60]
  - leaving jail or prison[34,47,59]
  - immigrant status[30,58,63,62]
  - substance abuse[28,30,43,45,61]

TST=tuberculin skin test.

Tables

Table 4.1: Characteristics associated with completed screening

	Number of cohorts	Screened/eligible (n/N)*	Pooled event rate (95% CI)†	I²
Country income level				
High	57	513 880/728 442	75·6% (67–84)	100·0%
Low or middle	8	3666/6295	51·3% (19–83)	99·8%
Services				
Routine	33	298 207/405 143	66·9% (53–81)	100·0%
Outbreak investigation	9	2245/2672	88·0% (75–100)	96·7%
Pilot intervention	23	217 094/326 922	74·1% (60–89)	100·0%
Study populations				
Medical	5	2619/3363	86·1% (68–100)	96·0%
Contacts	27	151 911/180 420	79·3% (69–90)	99·9%
Marginalised	11	206 406/277 763	83·3% (69–98)	100·0%
Migrants	12	15 062/54 011	43·4% (20–67)	100·0%
General population	10	141 548/219 180	62·1% (37–87)	100·0%
Age				
Adults only	37	236 047/358 323	66·9% (54–80)	99·5%
Children only	9	58 448/68 934	60·4% (33–88)	99·8%
All ages (or not reported)	19	223 051/307 480	86·4% (77–96)	100·0%
Testing for latent tuberculosis‡				
TST alone	57	507 781/717 436	75·1% (66–84)	100·0%
IGRA with or without TST	6	8998/16 059	62·3% (28–97)	99·9%
Not specified	2	767/1242	39·4% (0–100)	99·8%
Treatment for latent tuberculosis				
Isoniazid	42	301 609/399 086	71·5% (60–83)	100·0%
Rifamycin containing (with or without isoniazid)	12	138 805/212 759	80·3% (64–97)	99·9%
Moxifloxacin and ethambutol	1	139/232	59·9% (0–100)	..
Not specified	10	76 993/122 660	71·5% (48–95)	100·0%
Years of data collection				
Up to 2000	25	362 480/461 814	79·0% (67–91)	98·0%
After 2000	40	155 066/272 923	69·0% (56–81)	99·0%

TST=tuberculin skin test. IGRA=interferon-gamma release assay. *Numerator is participants who successfully completed screening (ie, results available; if number not reported, data are for those initially tested; N=517 546); denominator is participants who were eligible for screening (N=734 737). †Pooled estimates and 95% CIs for participants with latent tuberculosis infection who completing screening from random effects meta-analysis. ‡TST read or valid IGRA results obtained by provider.

Table 1: **Characteristics associated with completed screening**

Table 4.2: Characteristics associated with starting treatment

	Number of cohorts	Started treatment/ eligible (n/N)*	Pooled event rate (95% CI)†	I^2
Country income level				
High	57	56 514/90 798	64·6% (56–74)	99·1%
Low or middle	6	1023/1351	72·2% (48–96)	95·1%
Services				
Routine	33	32 735/53 519	62·7% (51–75)	99·5%
Outbreak investigation	8	368/465	80·9% (63–99)	99·7%
Pilot intervention	22	24 434/38 165	63·9% (49–78)	88·4%
Study populations				
Medical	4	720/851	84·8% (67–100)	80·1%
Contacts	25	26 258/38 667	74·8% (64–85)	99·3%
Marginalised	11	22 464/36 363	56·4% (35–77)	90·3%
Migrants	13	2005/3998	54·6% (36–73)	0·0%
General population	10	6090/12 270	50·8% (29–73)	99·9%
Age				
Adults only	36	28 154/45 766	62·6% (51–74)	100·0%
Children only	8	22 013/35 622	69·1% (47–91)	99·9%
All ages (or not reported)	19	7370/10 761	68·9% (54–84)	99·9%
Testing for latent tuberculosis				
TST alone	57	56 712/90 610	64·2% (55–73)	99·2%
IGRA with or without TST	6	825/1539	75·3% (53–98)	0%
Not specified	0	..	..	..
Treatment for latent tuberculosis				
Isoniazid	41	31 987/53 498	62·3% (52–72)	99·4%
Rifamycin containing (with or without isoniazid)	12	13 021/20 200	83·3% (72–94)	0%
Moxifloxacin and ethambutol	1	104/119	87·7% (58–100)	..
Not specified	9	12 425/18 332	43·1% (20–66)	90%
Years of data collection				
Up to 2000	26	42 265/67 728	58·0% (44–72)	89·0%
After 2000	37	15 272/24 421	70·0% (60–80)	99·0%

TST=tuberculin skin test. IGRA=interferon-gamma release assay. *Numerator is participants who successfully started treatment (if number missing, data were for participants recommended to start; N=57 537); denominator is participants who were eligible for treatment (ie, those who tested positive; N=92 149). †Pooled estimates and 95% CIs for participants with latent tuberculosis infection who started treatment from random-effects meta-analysis.

Table 2: Characteristics associated with starting treatment

Table 4.3: Characteristics associated with completing treatment

	Number of cohorts	Completed treatment/eligible (n/N)*	Pooled event rate (95% CI)†	I^2
Country income level				
High income	59	35062/134329	23·4% (16–30)	99·9%
Low or middle income	11	889/3603	16·7% (4–29)	99·3%
Services				
Routine	36	21670/71782	21·2% (13–29)	99·7%
Outbreak investigation	9	330/627	45·5% (20–71)	98·2%
Pilot intervention	25	13951/65523	18·0% (9–27)	99·9%
Study populations				
Medical	5	479/1176	50·4% (20–81)	99·7%
Contacts	31	17914/48320	29·3% (19–40)	99·8%
Marginalised	11	12603/48844	21·0% (7–35)	99·2%
Migrants	13	1608/20104	14·3% (5–24)	92·8%
General population	10	3347/19488	9·7% (2–17)	99·8%
Age				
Adults only	37	16609/77491	18·3% (11–26)	99·8%
Children only	12	4735/14749	18·3% (6–31)	99·8%
All ages (or not reported)	21	14607/45692	33·5% (19–48)	99·7%
Testing for latent tuberculosis				
TST alone	60	35028/134184	21·1% (15–28)	99·9%
IGRA with or without TST	6	629/2959	35·1% (8–63)	99·4%
Not specified	4	294/789	21·6% (0–47)	98·1%
Treatment for latent tuberculosis				
Isoniazid	47	20089/75438	18·5% (12–25)	99·8%
Rifamycin containing (with or without isoniazid)	12	7790/27672	49·6% (30–69)	99·5%
Moxifloxacin and ethambutol	1	93/199	46·7% (0–100)	..
Not specified	10	7979/27672	14·0% (3–25)	99·9%
Years of data collection				
Up to 2000	27	25935/88287	18·0% (10–27)	99·9%
After 2000	43	9754/49645	24·0% (16–33)	99·3%

TST=tuberculin skin test. IGRA=interferon-gamma release assay. *Numerator is participants who successfully completed prescribed treatment once started (if number not reported, data are for those who were recommended treatment by the provider; N=35951); denominator is participants who started treatment (N=137932). †Pooled estimates and 95% CIs for participants with latent tuberculosis infection who completed treatment are from random-effects meta-analysis.

Table 3: **Characteristics associated with completing treatment**

4.3 Appendix 1– Supplemental Tables and Figures

List of Supplement tables:

1: Detailed characteristics of the included studies (* References are found in main text).
2: Summary of characteristics of the included studies.
3: Completed screening as a percentage of initially tested.
4: Characteristics associated with Positive tests for Latent TB - *as a percentage of completed Screening*
5: Referred for medical evaluation as a percentage of Test Positives.
6: Completed medical evaluation as a percentage of Referred.
7: Recommended Treatment as a percentage of those completing medical evaluation
8: Started Treatment as a percentage of recommended treatment
9: Characteristics associated with completing treatment for latent TB – *as a percentage of Number who started.*
10: Sensitivity Analyses

List of Supplement Figures:

Figure 1A: Forest plot of treatment completion among those estimated with LTBI among all Intended for Screening- High Income countries.
Figure 1B: Forest plot of treatment among those estimated with LTBI among all Intended for Screening - Low and Middle Income countries.

Systematic Review Protocol

The Cascade of Care in Latent Tuberculosis Infection diagnosis and treatment – Protocol for a systematic review and meta-analysis

Supplemental Table 4.S1: Detailed Characteristics of the studies included in the review

Reference	Author,Yr	Years of Study	Countries	Services	Population:	HIV %	Age	TEST:	LTBI ttx
10	DasGupta 2000	1996-97	Canada	Routine	Migrants	1%	NR	CXR, TST	INH
17	Schluger 1999	1994-97	USA	Routine	Homeless	NR	Adults	TST	INH
18	Duarte 2012	2001-2003	Portugal	Routine	Contacts	NR	NR	TST	INH or RIF
19	Kall BMC 2012	2006-09	United Kingdom	Pilot	HIV	100%	Adults	IGRA	INH or RIF
20	Langenskiold 2008	1993-2002	Switzerland	Routine	General	NR	Adults	TST	INH
21	Lorvick 1999	1997	USA	Pilot	Substance users	14%	Adults	TST	INH
26	Levesque 2004	1999	Canada	Pilot	Migrants	NR	All	TST	INH
27	Carvalho 2005	2001	Italy	Routine	Migrants	NR	Adults	TST	NR
28	Marks 2000	1996-97	USA	Routine	Contacts	2%	Adults	TST	INH or RiF
29	Alvarez 2014	2011-12	Canada	Pilot	General	0	Adults	TST&IGRA	INH
30	Lashley 2007	2005-07	USA	Pilot	Homeless	7%	NR	TST	INH
31	Brassard 2008	2005-06	Canada	Pilot	General	6%	Adults	TST	INH
32	Gomes 2011	2005-07	Guinea-Bissau	Pilot	Contacts	NR	Children	no testing	INH
33	Bennett 2014	2010-12	USA	Routine	Migrants	0.07%	Adults	IGRA >2; <2 = TST	INH
34	Nolan 1997	1992-94	USA	Pilot	Prison	NR	All	TST	INH
35	Yuan 1995	1992-93	Canada	Routine	Migrants	NR	Children	TST	INH
36	Driver 2003	1995-2000	USA	Routine	Contacts	NR	NR	TST	INH
37	Banu 2009	2008	India	Routine	Contacts	NR	Children	NR	INH
38	Cain 2012	2002-06	USA	Routine	General	NR	All	TST	INH or RIF
39	Chakaia 2014	2010-2011	Georgia	Routine	Contacts	NR	Adults	TST	INH
40	Rutherford 2013	2009-12	Indonesia	Routine	Contacts	NR	Children	TST	INH
41	Adhikari 1995	1987-89	Canada	Routine	General	NR	All	TST	INH
42	Balkhy 2014	2008-2010	Saudi Arabia	Routine	Contacts	NR	Adults	TST	INH
43	Diaz 2010	2000-2003	Spain	Pilot	HIV	100%	Adults	TST	INH or RIF
44	Zachariah 2003	2001-02	Malawi	Routine	Contacts	NR	Children	NR	INH
45	Brassard 2004	1999	Canada	Pilot	Substance users	24%	Adults	TST	INH
46	Breuss 2002	1993	Switzerland	Routine	Migrants	NR	Adults	TST	NR
47	Lobato 2003	1990-97?	USA	Pilot	Prison	5.90%	Adults	TST	INH
48	CDC 2013	2011-2012	USA	Outbreak	Contacts	NR	All	TST or IGRA	INH or RIF
49	Chee 2004	1998	Singapore	Routine	Contacts	1%	Adults	TST	INH
50	Yun 2007	2004-2006	Korea	Routine	Medical (TNFa)	NR	Adults	TST	RIF
51	Richards 2005	1999-2000	Canada	Routine	Migrants	0%	Adults	TST	INH
52	Chee 2005	1999-2001	Singapore	Routine	Prison	NR	Adults	TST	INH
53	Martinez-Sanchis 2005	1997-2002	Spain	Routine	Contacts	0%	Adults	TST	INH
54	Jereb 2013	1999	USA	Routine	Contacts	NR	NR	TST	NR
55	Sprinson 2003	1999-2000	USA	Routine	Contacts	NR	NR	TST	NR

56	Reichler 2002	1996	USA	Pilot (Cohort)	Contacts	0.60%	Adults	TST	INH
57	Sloot 2014	2008-11	Netherlands	Routine	Contacts	6%	Adults	TST & IGRA	NR
58	Minodier 2010	1997-2007	Canada	Pilot	Migrants	NR	Children	TST	INH
59	Bur 2003	2000-01	USA	Outbreak	Prison	NR	Adults	TST	NR
60	Cegielski 2013	1996	USA	Pilot	General	NR	Adults	TST	INH
61	Sarivalasis 2013	NR	Switzerland	Pilot	Migrants	NR	All	IGRA	INH or RIF
62	Bibi 2002	1995-1999	Israel	Routine	General	NR	Children	TST	INH
67	Gallardo 2014	2006-11	Spain	Routine	Contacts	NR	Adults	TST	INH
68	Davidow 2003	1996	USA	Routine	Contacts	0.05%	Adults	TST	INH
69	Anger 2012	1997-2003	USA	Routine	Contacts	19%	Children	TST	INH or RiF
70	Aisu 1995	1991-1992	Uganda	Pilot	HIV	100%	Adults	TST	INH
71	Bodenmann 2009	2007	Switzerland	Pilot	Migrants	NR	Adults	TST	INH
72	Defang 2014	2011	Micronesia	Pilot	Diabetics	NR	Adults	TST	INH
73	Brassard 2006	1998-2003	Canada	Routine	Migrants	NR	Adults	TST	INH
74	Desale 2013	2006-2010	USA	Pilot	Migrants	NR	Adults	TST	NR
75	Fraser 1994	1992	USA	Pilot	General	NR	Adults	TST	INH
76	Pevzner 2010	2005-06	USA	Outbreak	Subtance users	0%	All	TST	INH
77	Trueba 2006	2004	France	Outbreak	Contacts	NR	NR	TST	NR
78	Webb 2003	1990-1998	USA	Routine	Contacts	NR	All	TST	INH
79	Yeo 2006	1996-2000	Canada	Routine	Contacts	NR	Children	TST	INH
80	Lopez 1990	1987-1989	Spain	Pilot	General	NR	Adults	TST	INH
81	Bamrah 2014	2009-12	Micronesia	Outbreak	Contacts	0	Adults	TST	12MfxEmb
58	**Total**								

(* References are found in main text)

Supplemental Table 4.S2: Summary of characteristics of the included studies

Factor/Parameter	Cohorts	Participants
Overall (all studies)	70	748,572
Collection of data		
Prospective	34	328,964
Retrospective	36	419,608
Country		
High income	59	741,540
Low-middle income	11	7,032
Populations screened		
Contacts	31	181,357
Migrants	13	66,909
Medical - HIV	3	3,172
Diabetes, TNFa/Transplant	2	191
Marginalized - Homeless	2	4,110
Substance users	3	3,446
Prisoners	6	270,207
General population	10	219,180
Services		
Routine services	36	418,367
Outbreak investigation/control	9	2,672
Pilot intervention	25	327,533
Tests to detect Latent TB:		
Tuberculin skin test (TST) alone	60	731,032
IGRA or TST then IGRA	6	16,059
Not reported	4	1,481
Treatment for Latent TB:		
INH	47	412,921
Rifamycin containing (RIF alone, or INH&RIF)	12	212,759
Mfx&EMB	1	232
Not reported	10	122,660

Supplemental Table 4.S3: Characteristics associated with completed screening - as a percent of all who initiated screening (Initially tested)
Cohorts (N) = 33; Subjects (N): 378,505 / 407,994

Factor	Cohorts (N)	Events/Subject (N)	Pooled Event rate	(95% CI)	I^2
Country Income Level					
High Income	32	377,411 / 406,650	95.4%	(92,98)	99.9%
Low or middle Income	1	1,094, / 1,344	81.4%	(24,100)	------
Services					
Routine	15	167,960 / 195,316	81.6%	(81,98)	99.9%
Outbreak Investigation	2	251 / 251	100.0%	-------	0.0%
Pilot Intervention	16	210,294 / 212,427	96.6%	(94,99)	98.2%
Study Populations					
Medical	4	2,548 / 2,823	97.9%	(94,100)	99.0%
Contacts	6	30,669 / 33,186	98.3%	(95,100)	99.8%
Marginalized	6	202,340 / 203,894	92.4%	(92,100)	97.6%
Migrants	10	10,023 / 11,214	91.3%	(82,100)	99.6%
General population	7	132,925 / 156,877	89.6%	(77,100)	100.0%
Age					
Adults only	20	215,285 / 219,183	91.7%	(85,98)	99%
Children only	5	56,488 / 59,438	97.8%	(94,100)	99%
All ages (or not reported)	8	106,732 / 129,373	98.1%	(96,100)	99%
Testing for LTBI					
TST alone	29	373,093 / 402,457	94.3%	(90,98)	99.9%
IGRA $\pm$ TST	4	5,412 / 5,537	98.4%	(95,100)	97.3%
Not specified	0	----	---	---	---
Treatment for LTBI					
INH	21	243,280 / 247,388	93.7%	(89,99)	99.4%
Rifamycin containing (with or without INH)	8	134,370 / 159,228	97.6%	(94,100)	100.0%
Mfx & Emb	NR	NR	NA	NA	NA
Not specified	4	855 / 1,378	95.3%	(86,100)	99.8%

Supplemental Table 4.S4: Characteristics associated with a positive test for LTBI - *as a percentage of those who were tested and received a result (completed screening)*[3].

Cohorts (N) = 61; Subjects (N): 92,160 / 515,712

Factor	Cohorts (N)	Events/Subjects (N)	Pooled Event rate	(95% CI)	I^2
Country Income Level					
High Income	56	89,968 / 512,884	24.8%	(20,30)	99.9%
Low or middle Income	5	1,192 / 2,828	61.3%	(38,84)	99.4%
Services					
Routine	31	52,678 / 297,180	31.2%	(23,41)	99.9%
Outbreak Investigation	9	476 / 2,245	24.2%	(10,38)	98.8%
Pilot Intervention	21	38,006 / 216,287	22.2%	(14,31)	99.3%
Study Populations					
Medical	4	851 / 2,548	27.6%	(6,49)	99.1%
Contacts	24	38,400 / 150,148	32.2%	(23,42)	99.6%
Marginalized	11	36,363 / 206,406	27.5%	(15,40)	99.5%
Migrants	12	3,276 / 15,062	32.2%	(19,46)	99.6%
General population	10	12,270 / 141,548	13.2%	(6,21)	99.9%
Age					
Adults only	36	45,766 / 235,976	33.7%	(26,42)	99.6%
Children only	7	10,602 / 57,681	27.4%	(11,43)	99.9%
All ages (or not reported)	18	34,792 / 222,055	16.8%	(10,24)	99.9%
Testing for LTBI					
TST alone	55	89,621 / 506,714	28.6%	(22,35)	99.9%
IGRA $\pm$ TST	6	1,539 / 8,998	16.5%	(4,29)	97.3%
Not specified	0	-------	-------	------	------
Treatment for LTBI					
INH	38	52,498 / 299,775	30.9%	(24,38)	100.0%
Rifamycin containing (with or without INH)	12	20,200 / 138,805	17.4%	(9,26)	99.9%
Mfx & Emb	1	119 / 139	85.9%	(60,100)	------
Not specified	10	18,343 / 76,993	22.4%	(11,34)	100.0%
Years of data collection					
Up to 2000	24	66,887 / 361,484	27.0%	(18,36)	99.0%
After 2000	37	24,273 / 154,228	27.0%	(20,35)	95.0%

Notes:

1. Numerator represents persons who successfully completed each step. Denominator represents person who were eligible for this step.
2. Pooled estimates and 95% CI from random effects meta-analysis.
3. Completed screening means the results were available – TST read, or valid IGRA results obtained by provider.

Supplemental Table 4.S5: Characteristics associated with referral for medical evaluation[3] – *as a percent of those with Screening test positive*

Cohorts (N) = 18; Subjects (N): 5,337 / 6,352

Factor	Cohorts (N)	Events/Subject (N)	Pooled Event rate	(95% CI)	I^2
Country Income Level					
High Income	18	5,337 / 6,352	94.7%	(93,96)	99.1%
Low or middle Income	0	0 / 0	NA	NA	-------
Services					
Routine	9	3,982 / 4,933	89.9%	(87,93)	99.5%
Outbreak Investigation	1	162/ 162	100.0%	-------	--------
Pilot Intervention	8	1,193 / 1,257	98.8%	(98,100)	88.4%
Study Populations					
Medical	2	91 / 91	100.0%	(99,101)	80.1%
Contacts	3	334 / 344	99.9%	(99,101)	99.3%
Marginalized	2	608 / 1,233	73.1%	(20,126)	90.3%
Migrants	7	1,894 / 1,958	99.0%	(98,100)	0.0%
General population	4	2,410 / 2,726	92.2%	(87,98)	99.9%
Age					
Adults only	10	1,783 / 2,720	99.3%	(97,100)	99.5%
Children only	2	1,647 / 1,700	99.6%	(99,100)	98.1%
All ages (or not reported)	6	1,907 / 1,932	99.9%	(99,100)	86.6%
Testing for LTBI					
TST alone	15	5,027 / 6,042	93.2%	(91,95)	99.2%
IGRA $\pm$ TST	3	310 / 310	100.0%	(100,101)	0.0%
Not specified	------	-------	-------	-------	--------
Treatment for LTBI					
INH	12	4,709 / 5,713	91.8%	(89,94)	99.4%
Rifamycin containing (with or without INH)	4	351 / 351	100.0%	(100,101)	0.0%
Mfx & Emb	0	--	--	--	--
Not specified	2	277 / 288	97.0%	(90,103)	90.0%

Notes:

1. Numerator represents persons who successfully completed each step. Denominator represents person who were eligible for this step.
2. Pooled estimates and 95% CI from random effects meta-analysis.
3. Referred for medical evaluation, Chest X-ray, and consideration for latent TB therapy

Supplemental Table 4.S6: Characteristics associated with completing medical evaluation[3] -
as a percent of those with Screening test positive
Cohorts (N) = 29; Subjects (N): 14,967 / 17,474

Factor	Cohorts (N)	Events/Subject (N)	Pooled Event rate	(95% CI)	I^2
Country Income Level					
High Income	28	14,967 / 17,474	89.2%	(80,98)	99.1%
Low or middle Income	1	579 / 579	100%	------	------
Services					
Routine	14	12,791 / 14,995	92.4%	(82,100)	99.5%
Outbreak Investigation	3	173 / 178	93.9%	(75,100)	------
Pilot Intervention	12	2,003 / 2,301	88.9%	(73,100)	88.4%
Study Populations					
Medical	4	795 / 851	99.5%	(98,100)	0.0%
Contacts	6	8,605 / 8,630	97.6%	(93,100)	80.1%
Marginalized	3	554 / 1,288	61.5%	(2,100)	99.9%
Migrants	11	3,294 / 3,750	88.9%	(76,100)	90.3%
General population	5	1,719 / 2,955	60.6%	(14,100)	99.3%
Age					
Adults only	17	4,015 / 5,394	90.4%	(79,100)	85.5%
Children only	4	9,361 / 10,132	89.1%	(70,100)	96.6%
All ages (or not reported)	8	1,591 / 1,948	96.0%	(86,100)	------
Testing for LTBI					
TST alone	25	13,813 / 16,248	88.2%	(77,99)	99.2%
IGRA $\pm$ TST	4	1,154 / 1,226	99.0%	(96,100)	0.0%
Not specified	0	--	--	--	--
Treatment for LTBI					
INH	18	5,895 / 8,196	83.2%	(68,98)	99.4%
Rifamycin containing (with or without INH)	6	8,735 / 8,802	99.6%	(99,100)	0.0%
Mfx & Emb	0	--------	--------	---------	--------
Not specified	5	337 / 476	83.1%	(52,100)	--------

Notes:
1. Numerator represents persons who successfully completed each step. Denominator represents person who were eligible for this step.
2. Pooled estimates and 95% CI from random effects meta-analysis.
3. Completed medical evaluation, Chest X-ray, and consideration for latent TB therapy

Supplemental Table 4.S7: Recommended treatment as a percent of completed medical evaluation
Cohorts (N) = 26; Subjects (N) = 11,504/14,363

Factor	Cohorts (N)	Events/Subjects (N)	Pooled Event rate	(95% CI)	I^2
Country Income Level					
High Income	24	10,944/13,740	70.3%	(66,74)	99.7%
Low or middle Income	2	560/623	89.9%	(87,92)	0.0%
Services					
Routine	13	9,800/12,307	64.5%	(56,73)	99.8%
Outbreak Investigation	2	162/163	53.3%	(-44,151)	93.5%
Pilot Intervention	11	1,542/1,893	79.9%	(73,87)	90.9%
Study Populations					
Contacts	6	7,936/8,639	90.8%	(85,97)	99.2%
General population	5	1,274/1,719	73.6%	(53,94)	99.4%
Migrants	10	1,606/2,810	62.2%	(47,78)	98.7%
Medical	3	605/670	93.2%	(85,102)	96.3%
Marginalized	2	83/525	29.0%	(-6,64)	96.0%

Factor	Cohorts (N)	Events/Subjects (N)	Pooled Event rate	(95% CI)	I^2
Timing of data collection					
Prospective	15	1,821/2,322	73.4%	(65,82)	98.1%
Retrospective	11	9,683/12,041	68.0%	(59,77)	99.8%
Testing for LTBI					
TST alone	21	10,694/13,165	67.6%	(61,74)	99.7%
IGRA + TST	4	770/1,154	82.8%	(56,109)	9.5%
Not Specified	1	40/44	90.9%	-----	-----
Treatment for LTBI					
INH	17	3,385/5,426	55.8%	(43,68)	99.8%
Rifamycin containg (with or without INH)	5	7,919/8,610	94.4%	(89,100)	99.3%
Mfx & Emb	0	NR	NA	NA	-----
Not Specified	4	200/327	51.1%	(18,84)	97.5%

Supplemental Table 4.S8: Started Treatment as a percent of recommended treatment*
Cohorts (N) = 25; Subjects (N): 31,855/36,095

Factor	Cohorts (N)	Events/Subjects (N)	Pooled Event rate	(95% CI)	I^2
Country Income Level					
High Income	23	31,310/35,535	90.3%	(87,94)	98.9%
Low or middle Income	2	545/560	82.2%	(45,119)	95.1%
Services					
Routine	11	8,689/10,717	88.0%	(81,95)	99.2%
Outbreak Investigation	2	181/187	95.8%	(87,104)	43.7%
Pilot Intervention	12	22,985/25,191	92.3%	(88,96)	99.6%
Study Populations					
Contacts	8	8,112/9,758	74.5%	(35,114)	99.5%
General population	3	595/715	86.1%	(75,97)	86.5%
Migrants	8	849/994	93.8%	(90,97)	95.8%
Medical	3	598/605	95.9%	(89,102)	65.8%
Marginalized	3	21,701/24,023	90.3%	(90,91)	0.0%

Factor	Cohorts (N)	Events/Subjects (N)	Pooled Event rate	(95% CI)	I^2
Timing of data collection					
Prospective	16	23,277/25,495	93.3%	(90, 96)	99.4%
Retrospective	9	8,578/10,600	86.3%	(80, 92)	98.0%
Testing for LTBI					
TST alone	20	31,183/35,285	84.9%	(56,114)	99.6%
IGRA + TST	4	647/770	91.5%	(83,101)	97.9%
Not Specified	1	25/40	62.5%	------	-----
Treatment for LTBI					
INH	16	24,104/26,614	89.1%	(85,93)	99.5%
Rifamycin containing (with or without INH)	6	7,590/9,300	92.2%	(82,102)	99.6%
Mfx & Emb	NR	NR	NR	NR	------
Not Specified	3	161/181	91.0%	(78,104)	90.1%

* Trueba 2006 (personnel outbreak) and Zachariah 2013 (passive program) were excluded from analysis although they reported here. There were 0 started out of 0 recommended.

Supplemental Table 4.S9**:** Characteristics associated with completing treatment[3] –
as a percent of Started (or recommended if number starting not reported)
Cohorts (N) = 69; Subjects (N): 35,945 / 58,421

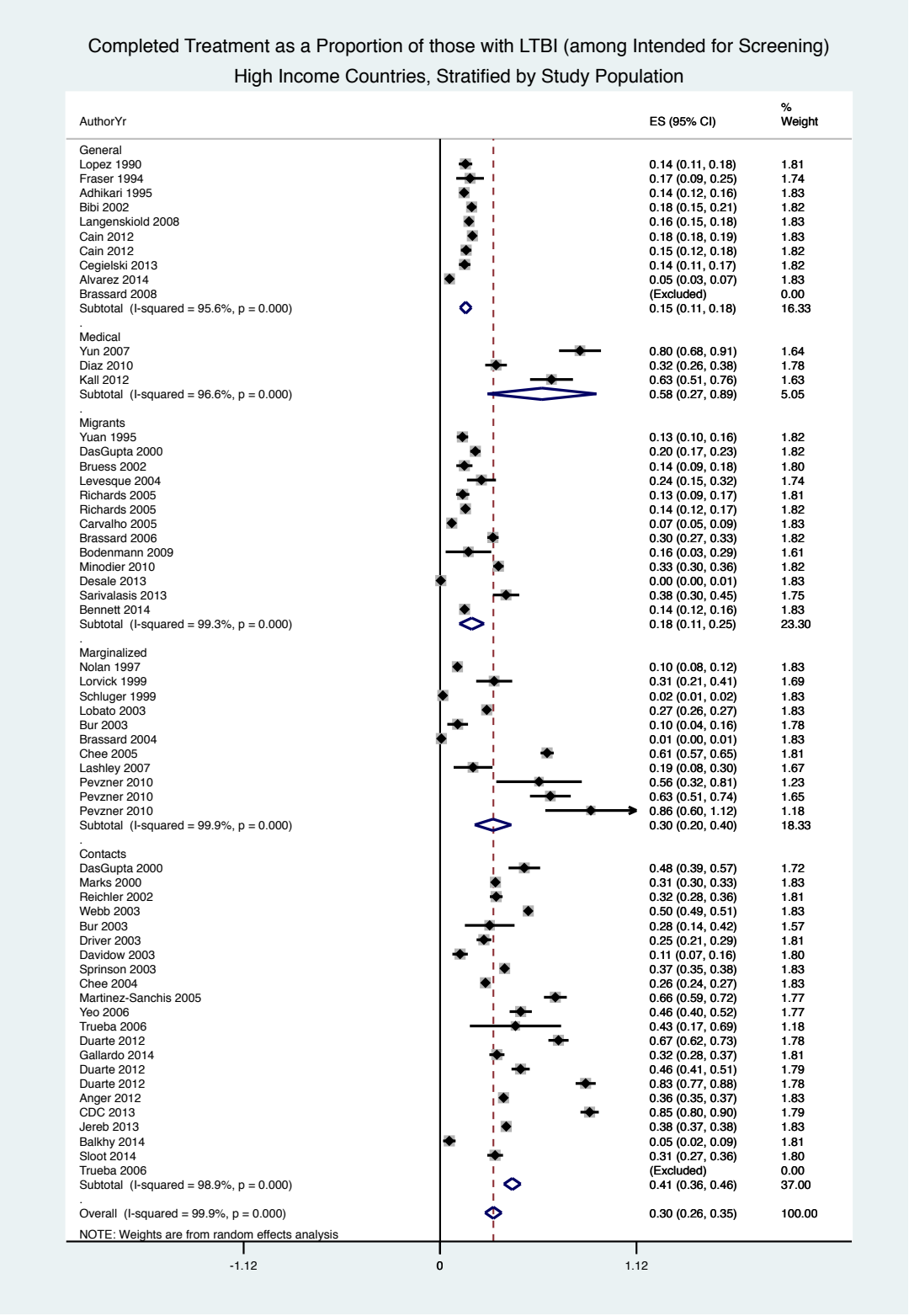
Factor	Cohorts (N)	Events/Subjects (N)	Pooled Event rate	(95% CI)	I^2
Country Income Level					
High Income	58	35,056 / 56,712	70.0%	(64,76)	99.9%
Low or middle Income	11	889 / 1,709	52.0%	(37,68)	99.6%
Services					
Routine	36	21,670 / 32,970	67.6%	(60,75)	99.9%
Outbreak Investigation	8	324 / 369	85.1%	(74,96)	99.9%
Pilot Intervention	25	13,951 / 25,082	61.6%	(52,71)	99.9%
Study Populations					
Medical	5	479 / 742	77.8%	(62,94)	99.9%
Contacts	30	17,908 / 27,120	67.1%	(59,75)	99.9%
Marginalized	11	12,603 / 22,464	67.6%	(53,82)	92.1%
Migrants	13	1,608 / 2,005	72.5%	(61,84)	94.9%
General population	10	3,347 / 6,090	54.6%	(38,71)	98.3%
Age					
Adults only	37	16,609 / 28,176	67.9%	(60,75)	99.9%
Children only	12	4,735 / 8,034	57.2%	(43,72)	99.9%
All ages (or not reported)	20	14,601 / 22,211	72.4%	(63,82)	99.5%
Testing for LTBI					
TST alone	59	35,022 / 56,932	65.5%	(60,71)	99.9%
IGRA $\pm$ TST	6	629 / 825	87.4%	(78,96)	96.8%
Not specified	4	294 / 664	54.2%	(29,79)	99.4%
Treatment for LTBI					
INH	47	20,089 / 32,870	61.6%	(55,68)	99.9%
Rifamycin containing (with or without INH)	12	7,790 / 13,021	81.4%	(73,90)	98.8%
Mfx & Emb	1	93 / 104	89.8%	(72,100)	------
Not specified	9	7,973 / 12,426	70.3%	(56,85)	100.0%

Notes:
1. Numerator represents persons who successfully completed each step. Denominator represents person who were eligible for this step.
2. Pooled estimates and 95% CI from random effects meta-analysis.
3. Patients who completed latent TB treatment as prescribed, out of all who started, (or whose provider recommended treatment if started not reported).

Supplement Table 4.S10: Sensitivity Analyses
Outcome is the Percent completing LTBI therapy of estimated with LTBI

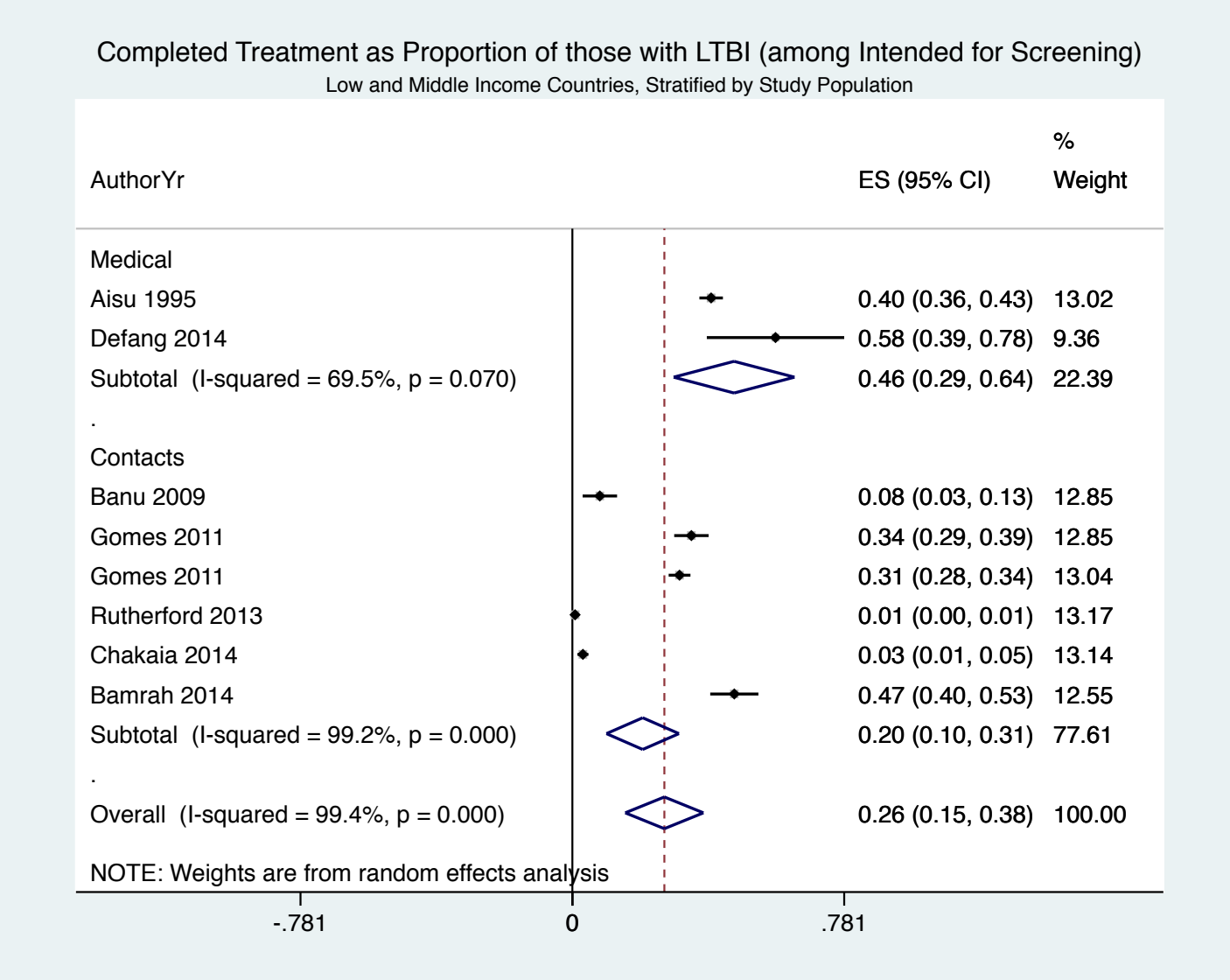
	All studies *Pooled estimate 95%CI*	**Dropping 3 studies in HIV pop.** *Pooled estimate 95% CI*	**Dropping 6 studies in prisons pop.** *Pooled estimate 95% CI*	**Dropping 10 studies in general pop.** *Pooled estimate 95% CI*
Overall				
	22 (17, 29)	21 (16, 28)	21 (16, 28)	25 (18, 33)
Country Income Level				
High Income	23 (16, 30)	22 (15, 29)	22 (15, 29)	27 (19, 35)
Low or middle Income	17 (4, 29)	15 (3, 27)	17 (4, 29)	17 (4, 29)
Services				
Routine	21 (13, 29)	21 (13, 28)	20 (12, 27)	22 (13, 30)
Outbreak Investigation	45 (20, 71)	45 (20, 70)	46 (15, 76)	45 (20, 70)
Pilot Intervention	18 (9, 27)	15 (7, 24)	18 (9, 27)	23 (12, 34)
Study Populations				
Medical	50 (20, 81)	60 (12, 100)	50 (21, 80)	50 (20, 81)
Contacts	29 (19, 40)	29 (19, 40)	29 (20, 39)	29 (19, 40)
Marginalized	21 (7, 35)	21 (7, 35)	10 (0, 21)	21 (7, 35)
Migrants	14 (5, 24)	13 (4, 22)	13 (5,21)	13 (4, 22)
General population	10 (2, 17)	10 (2, 17)	10 (2, 17)	--------
Testing for LTBI				
TST alone	21 (15, 28)	20 (14, 27)	19 (13, 26)	23 (16, 31)
IGRA $\pm$ TST	35 (8, 63)	30 (2, 58)	35 (8, 62)	46 (14, 78)
Not specified	22 (10, 47)	22 (0, 47)	22 (0, 47)	22 (0, 46)
Treatment for LTBI				
INH	19 (12, 25)	18 (12, 24)	16 (11, 22)	21 (14, 28)
Rifamycin containing (with or without INH)	50 (30, 69)	50 (29, 72)	50 (30, 69)	59 (39, 79)
Mfx & Emb	47 (0, 100)	47 (0, 100)	47 (0, 100)	47 (0, 100)
Not specified	14 (3, 25)	14 (3, 25)	15 (3, 26)	14 (4, 24)
Years of data collection				
Up to 2000	18 (10, 27)	18 (9, 26)	19 (10, 27)	19 (10, 29)
After 2000	24 (16, 33)	24 (16, 32)	23 (15, 31)	29 (19, 39)

Supplemental Figure 4.S1A: Forest plot of treatment completion among those estimated with LTBI among all Intended for Screening- High Income countries.



* ES = Effect size

Supplemental Figure 4.S1B: Forest plot of treatment among those estimated with LTBI among all Intended for Screening - Low and Middle Income countries.



* ES = Effect size

4.4 Appendix 2 – Protocol for systematic review and meta-analysis

The Cascade of Care in Latent Tuberculosis Infection diagnosis and treatment

Introduction:

Overall it has been estimated that 2 billion persons, or one-third of the entire world's population has LTBI. From this vast reservoir, assuming a cumulative lifetime risk of 10% for the development of active TB, it ca be estimated that approximately 200 million persons will develop active, contagious tuberculosis (TB) over their lifetimes. LTBI management is considered one of the core interventions for TB Elimination, but poor acceptance and completion of Isoniazid (INH) treatment of LTBI will reduce the cost-effectiveness and the population-level epidemiologic impact of this approach to TB prevention. As a result, in the past two decades, multiple randomized trials have been conducted to identify shorter regimens that are as effective, yet safer and more acceptable than INH. These trials have identified several alternative regimens, including 4 months Rifampin alone, 3-4 months of INH and Rifampin together, and 3 months of once weekly INH and Rifapentine. All of these regimens have recently been recommended by WHO for treatment of LTBI in countries with incidence of TB less than 100/100,000.

Non-completion of LTBI treatment, among those who start therapy, has received considerable attention – a recent systematic review identified 68 studies investigating this problem from North American centres alone. The authors of this review noted the importance of determining strategies for better treatment adherence that are specific to the context and populations being served, rather than a "one-size fits all" approach. However, there has been very little recognition of the impact of losses during the multiple steps in patients' trajectories before LTBI therapy is begun. Persons with LTBI may not be identified for screening, or even if they are intended for screening, may fail to be tested for LTBI (with TST or IGRAs). If a TST is performed, this may not be read, or the IGRA result may not be received by providers. Persons with a positive TST or IGRA may not be seen in follow-up for medical evaluation (e.g. symptom check, physical exam and chest radiography (CXR), or providers may fail to recommend therapy to them. Finally those for whom therapy is recommended may fail to start, or complete, treatment.

Study Questions:

The primary question was to estimate the cumulative proportion of persons investigated for latent TB and identified with LTBI who complete LTBI therapy? Additional objectives were to estimate: (i) the number eligible for testing for LTBI; the number who (ii) initiated, and (iii) completed screening with IGRA and/or TST; and the number with positive tests who: (iv) completed CXR and medical evaluation; (v) were prescribed (vi) started and, (vii) completed LTBI therapy. We also investigated risk factors for non-completion of each of these steps.

Search:

4 data bases: Cochrane data base of Systematic reviews, Embase, Medline (via Ovid) Health Star. 1946 to present. Humans. Any language.
Terms:
#1: Latent TB OR latent tuberc* OR tuberc* infection or inactive tuber*
#2: Screening OR contact OR investigation OR finding OR tuberc* screening
#3: Adherence OR completion OR compliance OR yield
1 AND 2 AND 3
Plus – will review reference lists from all identified systematic reviews of LTBI investigation, treatment adherence, or TB contact investigation.

Study Selection:
Duplicate review – 2 reviewers at each stage for inclusion of studies: Titles & Abstracts, then full texts. Decision – by consensus
Inclusion criteria:
1. Population: Being screened and treated for latent TB. Must give reason for screening. Can include if reported yield of screening for active TB as well, but will not include if ONLY the yield of screening for active TB is provided.
2. Must give number identified as eligible for initial testing (with IGRA and/or TST). ***This is critical for inclusion.*** However, only for studies of ***contact investigations,*** if the number identified is not known, but the number of index cases is known then these studies can be included. This is because the number of contacts identified can be extrapolated based on the number of index cases, and the average number of contacts from recent systematic reviews. For studies in other populations, no such extrapolation is possible, so these are eligible only if the number eligible for (intended for) screening is reported.
3. Must report the number completing LTBI therapy. (Critical to know end of cascade). Studies who do not report completion of LTBI therapy can be included if the number who start LTBI therapy is reported, as it is possible to extrapolate treatment completion based on population stratified rates of LTBI completion in a recent systematic review.[1]
4. Article (full text) must be accessible. Publications will be considered not accessible only if request through inter-library loan, and writing to authors have failed.
Exclusion criteria:
1. Language. There will be no language restrictions at the search, but if the full text is not available in English, French, Spanish, or Italian – then the publication will be excluded.

Data abstraction:
Data will be abstracted into an excel file listing all variables of interest. Data abstraction will be performed in duplicate for 20% of articles, and the concordance compared. If >95% concordance on all data points, or if discordance can be resolved through discussion and consensus, then the remainder will be abstracted by one reviewer only.
Data abstracted: Study Author, years of study, citation, country, setting (clinic, hospital, geographic area, etc), population screened, risk factors for LTBI and for reactivation, screening test (TST vs IGRA), characteristics of population (age, sex etc), LTBI treatment regimen.
Numbers: (i) Identified, (ii) tested, (iii) test result available (TST read, IGRA adequate), (iv) Seen for medical evaluation (CXR etc), (v) Recommended to start therapy, (vi) accepted to start therapy, (vii) completed therapy.
Risk factors for drop-outs at each of these steps above.

We will use the Meta-analysis in Observational Studies in Epidemiology (MOOSE) guidelines for reporting of observational studies.[2] However, quality of the studies will not be assessed. Most of the suggested 8 criteria of the Ottawa Newcastle scale (also commonly used to assess cohort studies) are not applicable for this review. Of 8 items suggested for quality assessment in this scale, the following 6 items are not applicable: 1) Representativeness of the Exposed Cohort; 2) Selection of the Non-

[1] Hirsch-Moverman Y, Daftary A, Franks J, Colson PW. Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada. *Int J Tuberc Lung Dis* 2008;**12**:1235-54.
[2] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**:2008-12.

Exposed Cohort; 3) Comparability of Cohorts on the Basis of the Design or Analysis; 4) Demonstration that the outcome of interest was not present at the start of the study; 5) Length of follow-up long enough for outcomes to occur; and 6) Adequacy of follow up of cohorts (minimal losses or drop-outs)

The only two items that could be considered applicable are "objective and clearly described methods for ascertainment of: 1) Exposures and 2) Outcomes". However, 'exposures' at each stage of the Cascade will be considered outcomes for the preceding stage (for example - persons with a positive LTBI test had to be evaluated in order to have a recommendation for therapy). This leaves only one criterion to judge – objective and clearly described outcomes. Since studies will be selected only if they reported the numbers of patients being seen at the different steps, we consider that included studies must have reported objective patient/provider actions – hence they must all pass this one quality indicator to be included.

Data analysis:

The proportion who completed each step in the Cascade will be estimated using random effects analyses with PROC NLMixed in SAS (SAS Institute, N Carolina). To account for heterogeneity analyses will be performed in sub-groups stratified by different characteristics. These characteristics will be: Income level of country (World Bank classification – High income, and low-Middle income), Population (medical, contacts, marginalized, migrants and general population), type of program (routine, pilot study, and outbreak – as characterized by authors), LTBI test (TST, IGRA), LTBI regimen (INH, Rifamycin containing, other), and years of data gathering (up to 2000, and after 2000). A key outcome of interest will be the proportion who complete LTBI therapy of all those estimated to have latent TB in the population screened. This will be calculated by dividing the number who completed therapy by those estimated to have latent TB (the total number intended to be screened multiplied by the proportion with a positive test in those who complete screening (ie TST placed and read or a valid IGRA results received by the provider). Forest plots of this parameter will generated using STATA (Stata Corp). To estimate the cumulative overall losses at each step along the cascade, the pooled estimated proportion remaining at that step will be multiplied times the estimated proportion remaining after the preceding step; these proportions will be pooled using fixed meta-analyses (Proc Glimmix in SAS). Heterogeneity will be estimated using the I squared statistic.[3] Publication bias will not be assessed as funnel plots are designed for use with randomized trials, not observational studies.

Version date: April 13, 2015.

[3] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539-58.

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Chapter 5 Resource implications of the latent tuberculosis cascade of care. A time and motion study in five countries

5.1 *Preface: Manuscript 2*

While studies have quantified commonly performed work activities, such as nurses placing or reading a TST, there was not comprehensive data available on each of the unique steps along the LTBI cascade of care, the patient journey from being identified as a household contact (HHC) of someone with active TB disease, through to starting and completing LTBI treatment. The manuscript presented here fills this gap by quantifying the personnel time-requirements to conduct all work activities along the LTBI cascade of care.

The main goal of the study presented here was to provide estimates of total human resource needs (i.e. the total HCW time requirements) to perform all of the clinical work activities to provide LTBI-services to HHC. From these estimates of time, we extrapolated country-specific estimates of the number of additional HCWs that will be needed to provide expanded LTBI services, based on the country-level, WHO-reported TB program data: the annual number of newly confirmed pulmonary TB patients.

The following manuscript is entitled "**Resource implications of the latent tuberculosis cascade of care. A time and motion study in five countries**". This work has been submitted for peer-review and consideration at the *Bulletin of the World Health Organization*.

5.2 *Manuscript 2*

Resource implications of the latent tuberculosis cascade of care:

A time and motion study in five countries

Abstract:

Background

The End TB Strategy calls for global scale-up of preventive treatment for latent tuberculosis infection (LTBI), but little information is available about the associated human resource requirements. Our study aimed to quantify the healthcare worker (HCW) time needed to perform the tasks associated with each step along the LTBI cascade of care for household contacts (HHC) of TB patients.

Methods

We conducted a time and motion (TAM) study, in which consenting HCWs were observed throughout a typical workday. The precise time spent was recorded in pre-specified categories of work activities for each step along the cascade. A linear mixed model was fit to estimate the time at each step.

Findings

A total of 173 HCWs in Benin, Canada, Ghana, Indonesia, and Vietnam participated. The greatest amount of time was spent for the medical evaluation (median: 11 minutes; IQR: 6-16), while the least time was spent on reading a tuberculin skin test (median: four minutes; IQR: 2-9). The greatest variability was seen in the time spent for each medical evaluation, while TST placement and reading showed the least variability. The total time required to complete all steps along the LTBI cascade, from identification of HHC through to treatment initiation ranged from 1.8 hours per index TB patient in Vietnam to 5.2 hours in Ghana.

Interpretation

Our findings suggest that the time requirements are very modest to perform each step in the latent TB cascade of care, but to achieve full identification and management of all household contacts will require additional human resources in many settings.

Funding

Canadian Institutes of Health Research

Introduction

Tuberculosis (TB) is the leading cause of death due to an infectious disease, killing more people than HIV/AIDS(6). It is estimated that 1.7 billion people or one quarter of the world's population have latent TB infection (LTBI)(6, 74). Between 5-15% of these people will develop active TB disease over the course of their lifetime, with higher rates among certain subgroups, such as persons living with HIV, children under five years of age and close household contacts (HHC) of persons with pulmonary TB(6). One of the three pillars of the World Health Organization's (WHO) End TB Strategy is to provide integrated, patient-centered care, particularly therapy aimed at preventing the development of active TB disease in HHC(15). The 2018 United Nations' High-Level Meeting (UNHLM) on Tuberculosis resulted in a declaration calling for the scale-up of evaluation and treatment for 20 million adult HHC by 2022(18).

The LTBI cascade of care is a term for the entire patient journey for LTBI, from identification of a person at risk for LTBI (for example, HHC of a patient with pulmonary TB), to completion of LTBI treatment. In 2016, we published a systematic review and meta-analysis of the LTBI cascade of care which demonstrated that losses at each step of the cascade resulted in fewer than 20% of eligible contacts completing preventive therapy(1). The healthcare worker (HCW) time required to provide clinical services for many steps along this LTBI cascade of care remains largely unknown; yet this information is critical for decisions regarding the provision of health care services and to estimate the personnel needed for scale-up of LTBI testing and therapy.

The objectives of our study were to: quantify the time it takes HCWs to perform the work tasks associated with each step along the LTBI cascade of care for HHC in Canada (a high-income country), and in four low-and middle-income countries (LMIC); and to estimate the human resource needs to provide LTBI care to all HHC of new, confirmed, pulmonary TB patients in each of the participating countries.

Methods

Parent study

This time and motion (TAM) study was conducted as part of a larger pragmatic, cluster-randomized trial which took place in 24 health facilities in Benin, Canada, Ghana, Indonesia, and Vietnam. The main objective of the parent trial was to evaluate and strengthen the LTBI cascade of care in these settings. The parent trial is described in detail elsewhere(48).

Time and motion (TAM) study

HCWs who worked at least one full day per week delivering TB care at all participating health facilities were eligible for the TAM study. At each participating health facility, purposive sampling was used and we aimed to include a minimum of ten HCWs, with at least three HCWs working in each of three cadres: 1) doctors; 2) nurses; 3) other HCWs (i.e. social workers, health assistants, pharmacists, and community health workers).

For each TAM, a participating HCW was observed continuously throughout a typical workday. After completion of each discrete activity, the worker was asked to categorize that activity into one of three main types: 1) Direct patient care (i.e. any face-to-face encounter or phone call with a patient); 2) Other clinical activities (i.e. charting, dictations, reviewing laboratory results or x-rays); and 3) Training or administrative tasks (i.e. supervising trainees, meetings or emails). Time spent on breaks (i.e. restroom, meals or personal phone calls) was recorded on the TAMs but removed from all analyses. For each patient encounter, the time recorded included time spent on initial greetings and introductions, explanation, actually performing the activity, then education and instructions, arranging further follow-up if required and finally completing all related documentation (e.g. charting, completing forms, or filling registries). After these encounters, the HCW were asked to categorize each patient into three broad types of medical conditions: 1) LTBI; 2) active or suspected active TB; and 3) non-TB, meaning any other medical condition. LTBI patient

encounters were further categorized into six specific activities : 1) Identification of contacts; 2) Placing TST or drawing blood samples for IGRA[4]; 3) Reading TST; 4) Conducting medical evaluation; 5) Recommending and discussing LTBI treatment; and 6) LTBI treatment follow-up visits.

TAMs were scheduled in advance with each HCW for a typical workday, defined as a day in which the HCW did not have any planned or likely change in their normal schedule (such as leaving early to pick up a child or attending a personal appointment). At the start of the TAM day, the local research staff confirmed with the HCW that it should be a typical workday. If there was an unanticipated event during that day, the TAM was stopped and rescheduled for another time.

Data Collection

Data was collected between January 2018 and March 2019. To ensure standardized measurements, all research staff performing the TAMs received initial and refresher training from one investigator (HA) on how to observe and record HCWs time using standard data collection forms, and properly classify and code each observation. All data was recorded on paper data collection sheets, and then de-identified data transferred to Excel spreadsheets with pre-specified drop-down menus.

Analyses

Characteristics of the HCWs who performed at least one LTBI patient encounter were compared to HCWs observed with TAMS that did not perform any LTBI patient encounters using a chi-square test for categorical variables.

Data was analyzed for individual LTBI patient encounters. If the time recorded reflected visits with multiple patients simultaneously or activities spanning multiple cascade steps, these observations were excluded from analysis. The mean and median time in minutes each individual HCW spent on each LTBI patient encounter, at each step in the cascade, was estimated for: 1) the

[4] There were only 13 observations noted specifically to be IGRA blood draws at Canadian sites

type of setting (Canada versus LMIC) and 2) HCW cadre (i.e. doctors, nurses, other HCWs). A linear mixed model (LMM) was fit for each HCW cadre and type of setting, for all steps in the LTBI cascade of care. We present estimates for the HCW cadre in each setting that were found to perform the majority of LTBI patient encounters at each step. Data were analyzed using SAS version 9.4 (SAS Institute, Cary, USA).

To estimate the human resource requirements for country wide scale-up of LTBI care for all HHC of newly confirmed pulmonary TB patients, we used the linear mixed model estimates for Canada or LMIC settings, of HCW time to complete work tasks for each step in the LTBI cascade of care. For each country, the estimates of time (in hours) from the linear mixed models (from Canada for high income countries and from LMIC for all other countries) at each step were multiplied by the country-specific average number of household contacts per index TB patient (from unpublished parent study results). For the first step of the identification of all household contacts for one index patient, the time per index case was used rather than the time per contact. The time HCWs spent on medical evaluation and recommending / discussing LTBI preventive therapy was multiplied by the prevalence of TST positive contacts in that setting - assumed to be 50% in LMIC and 28% in Canadian sites, based on a published systematic review(10).

Based on the predominance of HCW cadres we observed performing each of the cascade steps, for our extrapolations we assumed that: 1) nurses would perform the contact identification, TST administration and reading, and the LTBI treatment follow-up visits; 2) doctors would perform the medical evaluations; and 3) both doctors and nurses would recommend /discuss LTBI treatment initiation. We assumed monthly follow-up visits during LTBI therapy - meaning three visits for four months of rifampin (4R) in Canada, and five visits for six months of isoniazid (6H) in LMIC. Time for follow-up visits was multiplied by the prevalence of TST positive household contacts and number of visits (i.e. three visits in Canada and five in LMIC). Next, the HCW time to conduct all

activities at all steps was summed, by HCW cadre, to provide country-specific estimates for the predicted total health care personnel time for all household contacts of one index patient. Finally, the country-specific cumulative total predicted time, by HCW cadre, to perform all cascade steps for all household contacts of one index patient was multiplied by the number of new, confirmed pulmonary TB patients reported in 2017(75) to give the total annual country-specific HCW time requirements(6). The full-time equivalent (FTE) personnel required was then calculated as the total time divided by 1,920 hours, which corresponds to the total hours worked by a full-time worker in one calendar year accounting for four weeks of vacation and other leave (assumes eight hours worked/day x five days/week x 48 weeks/year).

Ethics

The Research Ethics Board of the Research Institute of the McGill University Health Center approved the study. Verbal consent was obtained from all HCWs to permit research staff to observe their daily work activities. Research staff conducting the TAM did not enter patient rooms during encounters with observed workers.

Role of the funding source

This study was supported by the Canadian Institutes of Health Research (Grant #FND331745). This funding agency had no role in study design, interpretation or writing of this report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

In total, 184 HCWs were approached to participate in the TAMs, of whom 173 (94%) agreed (85 doctors, 76 nurses, and 12 other HCWs). Of these, 83 were observed to have at least one patient encounter at one or more steps along the LTBI cascade of care; the remaining 90 HCWs

were not observed to have any LTBI related patient encounters during the day selected for TAM observation (table 5.1).

Healthcare worker time requirements

The time to conduct a medical evaluation of a TST positive HHC was the longest, while reading a TST took the least time (table 5.2). Placing and reading a TST in LMIC took two and three minutes, respectively, compared to 11 and ten minutes, respectively, in Canada (table 5.2). The HCWs time to identify contacts, place and read TSTs, conduct medical evaluations and perform patient follow-up visits was very different in Canada compared to LMIC, as shown in the stratified analysis (table 5.2). There was considerable variation in HCWs time to conduct a medical evaluation, but much less variability in the time taken to read a TST (figure 5.2). The variability of the remaining steps is shown in figures 5.1 and 5.3. Nurses were responsible for most LTBI patient encounters for contact identification, TST administration and were the only HCW cadre to read TSTs across all sites, while doctors conducted most medical evaluations (table 5.3). Both doctors and nurses took part in recommending/discussing LTBI treatment initiation, but nurses performed the majority of follow-up visits (table 5.3). The linear mixed models show that the predicted HCW time required for the designated HCWs cadre to perform each step in the LTBI cascade varied significantly by setting (table 5.4).

Human Resource Requirements

As seen in the country-specific tables total predicted time (in hours) for each type of HCW to complete all the steps along the LTBI cascade for all household contacts of one index patient ranged from 1.8 hours (1.4 nurse hours and 0.4 doctor hours) in Vietnam to 5.2 hours (4.1 nurse hours and 1.1 doctor hours) in Ghana (table 5.4 and supplemental tables 5.S1-S5).

Discussion

This study provides important information on the staffing resources needed to ensure that all household contacts of new, pulmonary TB patients are provided with high quality patient-centered care, a focus of the End TB strategy(15). This study provides estimates of the amount of time taken by different cadres of HCW in very different settings on specific activities required at all the steps in the LTBI cascade, using a method developed to precisely measure time on specific work tasks(28). Although the overall estimated human resources required for direct LTBI related patient care appears modest in most settings, in the LMIC included in this study, there are fewer than four doctors and 12 nurses per 10,000 population(76). Hence, even a modest increase in number of HCWs would be an important undertaking for local health systems

There were a number of important limitations to our study. The TAMs relied upon HCWs to perform activities associated with the steps in the cascade during the selected TAM days in order to gather information on the time required for each step. However, many of the HCWs who participated in TAMs did not have LTBI-related patient encounters on the day of observation. Our predicted estimates of HCWs time are not based on the actual trajectory of individual household contacts through all steps of the LTBI cascade of care but are 'reconstructed' based on separate patient encounters for each cascade step. Following a single household contact would have required multiple TAM days specifically tracking each contact, which would have been impractical.

Since HCWs are being shadowed by an observer recording their every activity throughout their entire workday, it is impossible to eliminate the potential for the Hawthorne effect. While being observed on the TAM day, it is plausible that HCWs took fewer breaks and may have spent slightly more time with each patient encounter. However, all break time was removed in the analysis, and it seems unlikely there would have been a differential increase in HCWs time with one type of patient, or one particular activity, rather they may have increased slightly their time on all patient visits and

activities. For ethical reasons, the research staff did not directly observe patient encounters, but only recorded the time the encounter started with initial greetings and ended with completion of documentation. Hence there may have been time spent chatting about unrelated things (the weather, or Donald Trump) but this reflects the reality of human encounters, and so provides a more realistic estimate of the true time needed. The observers also relied on what the health care worker stated was the activity and type of patient, which may have led to some misclassification, although systematic misclassification seems implausible.

The estimates of HCWs resource needs for full contact investigation per index TB patient assumed a very efficient process and so may underestimate the human resource requirements. For example, two HCWs may perform the same task for one contact, or multiple patient visits may be required to complete the same step, such as medical evaluation. HCWs time on each step was based solely on observed patient encounters; other related activities such as checking lab results later, were not counted. Yet the time for direct patient care must be supported by time for other clinical activities such as correspondence and consultations, or reviewing investigations. Administrative, training and other non-patient care related activities also account for some part of clinical health care personnel time, but these activities were also not included. Hence, we may have underestimated the total personnel time requirements. We included the time required for treatment follow-up visits in our estimates; however, if treatment regimens were shorter (e.g. 4R), then required personnel time would be less.

The health facilities that participated in the parent study may not be generalizable to all health facilities in each country, or to all LMIC, since not all LMIC have similar LTBI practices. Patient and health system differences between facilities, such as greater or lesser need to use translation services for patient encounters in high-income countries (i.e. Canada) may lead to variation from the HCWs time measured in this study. A clinic-based healthcare service delivery

model was used for this study which may not be generalizable to other settings with community-based healthcare delivery.

Nevertheless, this study had a number of strengths, particularly that the TAMs captured data on many patient encounters at each step. For example, we observed 143 HCW-contact encounters for recommending LTBI treatment, and 276 LTBI follow-up visits. Selection bias should have been minimal as more than 94% of HCWs participated, and the characteristics of HCWs performing none, or at least one LTBI related activity, were similar. We counted the full time required for each patient encounter, from initial introduction to completion of documentation, and the patient encounters were part of workers' normal tasks on a routine day, ensuring a realistic estimation of the time required. Prior cost-effectiveness analyses (CEA)(49-56) have used time estimates from third party payment schemes(77-79) to calculate HCWs time required to perform an activity, like placing TST, and associated costs. However, we directly measured the time and estimated the variability of time by setting and cadre; these estimates should be useful to inform future costing studies as well as health administrators planning new LTBI programmes or scale-up of LTBI services. Another strength of our study is that time was estimated for each step in the LTBI cascade for Canada and LMIC separately, in order to provide setting-specific estimates. Other studies have outlined the treatment phase costs for each HHC to complete preventive therapy (54, 80) but our study includes the HCWs time for pre-treatment phase encounters – which accounted for more personnel time than treatment follow-up in this study.

WHO recommends scaling-up LTBI services for HHC, including all persons over five years of age(81); this is likely to dramatically increase the numbers of people accessing LTBI services globally, particularly in high burden LMIC(6). Our study demonstrates that additional health care workers will be needed in the workforce to ensure adequate human resources to identify, screen and treat all close contacts. Our study also demonstrates that tuberculin skin testing and reading in the

LMIC settings observed required very little time, which is an important consideration in terms of the implementation of LTBI testing as part of routine management of non-HIV infected household contacts. This study provides TB programs with the tools to calculate the additional personnel needed to perform all the steps of the LTBI cascade based on the number of active, pulmonary TB patients in their setting. These estimates could be used to benchmark efficient delivery of LTBI treatment, by determining the number of additional personnel hired and trained for LTBI program scale-up.

Conclusion

The UNHLM recognized the need for increased healthcare services in order to effectively decrease the reservoir of LTBI (18). Strong political and financial commitments will be needed from national TB programs to support the expansion of LTBI services in order to provide high quality patient-centered care at all steps in the LTBI cascade of care.

Table 5.1: Characteristics of 173 HCW participating in TAMs for the LTBI cascade of care

	HCW with one or more patient encounters along the steps in the LTBI Cascade of Care	**HCW with no patient encounters along the steps in the LTBI Cascade of Care**	**p-value[1]**
	(N=83)	(N=90)	
Sex			
Male	27 (33%)	23 (26%)	0.31
Female	56 (67%)	67 (74%)	
TB specific role			
Yes	73 (88%)	37 (41%)	<0.01
No	10 (12%)	53 (59%)	
HCW category			
Doctor	31 (37%)	54 (60%)	0.01
Nurse	45 (54%)	31 (34%)	
Other HCW	7 (9%)	5 (6%)	
Country			
Benin	5 (6%)	13 (14%)	<0.01
Canada	48 (58%)	4 (4%)	
Ghana	10 (12%)	7 (8%)	
Indonesia	12 (14%)	33 (37%)	
Vietnam	8 (10%)	33 (37%)	
Country setting			
High Income[2]	48 (58%)	4 (4%)	<0.01
LMIC[3]	35 (42%)	86 (96%)	

[1]p-values from χ^2 test for difference in characteristics of HCW performing at least one patient encounter along the LTBI cascade of care compared to HCW participating in TAMs but not performing any tasks along LTBI Cascade

[2]High income country (HIC) =Canada

[3]Low-and middle-income countries (LMIC) =Benin, Ghana, Indonesia, Vietnam

Table 5.2: HCW time* spent on patient encounters at each step along the LTBI Cascade of Care – Canada vs. low- and middle-income countries

LTBI Cascade of Care Steps	Number of HCW performing each Step on TAM day	Total number of LTBI patient encounters with HCW at each Step on TAM day	Mean time spent on each Step (Std. Dev.)	Median time spent on each Step (IQR)
1. Identify contacts (all sites)	33	73	10.5 (10.4)	6.0 (2-16)
Canada[1]	20	39	14.0 (11.2)	12.0 (5-21)
LMIC[2]	13	34	6.6 (8.0)	2.5 (2-7)
2. Place TST[3](all sites)	22	64	8.1 (7.5)	5.5 (2-12)
Canada	13	32	13.1 (7.1)	11.0 (9-15)
LMIC	9	32	3.1 (3.4)	2.0 (2-4)
3. Read TST[3](all sites)	17	59	6.4 (6.1)	4.0 (2-9)
Canada	11	22	11.9 (6.9)	10.5 (8-14)
LMIC	6	37	3.2 (1.6)	3.0 (2-4)
4. Conduct Medical Evaluation (all sites)	43	116	12.1 (7.8)	11.0 (6-16)
Canada	33	90	13.0 (7.9)	12.0 (7-17)
LMIC	10	26	9.0 (6.6)	7.5 (2-15)
5. Recommend and discuss LTBI treatment (all sites)	42	143	10.8 (8.5)	9.0 (4-13)
Canada	34	92	13.9 (8.9)	11.0 (8-18)
LMIC	8	51	5.3 (3.5)	4.0 (4-5)
6. LTBI treatment follow-up (all sites)	56	276	9.3 (9.5)	6.0 (2-12)
Canada	44	191	12.0 (9.9)	9.0 (5-16)
LMIC	12	85	3.4 (4.4)	2.0 (1-5)

*Time from 83 HCW participating in at least one LTBI patient encounter along the steps of the cascade

[1]Canada is the one high-income country

[2]Low-and middle-income countries (LMIC) include: Benin, Ghana, Indonesia, Vietnam

[3]Steps 2 & 3 may include HCW time spent on patient education, in addition to placing and reading a TST

Table 5.3: HCW time* spent on patient encounters at each step along LTBI Cascade of Care Steps – By HCW cadre

LTBI Cascade of Care Steps	Number of HCW observed performing each Step	Total number of observed HCW-patient encounters at each Step	Mean time (minutes) spent on each encounter (Std. Dev.)	Median time (minutes) spent on each encounter (IQR)
1. Identify contacts				
Doctor	16	22	13.0 (7.6)	15.0 (7-18)
Nurse	16	48	9.2 (11.3)	4.0 (2-12)
Other HCW**	1	3	14.7 (12.7)	10.0 (5-29)
2. Place TST				
Doctor	2	2	4.0 (-)	4.0 (-)
Nurse	19	50	9.7 (7.7)	8.5 (3-13)
Other HCW**	1	12	2.1 (0.7)	2.0 (2-3)
3. Read TST				
Doctor	-	-	-	-
Nurse	17	59	6.4 (6.1)	4.0 (2-9)
Other HCW**	-	-	-	-
4. Conduct Medical Evaluation				
Doctor	19	67	12.7 (6.2)	13.0 (8-16)
Nurse	21	37	11.6 (10.2)	7.0 (3-16)
Other HCW**	3	12	10.3 (7.9)	8.5 (6-14)
5. Recommend and discuss LTBI treatment				
Doctor	20	55	12.3 (7.4)	10.0 (9-14)
Nurse	20	77	9.7 (9.5)	5.0 (4-12)
Other HCW**	2	11	10.9 (5.2)	11.0 (7-15)
6. LTBI treatment follow-up				
Doctor	17	65	7.2 (5.0)	5.0 (4-10)
Nurse	34	176	11.0 (9.5)	7.0 (2-16)
Other HCW**	5	35	5.1 (6.6)	2.0 (2-7)

* Time from 83 HCW participating in at least one LTBI patient encounter along the steps of the cascade

**Note: Other HCWs include: health assistants, social workers, sociologists and pharmacist

Table 5.4: Linear mixed model of HCW time required for each encounter/activity in the LTBI Cascade of Care.

Model		Time (min)	95% CI*
1. Identify contacts	Nurse in Canada[1]	12.8	(5.1, 20.6)
	Nurse in LMIC[2]	7.5	(0.9, 14.2)
2. Place TST	Nurse in Canada	15.8	(11.4, 20.2)
	Nurse in LMIC	4.5	(0.0*, 9.5)
3. Read TST	Nurse in Canada	12.0	(9.5, 14.5)
	Nurse in LMIC	2.9	(0.0*, 5.8)
4. Conduct medical evaluation	Doctor in Canada	13.1	(10.2, 15.9)
	Doctor in LMIC	9.7	(5.0, 14.4)
5. Recommend and discuss LTBI treatment[3]	Doctor in Canada	14.3	(9.8, 18.8)
	Nurse in Canada	16.0	(11.3, 20.8)
	Doctor in LMIC	5.5	(0.0*, 11.7)
	Nurse in LMIC	7.2	(1.8, 12.5)
6. LTBI follow-up visit	Nurse in Canada	14.8	(10.3, 19.3)
	Nurse in LMIC	6.5	(1.2, 11.9)

[1]Canada is the one high-income country
[2]LMIC include: Benin, Ghana, Indonesia, and Vietnam
[3]In the LMM for Step #5, there was not a statistically significant interaction between type of HCW and setting, so the expected difference between doctors and nurses is the same whether in HIC or LMIC settings.
*Note: Where the CI lower limit is below zero, values were cut-off at 0 minutes.

Table 5.5: Total time[1] required for contact management and LTBI care for all steps along the LTBI Cascade of Care

	Identify contacts	**Place TST[2]**	**Read TST[2]**	**Conduct Medical Evaluation[2,3]**	**Recommend and Discuss LTBI Treatment[2,3]**	**LTBI Follow-up Visit[2,3,4]**	**Total Time Per Index Case (hours)**
Country	(A)	(B)	(C)	(D)	(E)	(F)	Σ (A-F)
LMIC							
Benin							**2.40**
Doctors	-	-	-	18.9	10.7	-	**0.50**
Nurses	7.5	17.6	11.3	-	14.0	63.4	**1.90**
Ghana							**5.24**
Doctors	-	-	-	42.7	24.2	-	**1.12**
Nurses	7.5	39.6	25.5	-	31.7	143.0	**4.12**
Indonesia							**2.05**
Doctors	-	-	-	16.0	9.1	-	**0.42**
Nurses	7.5	14.9	9.6	-	11.9	53.6	**1.63**
Vietnam							**1.76**
Doctors	-	-	-	13.6	7.7	-	**0.36**
Nurses	7.5	12.6	8.1	-	10.1	45.5	**1.40**
High-Income							
Canada							**3.35**
Doctors	-	-	-	13.1	14.3	-	**0.46**
Nurses	12.8	56.9	43.2	-	16.0	44.4	**2.89**

[1]Predicted time (min) for each step from linear mixed models (LMM) shown in supplementary tables S1-5.
[2]Assumes step accounts for all household contacts (HHC) for one index case; based on average number of HHC per index patient in each country observed in the main study: Benin = 3.9; Ghana = 8.8; Indonesia = 3.3; Vietnam = 2.8; Canada = 3.6
[3]Assumes a prevalence of TST positive for HHC of index patient is 50% in LMIC and 28% in Canada (Fox 2013)
[4]Assumes 5 follow-up visits for 6 months of INH treatment of LTBI in LMIC and 3 follow-up visits for 4 months of RIF treatment of LTBI in Canada.

Supplemental Table 5.S1: Predicted health care personnel time to perform all tasks in the LTBI Cascade of Care for all household contacts (HHC) of one index patient in **Benin** (observed data: 3.9 HHC per index patient)

	Predicted time, in minutes, for each cadre of HCW to perform each type of patient care encounter[1]	Predicted time, in hours, for each cadre of HCW to perform each patient care encounter	Multiplier[2]	Predicted total time, in hours, for HCW to perform each step for all contacts of one index patient
LTBI Cascade of Care Steps (type of HCW performing step)	(A)	(B)	(E)	(F) = (D) x (E)
1. Identify contacts[3]				
Nurse	7.5	0.13	1.0	0.13
2. Place TST				
Nurse	4.5	0.08	3.9	0.29
3. Read TST				
Nurse	2.9	0.05	3.9	0.19
4. Conduct Medical Evaluation				
Doctor	9.7	0.16	1.95	0.32
5. Recommend and Discuss LTBI Treatment				
Doctor	5.5	0.09	1.95	0.18
Nurse	7.2	0.12	1.95	0.23
6. LTBI Follow-up Visit				
Nurse	6.5	0.11	9.75	1.06
Total time to complete all steps - All personnel				2.40
Total time for a Doctor				0.50
Total time for a Nurse				1.90

[1]Predicted time (min) for each step from linear mixed models (LMM) is the average for all LMIC shown in Table 4. [2]The multiplier at steps #2-5 is 3.9 which was the average number of household contacts (HHC) per index patient in Benin observed in the main study; steps #4-5 are also multiplied by 0.50, assuming a prevalence of 50% TST positive among all HHC of index patients (Fox 2013); step #6 is multiplied by 9.75, based on an assumed 5 follow-up visits (5 x 1.95= 9.75) for 6 months INH treatment of LTBI in 1.95 HHC per index case. [3]The time on this step accounts for identification of all HHC of one index patient.

Supplemental Table 5.S2: Predicted health care personnel time required for HCW to perform all tasks in the LTBI Cascade of Care for all household contacts (HHC) of one index patient in **Canada** (observed data: 3.6 HHC per index patient)

	Predicted time, in minutes, for each cadre of HCW to perform each type of patient care encounter[1]	Predicted time, in hours, for each cadre of HCW to perform each patient care encounter	Multiplier[2]	Predicted total time, in hours, for HCW to perform each step for all contacts of one index patient
LTBI Cascade of Care Steps (type of HCW performing step)	(A)	(B)	(E)	(F) = (D) x (E)
1. Identify contacts[3]				
Nurse	12.8	0.21	1.0	0.21
2. Place TST				
Nurse	15.8	0.26	3.6	0.95
3. Read TST				
Nurse	12.0	0.20	3.6	0.72
4. Conduct Medical Evaluation				
Doctor	13.1	0.22	1.0	0.22
5. Recommend and Discuss LTBI Treatment				
Doctor	14.3	0.24	1.0	0.24
Nurse	16.0	0.27		0.27
6. LTBI Follow-up Visit				
Nurse	14.8	0.25	3.0	0.74
Total time to complete all steps - All personnel				3.35
Total time for a Doctor				0.46
Total time for a Nurse				2.89

[1]Predicted time (min) for each step from linear mixed models (LMM) is the average for all Canadian sites shown in Table 4. [2]The multiplier at steps #2-5 is 3.6 which was the average number of household contacts (HHC) per index patient in Canada observed in the main study; steps #4-5 are also multiplied by 0.28, assuming a prevalence of 28% TST positive among all HHC of index patients (Fox 2013); step #6 is multiplied by 3.0, based on an assumed 3 follow-up visits (3 x 1.0 = 3.0) for 4 months of RIF treatment of LTBI in 1.0 HHC per index case. [3]The time on this step accounts for identification of all HHC of one index patient.

Supplemental Table 5.S3: Predicted health care personnel time required for HCW to perform all tasks in the LTBI Cascade of Care for all household contacts (HHC) of one index patient in **Ghana** (observed data: 8.8 HHC per index patient)

	Predicted time, in minutes, for each cadre of HCW to perform each type of patient care encounter[1]	Predicted time, in hours, for each cadre of HCW to perform each patient care encounter	Multiplier[2]	Predicted total time, in hours, for HCW to perform each step for all contacts of one index patient
LTBI Cascade of Care Steps (type of HCW performing step)	(A)	(B)	(E)	(F) = (D) x (E)
1. Identify contacts[3]				
Nurse	7.5	0.13	1.0	0.13
2. Place TST				
Nurse	4.5	0.08	8.8	0.66
3. Read TST				
Nurse	2.9	0.05	8.8	0.43
4. Conduct Medical Evaluation				
Doctor	9.7	0.16	4.4	0.71
5. Recommend and Discuss LTBI Treatment				
Doctor	5.5	0.09	4.4	0.40
Nurse	7.2	0.12	4.4	0.53
6. LTBI Follow-up Visit				
Nurse	6.5	0.11	22.0	2.38
Total time to complete all steps - All personnel				5.24
Total time for a Doctor				1.11
Total time for a Nurse				4.13

[1]Predicted time (min) for each step from linear mixed models (LMM) is the average for all LMIC shown in Table 4. [2]The multiplier at steps #2-5 is 8.8 which was the average number of household contacts (HHC) per index patient in Ghana observed in the main study; steps #4-5 are also multiplied by 0.50, assuming a prevalence of 50% TST positive among all HHC of index patients (Fox 2013); step #6 is multiplied by 22.0, based on an assumed 5 follow-up visits (5 x 4.4= 22.0) for 6 months INH treatment of LTBI in 4.4 HHC per index case. [3]The time on this step accounts for identification of all HHC of one index patient.

Supplemental Table 5.S4: Predicted health care personnel time required for HCW to perform all tasks in the LTBI Cascade of Care for all household contacts (HHC) of one index patient in **Indonesia** (observed data: 3.3 HHC per index patient)

	Predicted time, in minutes, for each cadre of HCW to perform each type of patient care encounter[1]	Predicted time, in hours, for each cadre of HCW to perform each patient care encounter	Multiplier[2]	Predicted total time, in hours, for HCW to perform each step for all contacts of one index patient
LTBI Cascade of Care Steps (type of HCW performing step)	(A)	(B)	(E)	(F) = (D) x (E)
1. Identify contacts[3]				
Nurse	7.5	0.13	1.0	0.13
2. Place TST				
Nurse	4.5	0.08	3.3	0.25
3. Read TST				
Nurse	2.9	0.05	3.3	0.16
4. Conduct Medical Evaluation				
Doctor	9.7	0.16	1.65	0.27
5. Recommend and Discuss LTBI Treatment				
Doctor	5.5	0.09	1.65	0.15
Nurse	7.2	0.12		0.20
6. LTBI Follow-up Visit				
Nurse	6.5	0.11	8.25	0.89
Total time to complete all steps - All personnel				2.05
Total time for a Doctor				0.42
Total time for a Nurse				1.63

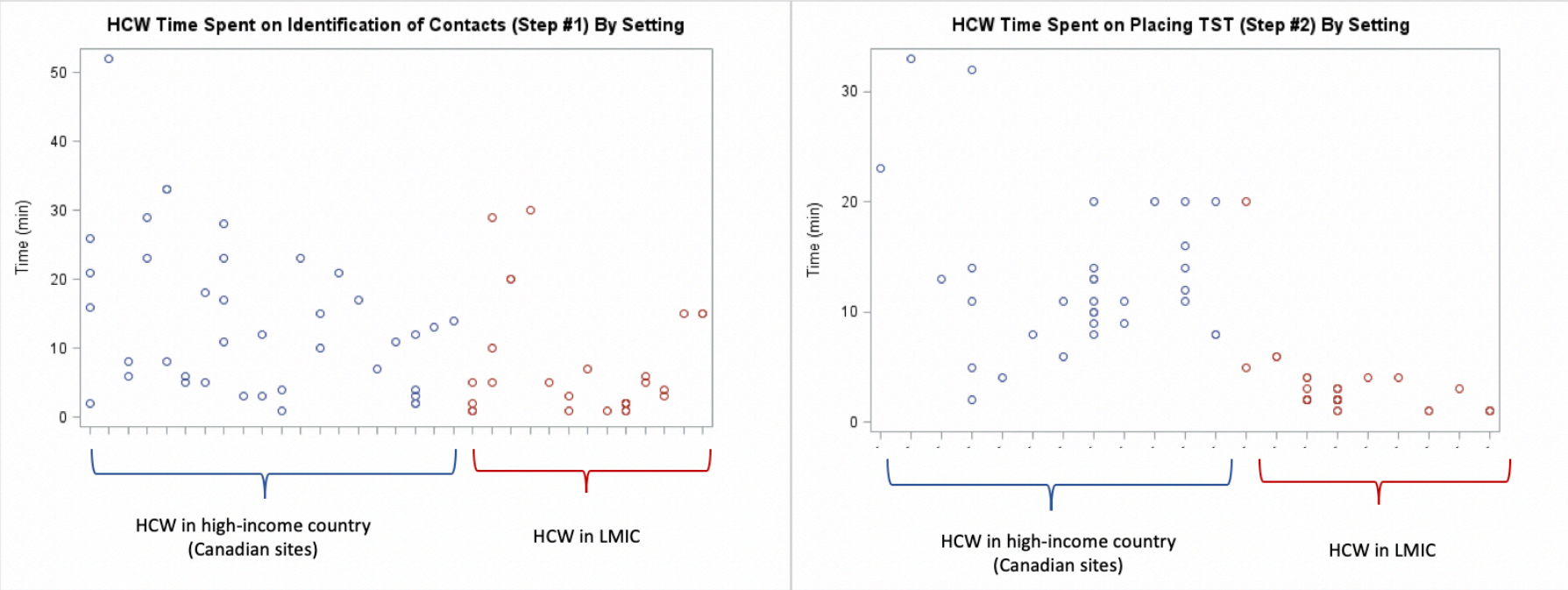
[1]Predicted time (min) for each step from linear mixed models (LMM) is the average for all LMIC shown in Table 4. [2]The multiplier at steps #2-5 is 3.3 which was the average number of household contacts (HHC) per index patient in Indonesia observed in the main study; steps #4-5 are also multiplied by 0.50, assuming a prevalence of 50% TST positive among all HHC of index patients (Fox 2013); step #6 is multiplied by 8.25, based on an assumed 5 follow-up visits (5 x 1.65=8.25) for 6 months INH treatment of LTBI in 1.65 HHC per index case. [3]The time on this step accounts for identification of all HHC of one index patient.

Supplemental Table 5.S5: Predicted health care personnel time required for HCW to perform all tasks in the LTBI Cascade of Care for all household contacts (HHC) of one index patient in **Vietnam** (observed data: 2.8 HHC per index patient)

	Predicted time, in minutes, for each cadre of HCW to perform each type of patient care encounter[1]	Predicted time, in hours, for each cadre of HCW to perform each patient care encounter	Multiplier[2]	Predicted total time, in hours, for HCW to perform each step for all contacts of one index patient
LTBI Cascade of Care Steps (type of HCW performing step)	(A)	(B)	(E)	(F) = (D) x (E)
1. Identify contacts[3]				
Nurse	7.5	0.13	1.0	0.13
2. Place TST				
Nurse	4.5	0.08	2.8	0.21
3. Read TST				
Nurse	2.9	0.05	2.8	0.14
4. Conduct Medical Evaluation				
Doctor	9.7	0.16	1.4	0.23
5. Recommend and Discuss LTBI Treatment				
Doctor	5.5	0.09	1.4	0.13
Nurse	7.2	0.12		0.17
6. LTBI Follow-up Visit				
Nurse	6.5	0.11	7.0	0.76
Total time to complete all steps - All personnel				1.77
Total time for a Doctor				0.36
Total time for a Nurse				1.41

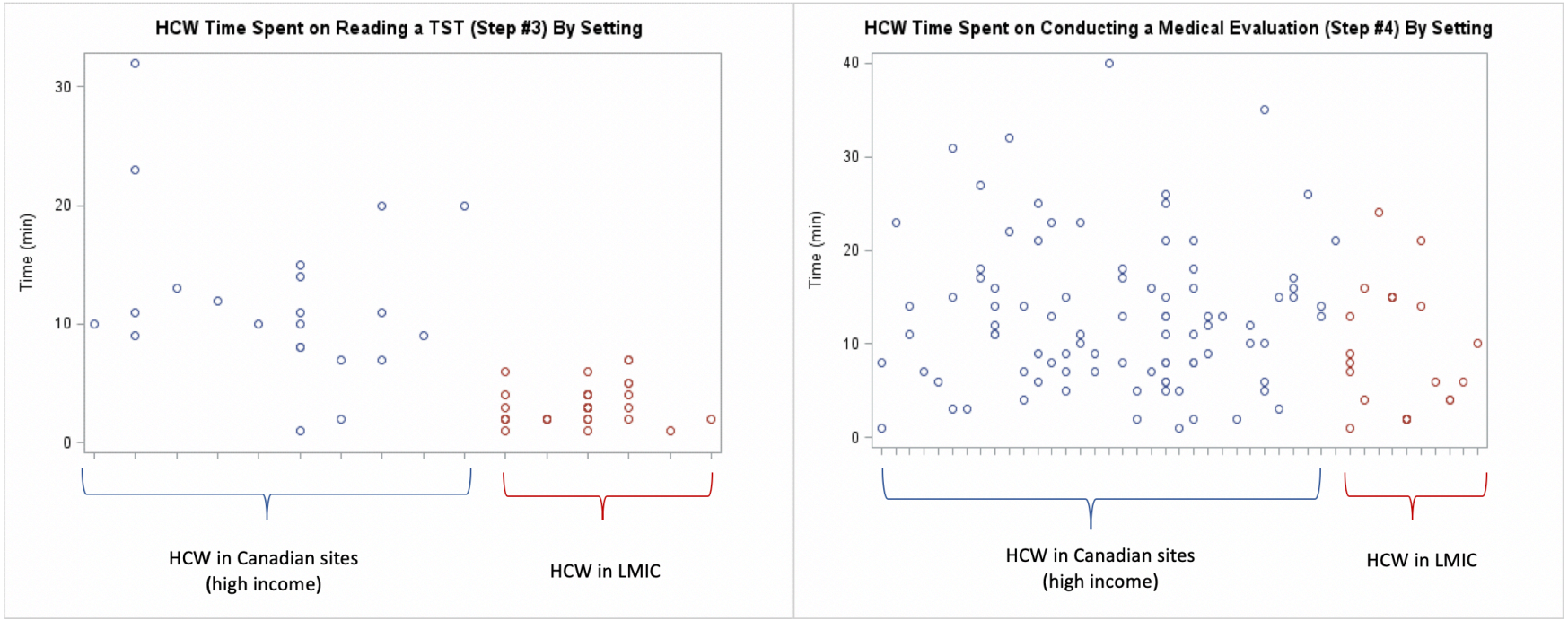
[1]Predicted time (min) for each step from linear mixed models (LMM) is the average for all LMIC shown in Table 4. [2]The multiplier at steps #2-5 is 2.8 which was the average number of household contacts (HHC) per index patient in Vietnam observed in the main study; steps #4-5 are also multiplied by 0.50, assuming a prevalence of 50% TST positive among all HHC of index patients (Fox 2013); step #6 is multiplied by 7.0, based on an assume 5 follow-up visits (5 x 1.4= 7.0) for 6 months INH treatment of LTBI in 1.4 HHC per index case. [3]The time on this step accounts for identification of all HHC of one index patient.

Figure 5.1: Scatterplot of time for individual HCW-contact encounters: for Identification of Contacts (Step #1) and Placing a TST (Step #2)



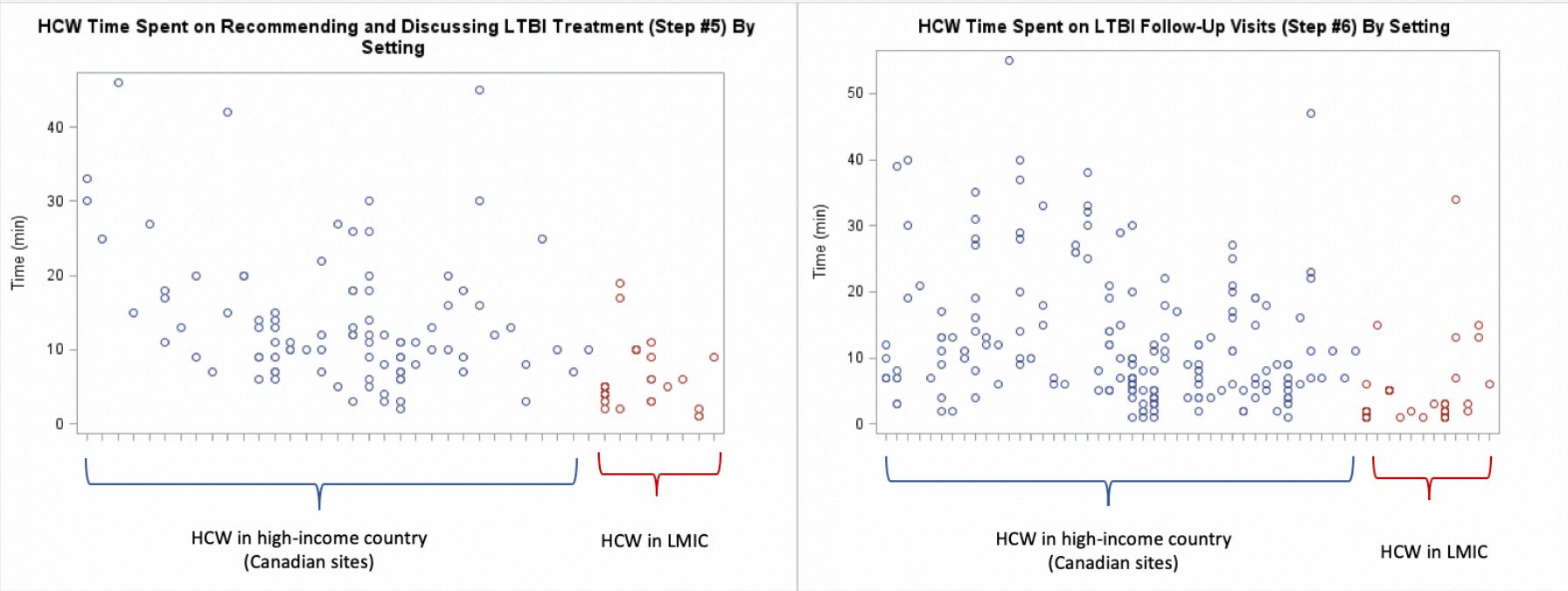
*Note: Each point on the x-axis denotes a separate, individual HCW; each circle is a unique LTBI patient encounter (blue=Canadian sites (high-income); red=LMIC).

Figure 5.2. Scatterplot of time for an individual HCW patient encounter for: Reading a TST (Step #3) and Conducting a Medical Evaluation (Step #4)



*Note: Each point on the x-axis denotes a separate, individual HCW; each circle is a unique patient encounter (blue=high-income; red=LMIC).

Figure 5.3. Scatterplot of time for individual HCW-contact encounters: for Recommending LTBI Treatment (Step #5) and LTBI Follow-Up Visit (Step #6)



*Note: Each point on the x-axis denotes a separate, individual HCW; each circle is a unique patient encounter (blue=high-income; red=LMIC

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Chapter 6 Human resource implications of expanding latent tuberculosis patient care activities

6.1 *Preface: Manuscript 3*

The World Health Organization (WHO) and the United Nations have declared increasing preventive services for latent tuberculosis infection (LTBI) a priority as part of global efforts to eliminate tuberculosis (TB) by 2035. While this focus on improving access to preventive TB services represent an important step towards TB elimination efforts, there is little information on how scale-up will shift the workload for healthcare workers (HCW) currently providing TB care. The manuscript presented here aims to fill the gap of understanding the human resource requirements for global scale-up of LTBI services.

The main goal of the study presented here was to quantify the changes in the proportion of HCW time spent on LTBI-related patient care activities following the parent trial intervention to evaluate and strengthen LTBI patient care services. And our second aim was to determine any changes in the amount of time devoted to clinical care activities for patients with active TB or non-TB related health problems following the intervention.

The following manuscript is entitled "**Human resource implications of expanding latent tuberculosis patient care activities**". This work is being prepared for submission to *Health Services Research*.

6.2 *Manuscript 3*

Human resource implications of expanding latent tuberculosis patient care activities

Abstract:

Background

The World Health Organization (WHO) declared increasing services for latent tuberculosis infection (LTBI) a priority to eliminate tuberculosis (TB) by 2035. There is little information about the human resource needs for LTBI treatment scale-up. Our study aimed to estimate the change in healthcare workers (HCW) time following an intervention to strengthen LTBI services.

Methods

We conducted a time and motion (TAM) study, observing HCW throughout a typical workday before and after the intervention (Evaluation and Implementation phases, respectively) at 24 health facilities in five countries: Benin, Canada, Ghana, Indonesia, and Vietnam. The precise time spent on pre-specified categories of work activities was recorded. A linear mixed model (LMM) was fit to estimate the change in HCW time following the intervention.

Findings

A total of 140 and 143 HCW participated in the TAMs during the Evaluation phase and Implementation phases, respectively. Results from LMMs showed an increase of 11% (95% CI: 3%, 19%) in the proportion of HCW time spent on LTBI-related services and a decrease of 12% (95% CI: -26%, 1%) in proportion of HCW time spent on active TB services.

Interpretation

Our findings suggest that scale-up of LTBI services will require additional HCW time and personnel to ensure that expanded services do not come at the expense of quality care for active TB patients.

Funding

Canadian Institutes of Health Research

Background

According to World Health Organization (WHO) estimates, there were over 10 million new cases of tuberculosis (TB) worldwide in 2017(1). It is further estimated that nearly 25% of the world's population is latently infected with TB, almost 2 billion people globally(1). In 2015, the WHO announced the End TB Strategy with the goal of ending TB by 2035 (i.e. incidence less than 10 / 100,000). The End TB strategy has three main pillars, one of which is to focus on integrated, patient-centered care and prevention(2). The WHO has further prioritized the identification and preventive treatment of people who are at high risk of latent TB infection (LTBI), of whom close household contacts (HHC) are the largest group(1). Following the United Nations High Level Meeting (UNHLM) on TB in 2018, support was declared to increase the health workforce providing TB services as part of a larger commitment to strengthen public health systems(3).

While this focus on improving access to preventive TB services represents an important step towards TB elimination efforts, there is little information in the published literature on how scale-up will shift the workload for healthcare workers (HCW) currently providing TB care. Furthermore, staffing challenges in health facilities already exist; particularly in low- and middle-income countries (LMIC), that face a shortage of well-trained, qualified staff(4). Another key barrier to scale-up of health services globally is ineffective health service delivery, which is often the result of low pay, poor supervision and lack of support for HCW especially in remote or rural areas(5, 6). In order to ensure high-quality, patient-centered care for scale-up of preventive services for LTBI, it is necessary to better understand how expanded services will affect human resource and staffing needs of healthcare facilities and providers.

In order to define the health care resource impact of LTBI scale-up, we used a time and motion study (TAM) to estimate the change in the amount of time HCW spent on LTBI-related patient care

activities, in the context of a trial testing a standardized intervention designed to improve the identification, diagnosis and treatment of household contacts with LTBI. Our study further aimed to determine any changes in the amount of time devoted to clinical care activities for patients with active TB or non-TB related health problems following the intervention to improve LTBI patient care services.

Methods

Parent study

Our study (the "TAM study") was conducted as part of a larger pragmatic, cluster-randomized trial conducted in 24 health facilities in Benin, Canada, Ghana, Indonesia and Vietnam which is described in detail elsewhere(7). The overall objective of the parent trial was to evaluate and strengthen the LTBI cascade of care for household contacts in these countries. There were two main study phases: Evaluation and Implementation. At intervention sites, the Evaluation phase consisted of a cascade review using patient registry data, from the identification and screening for LTBI through to starting and completing therapy, known as the LTBI cascade of care. Based on this evaluation, local health facilities identified the steps in their site-specific LTBI cascade of care with the greatest losses of patients, and potential solutions to address those losses. During the Implementation phase, strengthening activities to improve LTBI services were implemented. Examples of strengthening activities included: in-service trainings for HCW on LTBI testing and treatment, home visits to identify and test more household contacts, flipcharts for HCW education, SMS reminders for LTBI patients, or extended TB clinic hours to facilitate LTBI patient visits. The in-service training was a standard part of the intervention but otherwise the intervention was flexible and tailored to sites based on strengthening activities that each site selected in response to the local barriers identified in the Evaluation phase. The evaluation and strengthening activities done within the parent trial are activities that TB programs elsewhere will likely have to accomplish, for scale-up of LTBI services. Control sites continued to

provide TB services per standard programmatic care and did not receive the Evaluation nor the Implementation given to intervention sites.

Time and motion (TAM) study

The TAM study used a cohort design with purposive sampling of different cadres of HCW providing TB care. Consenting HCW at all participating health facilities who worked at least one full day per week delivering TB care were eligible to participate in the TAM study. At each health facility, we aimed to include a minimum of ten HCW, and at least three HCW in each cadre: 1) doctors; 2) nurses; 3) other HCW involved in TB care (i.e. social workers, health assistants, pharmacists, and community health workers).

On each TAM day, a participating HCW was observed continuously throughout a typical full workday. The TAM consisted of the research assistant noting down minute-by-minute each activity that the HCW performed throughout the day, and categorizing each activity based on a pre-specified list. TAMs were scheduled in advance with each HCW for a workday in which the HCW did not have any planned or likely changes in their normal patient care activities or clinical schedule (such as leaving early to pick up a child or attend a personal appointment), and this was confirmed at the start of the TAM day.

Measurement instruments

The work tasks performed by HCWs in the health facility were categorized into three main types of activities: 1) Direct patient care (i.e. any face-to-face encounter or phone call with a patient); 2) Other clinical activities (i.e. charting, dictations, reviewing laboratory results or radiographs); and 3) Training or administrative tasks (i.e. supervising trainees, meetings, or emails). Time spent on breaks (i.e. restroom, meals or personal phone calls) was recorded during the TAMs but was removed from analyses. Time spent on direct patient care was sub-categorized based on how it related to patients with one of three conditions: 1) LTBI; 2) active or suspected TB; and 3) non-TB (i.e. patients with any other medical condition).

Data collection

Data collection was conducted between January 2017 and December 2018. To ensure standardized measurements, all research staff performing the TAMs received initial, and refresher training from one investigator (HA) on how to observe and record HCW time using standard data collection forms and properly classify and code each observation. All data was recorded on paper data collection sheets and then, de-identified data was transferred to Excel spreadsheets with pre-specified drop-down menus. Verbal consent was obtained from all HCW to permit research staff to observe their daily work activities. Research staff conducting the TAMs did not enter patient rooms during encounters with observed workers.

Breakdown of time spent by personnel

Time spent on each of the three categories of activities (direct patient care, other clinical activity, and training/administrative tasks) was calculated as a proportion of total time worked on the day of observation (TAM day) for each participating HCW. We also calculated the time on care for patients with different health problems categorized as: active TB, LTBI, or non-TB, as a proportion of total time on direct patient care. The time spent on other clinical activities was apportioned to the three types of patients based on the proportion of direct patient care time, as calculated above. Total patient care time for the three categories of types of patients was calculated as observed time on direct patient care plus the apportioned time on other clinical activities. Finally, the total time for each type of patient (i.e. active TB, LTBI, and non-TB) was divided by total patient care time (i.e. direct patient care plus other clinical activity) to calculate the proportion of total patient care time by each type of patient. Formulas for the calculations are shown below:

Equation 1: Proportion of direct patient care on LTBI = Time on LTBI / total time on direct patient care (Active TB + LTBI + Non-TB)

Equation 2: Total LTBI patient care time = Total hours on LTBI + [(Proportion of time on LTBI (equation 1 above) x (time on other clinical activities)]

Equation 3: Proportion of total LTBI patient care time = Total LTBI patient care time (equation 2) / (total time on direct patient care + total time on other clinical activities (Active TB+LTBI+Non-TB))

Analyses

Descriptive statistics: Characteristics of all HCWs who participated in TAMs in the Evaluation or Implementation phase were compared by study phase. Boxplots were used to describe changes between Evaluation and Implementation phases in the proportion of HCWs' time spent on the three main categories of work activities, as well as the categories of patient care. These were shown separately for intervention and control sites. The mean and median number of hours worked, stratified by intervention and control sites, was estimated for the following categories: 1) Total time worked during the TAM day; and time spent on: 2) Direct patient care; 3) Other clinical activities; and 4) Training/administrative tasks.

Statistical analysis: A linear mixed model (LMM), by site and study phase, was fit for all categories of HCW time allocation including: 1) Total time worked; 2) Direct patient care; 3) Other clinical activities; 4) Training/Administrative tasks; 5) LTBI patient care; 6) Active TB patient care; and 7) non-TB patient care. For each model, the dependent variable was the number of hours worked in the given category, and the model included terms for phase, intervention and their interaction. A random intercept for site was included to account for correlation between health care workers in the same facility, and a random intercept for health care worker was included to account for correlation between observations on the same worker.

LMMs were also fit for each type of patient (i.e. active TB, LTBI, and non-TB) for intervention and control sites by study phase for proportion of total patient care time (i.e. direct patient care and other clinical activities). As above, for each model, the dependent variable was the proportion of hours worked in the given category, and the model included terms for phase, intervention and their

interaction. All models included a random intercept for site to account for correlation between health care workers in the same facility, and a random intercept for health care worker was included to account for correlation between the observations of the same worker. From these models, the difference in proportion of time before vs. after the intervention was estimated for control and intervention arms separately. The effect of the intervention was estimated using a model of the difference in the changes in the proportion of HCW time between the intervention and control groups.

Sensitivity analyses

To detect the role of subgroup characteristics, sensitivity analyses were done adjusting for the following covariates 1) sex, 2) TB-specific job position, 3) HCW cadre (i.e. doctor, nurse, other HCW), 4) country, 5) type of setting (Canada versus LMIC). Interactions, defined *a priori,* were considered between type of setting and HCW sex, cadre and TB-specific job. Data were analyzed using SAS version 9.4 (SAS Institute, Cary, USA).

Additional sensitivity analyses were performed for the subset of HCWs who participated in TAMs in both the Evaluation and Implementation phases (i.e. within-subject analysis) In this analysis, we calculated the change in proportion of time for each HCW, then calculated the mean difference across all HCW. Linear mixed models for the change in proportion of total patient care time (by type of patient) were run by site and study phase, then the differences between intervention and control arms were calculated in the same manner as for the full dataset.

Ethics

The Ethics Review Board of the Research Institute of the McGill University Health Center, and the Research ethics boards at all participating sites approved this study.

Results

In total, 140 and 143 HCW participated in the TAMs in the Evaluation and Implementation phases, respectively (main analysis). HCW who participated in the Evaluation phase were largely similar to those who participated in Implementation phase (table 6.1). Of these, 106 HCW completed TAMs in both study phases and were included in the sensitivity analyses (figure 6.1, table 6.S1). There were more doctors and other HCW, who had TAMs in both study phases compared to those who only participated in TAMs in one phase (table 6.S1). Indonesia had significantly more HCWs in TAMs during one study phase, compared to HCW who had TAMs in both phases (table 6.S1).

Overall, HCW worked approximately the same number of total hours per day in the Evaluation and Implementation phases and there was not a significant difference in the change in total hours worked between control and intervention sites (table 6.2). HCW time spent on direct patient care decreased from the Evaluation to Implementation phase, but there was no significant difference in this change between control and intervention sites (table 6.2, figure 6.2). Time on training and administrative tasks increased in both control and intervention arms and there was a statistically significant difference in this change in time, with control sites increasing training/administrative time by over 30 minutes more than intervention sites (table 6.2, figure 6.2).

At intervention sites, there was a significant increase of 9% (95% CI: 3%, 15%) in the proportion of total patient care time (see ***breakdown of personnel time*** above) spent on LTBI services, and a significant decrease of 11% (95% CI: -21%, -1%) in the proportion of HCW patient care time spent on active TB services (table 6.3). The difference in change from Evaluation to Implementation phases between control and intervention sites for LTBI-related activities was 11% (95% CI: 3%, 19%), and for active TB there was a decrease of 12% (95% CI: -26%, 1%), which was not statistically significant (table 6.3, figure 6.2). As seen in table 6.3 and figure 6.2, the proportion of total patient care time spent on

patients with other (non-TB) health problems did not change significantly. Sensitivity analyses for HCW with TAMs in both Evaluation and Implementation phases showed similar results (table 6.S3) and did not show any statistically significant differences by subgroup.

Discussion

Results from our TAM study demonstrated that an intervention to improve LTBI services resulted in an increase in the proportion of HCW time, corresponding to approximately one additional hour per day spent on providing LTBI-related patient care. This increase in HCW time may have contributed to improvements in LTBI services seen in participating health facilities in the parent trial (results not yet published). The total hours worked, and the proportion of total time spent on direct patient care activities did not change between the Evaluation and Implementation phases. Since additional staff were not hired to perform these LTBI related tasks, the additional time for the LTBI-related patient care activities was associated with a reduction in time spent on active TB patient care, an important unintended and potentially negative impact of the intervention.

Limitations

TAMs are designed to capture repetitive work tasks(8) but HCW often have substantial day-to-day variability in the work tasks they perform. Since TAMs require an external observer for an entire workday, they are costly to perform so it was not feasible for this study to include TAMs on each HCW more than once in the Evaluation and Implementation phases of the parent trial. Hence, we did not capture the potential day-to-day variability in the hours and type of work and may have missed time spent on LTBI or active TB on other workdays. However, the large number of participating HCW in our sample should have reduced the likelihood of a systematic bias in any particular direction. Although we pre-selected the days in which HCW were most likely to perform TB-related work tasks, the amount of HCW time spent on active TB or LTBI patient care was completely dependent on work tasks required on the specific TAM day. Results showed a significant increase in HCWs time on training and

administrative tasks at control sites, primarily for meetings, clerical work or end of year reporting. This finding highlights the limitations of the TAM methodology - that it can be difficult to select a day for observation that is truly typical of HCW time allocation over the many months' duration of this study. Our results showed a decrease in time on active TB, but this decrease in HCW time from TAM data could not be linked to active TB outcomes directly. However, the parent trial results did not show a drop in the number of active TB cases across all participating sites (data not shown) which suggests that the decrease in HCW time on active TB patient care activities is due to changes in HCW time allocation to prioritize LTBI patient care resulting from the focus on improving LTBI services at intervention sites.

The Hawthorne effect may have influenced results, since HCW were directly observed and thus may have taken fewer breaks or spent more time on each patient encounter. In order to reduce any such potential effects, HCW were informed that their supervisors would not have access to the TAM data and the observations would have no possible impact on their work performance evaluations to alleviate concerns. As well, for all HCW, the break time was removed from analysis. Any effect of spending more time per patient encounter should have been non-differential, as it would be expected to affect encounters with patients with all types of health problems, not just LTBI-related patient encounters.

Strengths

A key strength of our study was that we recruited a large number of HCW, in total 177 participants in Canada and LMIC. In previous continuous TAM studies we identified(9-11), including a systematic review of TAMs evaluating physicians in hospital settings(12), the number of HCW followed ranged from 1 to 35, although a recently published TAM study of HIV clinics in Zambia followed 104 HCW(13). Our study recruited many HCW to participate in multiple TAM measurements; over half of the HCW (60%) had TAMs in both the Evaluation and Implementation phases. Most TAM studies do

not follow HCW prospectively(9-13), thus our study was able to capture average changes in proportion of HCW time following the intervention by collecting TAMs prospectively at two time points.

By conducting TAMs at two time points, Evaluation and Implementation phases, we were able to quantify changes in HCW proportion of time for each type of work activity, and patient health problem. This allowed us to estimate the increase in proportion of HCW time on LTBI service provision, as well as the negative impacts on care for patients with other health problems, as a result of the intervention. Results from the linear mixed models, accounting for clustering at the site level, showed a significant increase in the proportion of total patient care time on LTBI-related patient care, as well as a corresponding decrease in the proportion of total patient care time on active TB patient care. Lastly, the findings of the primary analyses that included all HCW were consistent with the sensitivity analyses conducted in those HCW with repeated TAM measurements (i.e. within-subject analysis).

Implications

Scale-up of LTBI services added almost an hour of LTBI-related work tasks each day to the HCW observed in our study on TAM days. The WHO target to expand LTBI services globally will have an impact on the workload of HCW providing TB care. Our results suggest that staffing increases will be needed in order to provide these LTBI services, which is likely to have a dramatic impact on health facility staffing in LMIC. The estimated needs could be based on the numbers of active TB patients and household contacts who will require screening and potentially treatment.

Multiple systematic reviews have shown that task-shifting (i.e. substituting nurses or other cadres of HCW for physicians to perform certain work tasks) can result in comparable or better patient outcomes and can mitigate human resource shortages (4, 14-16). We found that increased HCWs time was required to scale-up LTBI services and that in settings where no personnel were added, this increased

time for LTBI patient care was provided at the cost of reduced time for active TB patient care. In order to address personnel requirements for expanded LTBI services, task-shifting for certain tasks, such as identification of household contacts, may need to be considered as a possible solution by TB programs.

Both the UNHLM's declaration on TB and the WHO's End TB Strategy have called for major expansions to LTBI services in TB programs globally(2, 3). The majority of efforts will need to be directed to identifying, testing and treating the estimated 20 million household contacts of people with active TB(3). Scale-up of LTBI services will require well-staffed TB programmes to conduct all the required work activities. Accurate estimation of the human resource needs to perform this additional workload will be key to TB programmes ability to provide the increased LTBI services.

Conclusion

TB programs globally need to assess the human resources requirements for expanded LTBI services to ensure scale-up does not come at the expense of quality care, particularly for active TB patients. This study contributes estimates of the HCW time allocation and workload needs to provide this patient care.

Table 6.1: Characteristics of HCWs[1] participating in the time and motion study (TAMs): Comparison of all HCWs participating in either Evaluation or Implementation phases

	Evaluation Phase	Implementation Phase
	(N = 140)	(N = 143)
Sex		
Male	45 (32%)	42 (29%)
Female	95 (68%)	101 (71%)
TB specific role		
Yes	87 (62%)	89 (62%)
No	53 (38%)	54 (38%)
HCW category		
Doctor	73 (52%)	70 (49%)
Nurse	56 (40%)	63 (44%)
Other HCW	11 (8%)	10 (7%)
Type of Site		
Intervention	63 (45%)	66 (46%)
Control	77 (55%)	77 (54%)
Country		
Benin	18 (13%)	18 (12%)
Canada	39 (28%)	41 (29%)
Ghana	14 (10%)	13 (9%)
Indonesia	28 (20%)	30 (21%)
Vietnam	41 (29%)	41 (29%)

[1]Data presented for all HCWs who participated in TAMs during that phase; note that 75% of HCW (N=106) participated in TAMs in both the Evaluation and Implementation phases

Table 6.2: Average change in the time (hours) worked on TAM study day for all HCWs participating in TAMs[1] - by type of work activity[2]

	Control Arm		Intervention Arm	
	Evaluation Phase	**Implementation Phase**	**Evaluation Phase**	**Implementation Phase**
Total Time (hours)				
Total HCW time worked on TAM day	5.28 (4.60, 5.96)	4.77 (4.09, 5.44)	5.42 (4.72, 6.12)	5.19 (4.49, 5.89)
Difference between Evaluation and Implementation Phases	-0.51 (-1.00, -0.03)*		-0.23 (-0.77, 0.30)	
Difference in change (hours) *(intervention – control)**	**0.28 (-0.44, 1.01)**			
Direct Patient Care (hours)				
HCW time (hours) on Direct Patient Care	2.91 (2.49, 3.33)	2.09 (1.67, 2.50)	2.76 (2.32, 3.20)	2.27 (1.83, 2.70)
Difference between Evaluation and Implementation Phases	-0.82 (-1.18, -0.46)**		-0.49 (-0.89, -0.09)*	
Difference in change (hours)	**0.33 (-0.21, 0.87)**			
Other Clinical Activities (hours)				
HCW time (hours) on Other Clinical Activities	1.95 (1.46, 2.43)	1.17 (0.69, 1.65)	1.44 (0.94, 1.95)	1.17 (0.67, 1.68)
Difference between Evaluation and Implementation Phases	-0.78 (-1.15, -0.41)**		-0.27 (-0.67, 0.14)	
Difference in change (hours)	**0.51 (-0.04, 1.06)**			
Training/Administrative Tasks (hours)				
HCW time (hours) on Training/Administrative Tasks	0.49 (0.02, 0.95)	1.55 (1.09, 2.02)	1.25 (0.76, 1.73)	1.75 (1.27, 2.23)
Difference between Evaluation and Implementation Phases	1.06 (0.69, 1.44)**		0.50 (0.09, 0.91)*	
Difference in change (hours)	**-0.56 (-1.12, -0.01)***			
Latent Tuberculosis Infection (LTBI) (hours)				
HCW time (hours) on LTBI patient care	0.59 (0.05, 1.14)	0.30 (-0.24, 0.85)	0.64 (0.07, 1.20)	0.80 (0.24, 1.37)
Difference between Evaluation and Implementation Phases	-0.29 (-0.62, 0.04)		0.16 (-0.20, 0.52)	
Difference in change (hours)	**0.45 (-0.03, 0.95)**			
Active TB (hours)				
HCW time (hours) on Active TB patient care	2.16 (1.54, 2.77)	1.36 (0.75, 1.97)	2.10 (1.46, 2.75)	1.54 (0.90, 2.19)
Difference between Evaluation and Implementation Phases	-0.80 (-1.24, -0.35)**		-0.56 (-1.05, -0.08)*	
Difference in change (hours)	**0.24 (-0.42, 0.89)**			
Non-TB (hours)				
HCW time (hours) on Non-TB patient care	2.02 (1.52, 2.52)	1.47 (0.97, 1.97)	1.43 (0.90, 1.96)	1.10 (0.58, 1.63)
Difference between Evaluation and Implementation Phases	-0.55 (-0.94, -0.16)**		-0.33 (-0.75, 0.10)	
Difference in change (hours)	**0.22 (-0.35, 0.80)**			

[1]Data presented for all HCWs who participated in TAMs in either Evaluation or Implementation phase; [2]HCWs time was estimated via LMM that accounted for clustering; *Statistically significant difference at $p<0.05$; **Statistically significant difference at $p<0.01$

Table 6.3: Average change in proportion of total patient care time[1] for all HCW participating in TAMs[2,3] – by type of patient

	Control Arm		Intervention Arm	
	Evaluation Phase	**Implementation Phase**	**Evaluation Phase**	**Implementation Phase**
Latent TB Infection (LTBI)				
Proportion of HCW time on LTBI patient care	0.09 (0.01, 0.18)	0.07 (-0.01, 0.16)	0.08 (-0.01, 0.17)	0.17 (0.08, 0.26)
Difference between Evaluation and Implementation Phases	-0.02 (-0.07, 0.03)		0.09 (0.03, 0.15)**	
Difference in change	**0.11 (0.03, 0.19)****			
Active TB				
Proportion of HCW time on active TB patient care	0.40 (0.27, 0.53)	0.41 (0.29, 0.54)	0.49 (0.37, 0.62)	0.38 (0.26, 0.51)
Difference between Evaluation and Implementation Phases	0.01 (-0.08, 0.10)		-0.11 (-0.21, -0.01)*	
Difference in change	**-0.12 (-0.26, 0.01)**			
Non-TB				
Proportion of HCW time on Non-TB patient care	0.50 (0.36, 0.65)	0.48 (0.34, 0.63)	0.44 (0.29, 0.59)	0.46 (0.31, 0.61)
Difference between Evaluation and Implementation Phases	-0.02 (-0.10, 0.07)		0.02 (-0.07, 0.11)	
Difference in change	**0.04 (-0.08, 0.16)**			

[1]Proportion of total patient care time which includes direct patient care and other clinical activities
[2]Data presented for all HCWs who participated in TAMs in either Evaluation or Implementation phase
[3]HCWs time was estimated via LMM that accounted for clustering;
*Statistically significant difference at $p<0.05$
**Statistically significant difference at $p<0.01$

Figure 6.1: Flow diagram of HCW participating in time and motion study (TAMs)

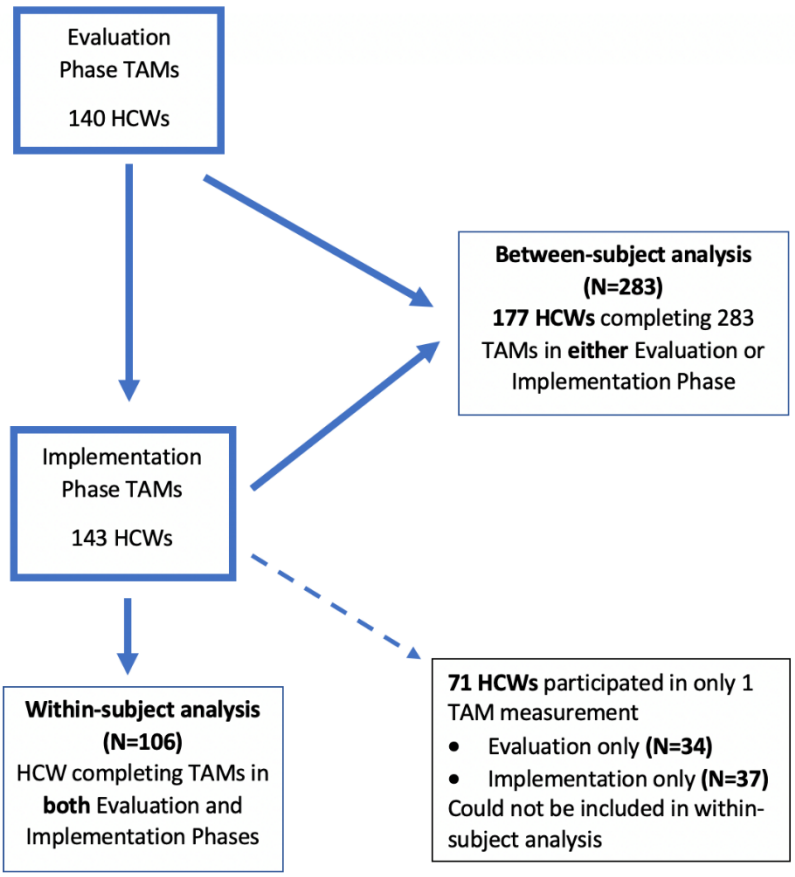


Figure 6.2: Boxplots of Proportion of HCW Time – By Study Phase

Figure 6.2A: Boxplots of Proportion of HCW time by Study Period **– All Intervention Sites**

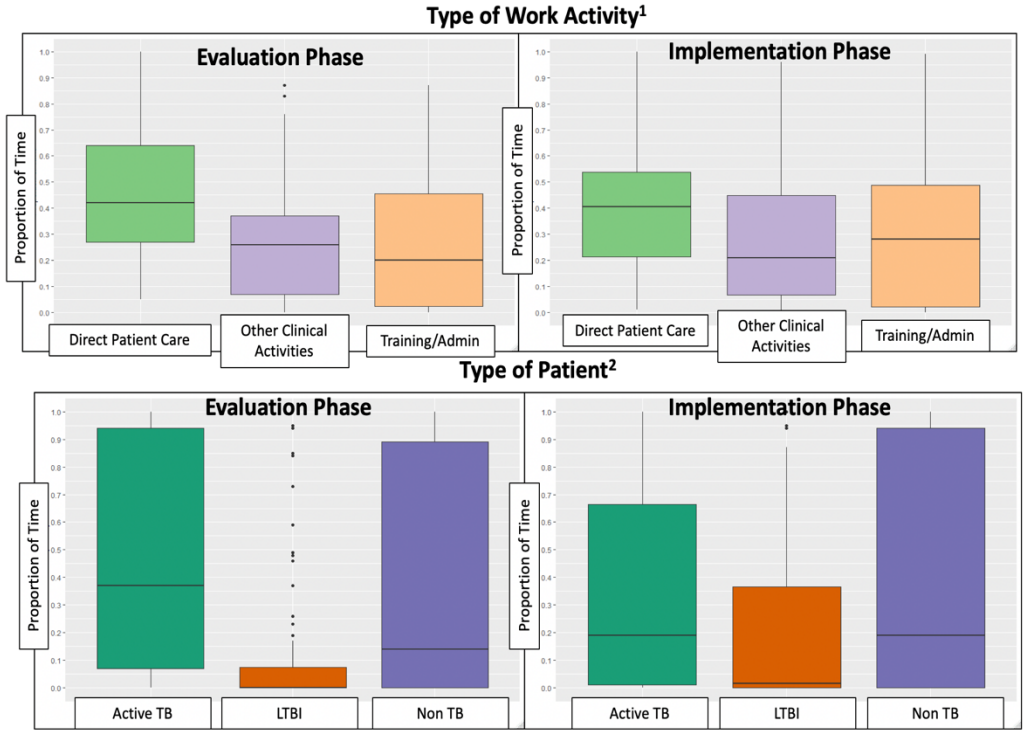
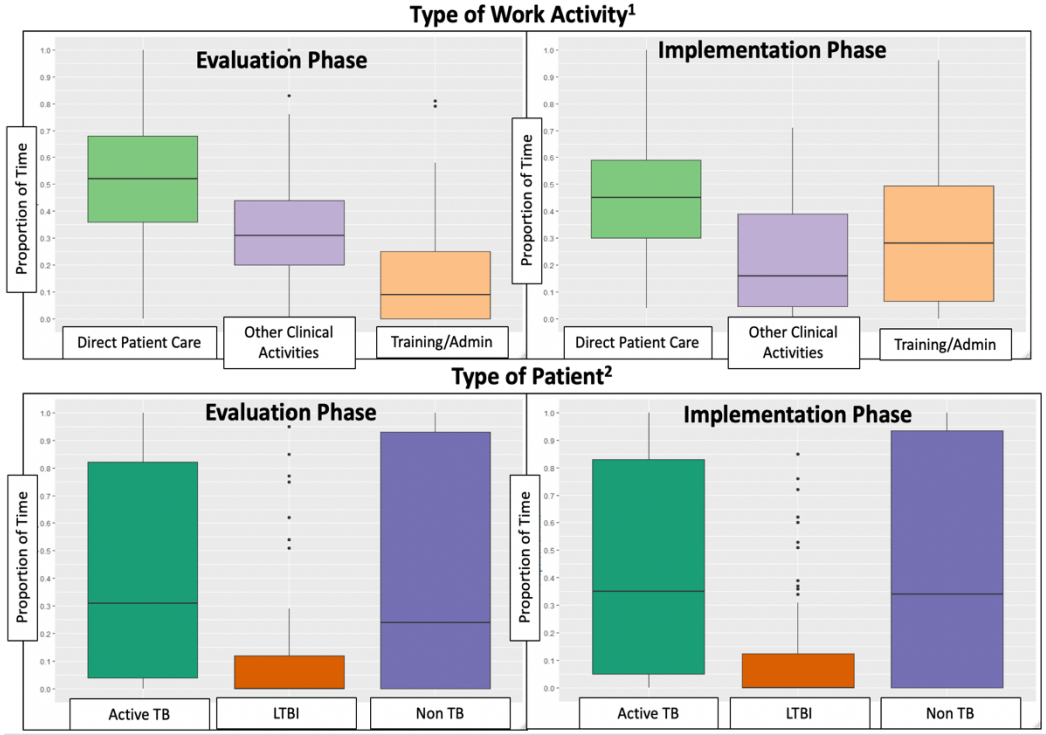


Figure 6.2B: Boxplots of Proportion of HCW time by Study Period **– All Control Sites**



[1]Proportion of total hours worked on TAM day, excluding breaks/pauses
[2]Proportion of time on total patient care time which includes direct patient care and other

Table 6.S1: Descriptive characteristics of HCWs participating in TAMs in both Evaluation and Implementation phases to HCWs with TAMs only in one phase

	Within-subject[1] analysis (BOTH Evaluation and Implementation)	HCW with only 1 TAM (Evaluation OR Implementation)
	(N = 106)	(N=71)
Sex		
Male	36 (34%)	18 (25%)
Female	70 (66%)	53 (75%)
TB specific role		
Yes	66 (62%)	45 (63%)
No	40 (38%)	26 (37%)
HCW category		
Doctor	58 (55%)	30 (42%)
Nurse	39 (37%)	39 (55%)
Other HCW	9 (8%)	2 (3%)
Type of Site		
Intervention	49 (46%)	32 (45%)
Control	57 (54%)	39 (55%)
Country		
Benin	15 (15%)	6 (8%)
Canada	33 (31%)	14 (20%)
Ghana	10 (9%)	7 (10%)
Indonesia	11 (10%)	36 (51%)
Vietnam	37 (35%)	8 (11%)

[1]Within-subject – Data presented for HCWs who participated in TAMs during both Evaluation and Implementation phases

Table 6.S2: Average time (hours) and proportion of total patient care time[1] for HCW participating in TAMs[2] – by type of patient

	Phase 1			Phase 2		
	N	**Mean time in hours (Std. dev.)**	**Mean Proportion of Time on Patient Care[1]**	**N**	**Mean time in hours (Std. dev.)**	**Mean Proportion of Time on Patient Care[1]**
Latent TB Infection (LTBI)						
Intervention	(63)	1.1 (2.4)	0.13	(66)	1.2 (1.8)	0.23
Control	(77)	0.9 (1.8)	0.13	(75)[3]	0.4 (1.1)	0.11
Active TB (ATB)						
Intervention	(63)	2.7 (2.7)	0.47	(66)	1.5 (1.6)	0.36
Control	(77)	2.6 (2.8)	0.43	(75)[3]	1.5 (1.7)	0.44
Non-TB						
Intervention	(63)	2.1 (2.3)	0.40	(66)	1.0 (1.3)	0.41
Control	(77)	2.2 (2.3)	0.44	(75)[3]	1.3 (1.6)	0.45

[1]Proportion of total patient care time which includes direct patient care and other clinical activities
[2]Data presented for all HCWs who participated in TAMs in either Evaluation or Implementation phases
[3]Two HCWs in Vietnam did not contribute data to the Direct Patient Care activities because they only performed Training/Administrative tasks on the TAM day in the Implementation phase

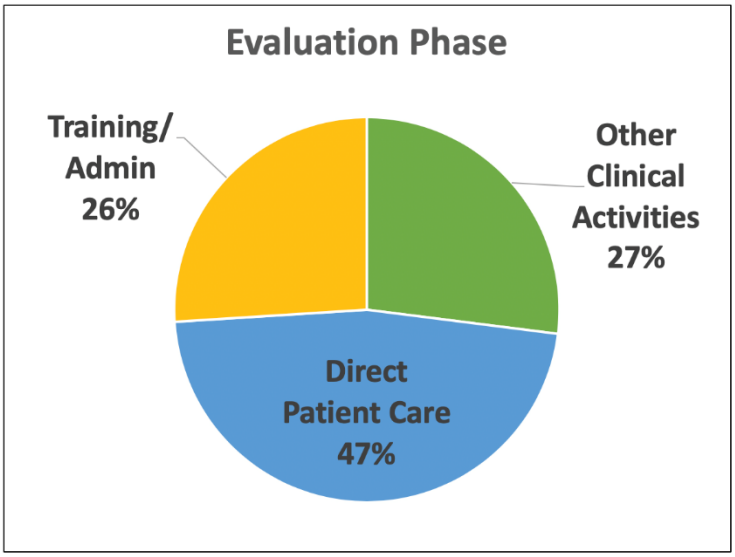
Table 6.S3: Average change in proportion of total patient care time[1] for HCW participating in TAMs in both Evaluation and Implementation phases[2,3] – by type of patient

	Control Arm		Intervention Arm	
	Evaluation Phase	**Implementation Phase**	**Evaluation Phase**	**Implementation Phase**
WITHIN-SUBJECT[2] ANALYSIS				
Latent TB Infection (LTBI)				
Proportion of HCW time on LTBI patient care	0.12 (0.02, 0.23)	0.09 (-0.01, 0.20)	0.11 (0.01, 0.21)	0.21 (0.11, 0.31)
Difference between Evaluation and Implementation Phases	-0.03 (-0.09, 0.03)		0.10 (0.03, 0.16)**	
Difference in change	**0.13 (0.04, 0.22)****			
Active TB				
Proportion of HCW time on active TB patient care	0.42 (0.27, 0.57)	0.44 (0.29, 0.59)	0.55 (0.40, 0.70)	0.43 (0.29, 0.58)
Difference between Evaluation and Implementation Phases	0.02 (-0.08, 0.12)		-0.12 (-0.22, -0.01)*	
Difference in change	**-0.14 (-0.28, 0.01)**			
Non-TB				
Proportion of HCW time on Non-TB patient care	0.52 (0.37, 0.66)	0.49 (0.34, 0.63)	0.42 (0.27, 0.57)	0.42 (0.27, 0.57)
Difference between Evaluation and Implementation Phases	-0.03 (-0.11, 0.05)		0.00 (-0.08, 0.09)	
Difference in change	**0.03 (-0.08, 0.16)**			

[1]Proportion of total patient care time which includes direct patient care and other clinical activities
[2]Within-subject – Data presented for HCWs who participated in TAMs during both Evaluation and Implementation phases
[3]HCWs time was estimated via LMM that accounted for clustering
*Statistically significant difference at $p<0.05$
**Statistically significant difference at $p<0.01$

Figure 6.S1: Change in Proportion of Total HCW Time Worked by Type of Activity

Figure S1A: All Intervention Sites



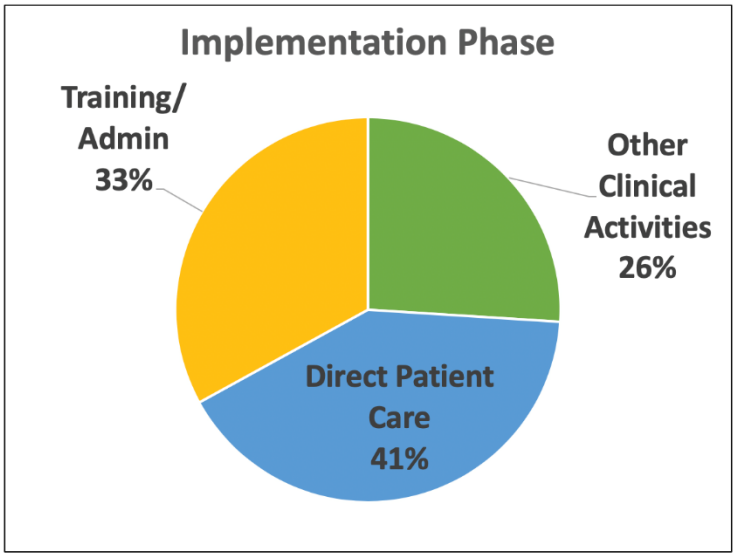
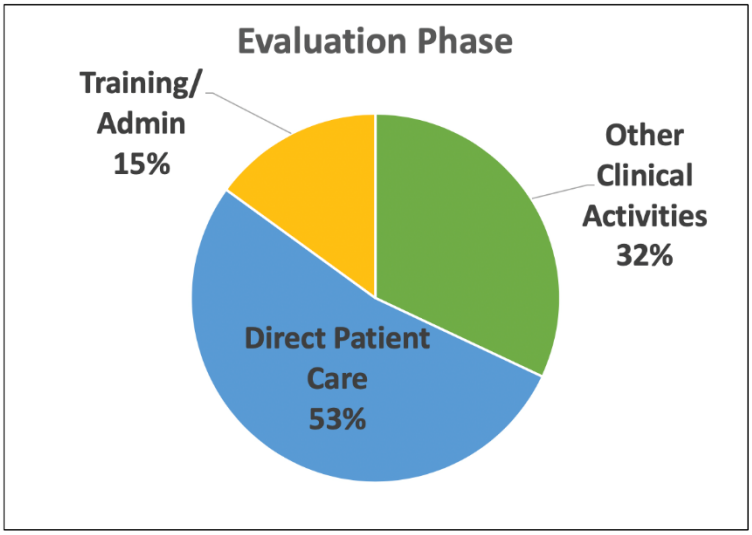


Figure S1B: All Control Sites



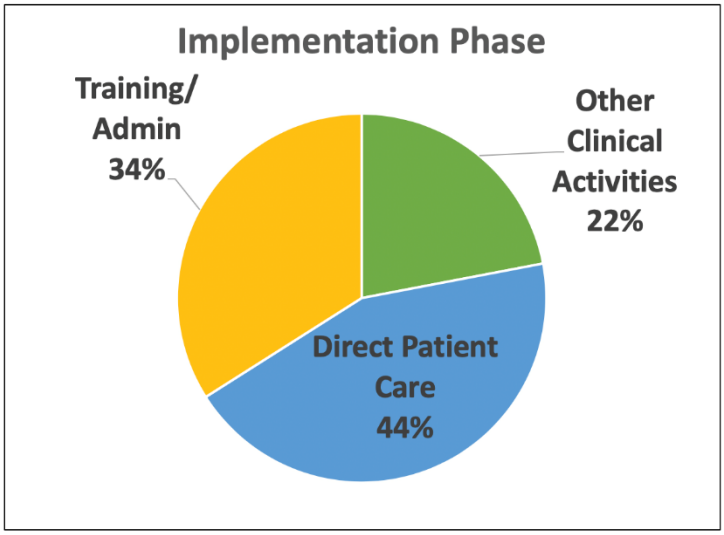


Figure 6.S2: Change in Proportion of HCW Time on Patient Care Activities[1] By Type of Patient

Figure S2A: All Intervention Sites

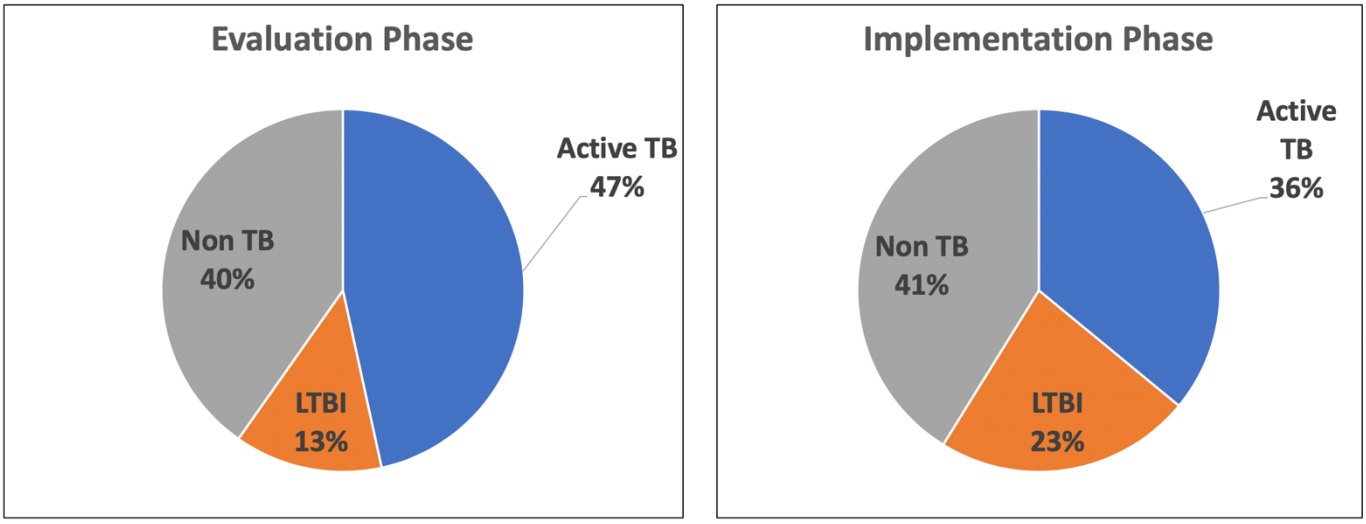
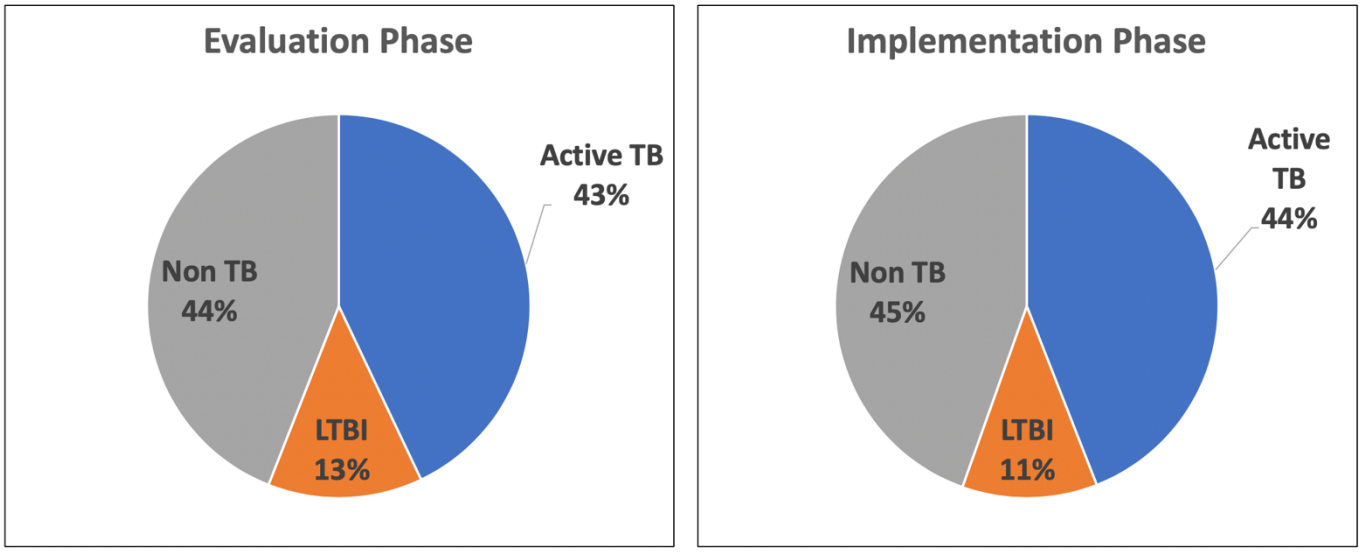


Figure S2B: All Control Sites



[1]Proportion of total patient care time which includes direct patient care and other clinical activities

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Chapter 7 How well do healthcare workers estimate their time spent on tuberculosis patient care activities? A validation study

7.1 *Preface: Manuscript 4*

Healthcare workers (HCWs) in the clinical setting are responsible for a variety of work tasks which often include multi-tasking (i.e. performing patient care and clinical documentation). It can be hard to capture how HCWs distribute their time between the numerous work tasks and job responsibilities. There are multiple measurement methods used to assess HCWs time on work tasks, however the most precise method, known as a time and motion (TAM) study is time-consuming and costly. Self-reporting is another method to assess HCWs time allocation, but there are conflicting findings about the reliability of self-reported data.

The aim of the study presented here was to validate the use of an interviewer-administered time-estimation questionnaire compared to a TAM study of HCW time spent on tuberculosis patient care activities in five countries: Benin, Canada, Ghana, Indonesia and Vietnam.

The following manuscript is entitled "**How well do healthcare workers estimate their time spent on tuberculosis patient care activities? A validation study**". This work is being prepared for submission to *Journal of Epidemiology and Community Health*.

7.2 *Manuscript 4*

How well do healthcare workers estimate their time spent on tuberculosis patient care activities? A validation study

Abstract

Background

Healthcare workers (HCW) in the clinical setting perform numerous and varied tasks throughout each workday. Continuous time and motion studies (TAMs) are considered the reference standard for quantifying workers' time spent on different work activities, but there are conflicting results on the performance of self-reported measures of work time. Our study aimed to validate the use of an interviewer-administered time-estimation questionnaire (TEQ) compared to a TAM study of HCW in five countries: Benin, Canada, Ghana, Indonesia and Vietnam.

Methods

We developed, piloted and tested the TEQ to capture HCWs' time allocation in seven categories of work activities. The TEQ was validated against the reference standard TAMs (same day) using visual agreement, correlation, and equivalence testing. A linear mixed model was fit to estimate how well the TEQ measurements predicted the time recorded on the TAMs, as another method to determine agreement.

Results

A total of 86 HCW participated in the pilot TEQ and 125 HCW in the final TEQ study. The mean difference between the TAM and TEQ was less than 30 minutes for all categories of direct patient care activities. Correlation of the interviewer administered TEQ with the TAM was above the criterion validity threshold of 0.70 in all categories of work activities.

Conclusion

Our findings suggest that the TEQ performed well and achieved the threshold for achieving criterion validity, as compared to the TAM.

Introduction

Healthcare workers (HCW) in the clinical setting are responsible for a variety of work tasks, which often include multi-tasking (i.e. performing both patient care and clinical documentation). It may be difficult for studies to capture how healthcare workers distribute their time between their multiple work tasks and job responsibilities, as well as variation in work tasks over a longer period of time (i.e. multiple days in a week, month or year)(1). Furthermore, this task fragmentation can make it difficult to quantify how workflow changes due to interventions in the clinical setting(1). In many countries, data about the allocation of HCW time is lacking or inadequate, yet it is an important component for understanding staffing needs, improving efficiencies in work and enabling human resource planning and costing of healthcare delivery(2).

There are many measures that have been used to assess HCW time spent on work tasks including: work task sampling, time and motion studies, patient flow analysis, provider interviews and self-reporting(3, 4). Time and motion studies (TAMs) were initially used in the early 20th century to improve efficiency in the manufacturing process and then applied to the healthcare industry(5). TAMs are considered the reference standard for precisely measuring HCW time spent on pre-defined categories of work activities(3, 6). However, continuous TAMs require an external observer to follow a HCW throughout their entire work day, which is labour-intensive, costly and potentially intrusive(7). The advantage of TAMs is the level of detail provided(8). But using TAMs to follow HCW can be challenging due to the unpredictability and task fragmentation of clinical work(5). Furthermore, TAMs are unable to capture the day-to-day variability in work tasks for HCW over longer periods of time since it is costly and impractical to conduct many repeated TAM measurements.

Self-reporting is a simple, low-cost method used to quantify HCW time allocation using tools such as questionnaires or surveys(7). Self-reported measures of HCW time have three key advantages over TAMs: 1) cheaper since no external observer is required; 2) decreased likelihood of a Hawthorne effect (i.e. HCW changing behavior due to observation); and 3) better capture within- and between-HCW variability in work tasks by measuring time

allotments over multiple days for numerous workers. Some studies have shown self-reported measures to provide reliable estimates of nurses' allocation of time when using broad categories of job activities (7). Yet there are conflicting findings about the reliability of HCW self-reported data(4, 7, 9). The main disadvantage of this method is that HCW may mis-report their time on activities, due to self-perceived versus actual job performance, or in a socially desirable manner (i.e. HCW may answer the way they believe is valued by the study or investigator)(7).

The purpose of this study was to assess the criterion validity of a time-estimation questionnaire (TEQ) compared to a time and motion study (TAM), which will be considered the reference standard, for measuring time spent on three pre-specified categories of clinical work: 1) Total hours worked; 2) hours spent on active TB patient care; and 3) hours spent on latent tuberculosis infection (LTBI) patient care. This study also aimed to assess the day-to-day variability in HCW time devoted to the same three pre-specified categories of clinical work, as measured with repeated TEQs over two full work weeks (i.e. 10 workdays).

Methods:

Parent study

This validation study of the TEQ was undertaken as part of a larger pragmatic, cluster-randomized controlled trial (RCT) conducted in 24 health facilities in Benin, Canada, Ghana, Indonesia and Vietnam. The main objective of the parent trial was to evaluate and strengthen the LTBI cascade of care for household contacts (HHC) in these countries; the objectives, design and methods of this trial are described elsewhere(10). The TAM study used a cohort design with purposive sampling of different cadres of HCW who worked at least one full day per week delivering TB care at all participating health facilities. Consenting HCW who participated in the TAM study were recruited to participate in the TEQ validation study.

Protocol development and piloting

An interviewer administered TEQ instrument was developed and tested in collaboration with all health facilities participating in the parent trial, to assess HCW time allocation for each workday throughout an entire work week. The results of the pilot (see Supplemental files) were used to finalize the methodology presented below.

The initial pilot TEQ study was conducted between January - March 2018 in all 24 participating health facilities on the same day as the TAM. The pilot version of the TEQ questionnaire was administered by the research assistant conducting the TAMs at the end of the day. Data from the pilot study were analyzed to assess agreement and correlation of the two measurement tools. Following these analyses, the TEQ questions were revised (see original and final TEQ in Supplemental file) to be more closely aligned with the TAM categories for clarity (see TEQ section below).

Data collection methods

Time and motion (TAM) study

In this TAM study, a research assistant followed each participating HCW continuously throughout a full workday. The research assistant recorded the time, in minutes, the HCW spent on all work activities throughout the entire day and noted the corresponding category of work activity for each task. HCW time was first categorized into three main types of activities: 1) Direct patient care (i.e. any face-to-face encounter or phone call with a patient); 2) Other clinical activities (i.e. charting, dictations, reviewing laboratory results or x-rays); and 3) Training or administrative tasks (i.e. supervising trainees, meetings or emails). Time spent on breaks (i.e. restroom, meals or personal phone calls) was recorded on the TAMs but removed from analyses. Direct patient care was then sub-categorized according to the patients' medical condition: 1) LTBI; 2) active or suspected TB; and 3) non-TB, meaning any other medical condition. In both the pilot and main TEQ study, the TAM and TEQ measurements were performed on the same day.

Time-estimation questionnaire (TEQ)

At the end of the TAM day, research assistants asked each HCW to estimate the number of hours they worked that day in the four main categories corresponding to the TAMs: 1) Total hours worked; 2) Direct Patient Care; 3) Other Clinical Activities; 4) Training/Administrative tasks. It was explained to HCWs that categories #2-4 should equal the total number of hours worked that day (category #1). Then, HCW were asked to estimate the number of hours they worked for three categories of patients: 1) Active TB; 2) LTBI; and 3) Non-TB. The time in those three categories of patient care should have added up to the time reported for direct patient care (main category #2, above). The final TEQ form was in a simple table format that included a box for each of the seven categories and a column for each day of one full work week. After reviewing the TEQ form in-person at the end of the TAM day to ensure each HCW clearly understood the categories of work tasks, the research assistant called the HCW to complete the TEQ form at the end of every day for two full weeks (i.e. 10 consecutive days of work).

Data collection

Data collection was conducted between January 2017 and March 2019. To ensure standardized measurements, all research staff performing the TAMs and TEQs received training from one investigator (HA) on how to observe and record HCW time using standard data collection forms (i.e. TAM and TEQ forms) and properly classify and code each observation.

Analyses - *Visual methods to assess agreement*

Scatterplots and Bland-Altman plots were used to visually assess agreement of the TEQ compared to the reference standard TAMs.

Testing correlation

The intra-class correlation coefficient (ICC) was used to measure the degree of correlation and agreement between the TAM and TEQ measurements (11-13). The McGraw and Wong convention, with a two-way, mixed effects for absolute-agreement with a single-measurement was used to calculate the ICC for the TAM and TEQ measurements

(11). The minimum level of correlation was set *a priori* at 0.70, based on the threshold used in the literature (14), in order for the TEQ to show acceptable validity. Correlation is interpreted as good for values between 0.75-0.90 and excellent for values above 0.90(11).

Equivalence testing

To assess equivalence in our study, the difference in the HCW time (hours) measured from the TAMs was compared to the time recorded on the TEQs in the three main activities of interest including: 1) Total hours worked; 2) active TB patient care; and 3) LTBI patient care. Since there was no previously established level of clinical equivalence in the published literature, we surveyed the principal investigators in the participating health facilities to determine how much difference in time would still be considered equivalent for the two methods. We provided them with a set of options for clinical equivalence of time in 15-minute increments for each of the three categories (see above) of activities separately. The responses from investigators were averaged for each category to set *a priori* the pre-defined limits for testing equivalence. Using this method, the limits of clinical equivalence were set at the following: 1) Total hours worked +/- 60 minutes (i.e. 1 hour); 2) Active TB +/- 25 minutes; and 3) LTBI +/- 20 minutes. If the estimate and its 95% confidence interval for the difference between TAM and TEQ was entirely within these limits, we concluded that the TAM and TEQ were statistically equivalent (15).

Linear mixed models (LMMs)

Linear mixed models (LMMs) were fit with HCW time from the TEQs as the predictor (independent variable) of time measured from the TAMs as the response (dependent variable). Random intercepts were included at the level of the site, to account for correlation between workers at the same site. Additional models were run to determine the effect of covariates including: 1) Sex; 2) HCW cadre (i.e. doctor vs. nurse/other HCW); and 3) resource level of the setting (i.e. Canada vs. low- and middle-income countries (LMIC)). Interaction terms for the TEQ with sex, HCW cadre, and setting were set *a priori* and added to each LMM to assess the potential of effect modification due to each covariate(16).

Day-to-day variability in work activities

In order to assess the day-to-day variability of HCW time spent on each category of work activity over the 10 days of consecutive TEQ measurements, we first used trajectory plots to visually assess the variability in hours worked for each category. We reported descriptive statistics (i.e. mean, range, and IQR) on the three main categories selected *a priori* due to programmatic interests (i.e. total hours worked, active TB and LTBI patient care). Then LMMs were fit for each of the three categories of time listed above as the dependent variable, and included an intercept and random intercept, respectively, for site and HCW to account for the clustering at site level and between observations on the same HCW (17). To quantify between- and within-subject variability (11) we estimated ICCs from these LMMs. The ICC was used to determine if the changes in work tasks were due to differences between individual HCWs or due to the variability in daily work tasks for each HCW.

Ethics

The Ethics Review Board of the Research Institute of the McGill University Health Centre, and the Research ethics boards at all participating sites approved this study.

Results:

During the pilot phase, 86 HCW participated in both the TAMs and TEQs, while 16 HCW participated in the TAMs but not the TEQs (table 7.S1). For the validation study, 125 HCW participated in the final TAMs and TEQs while seven HCW participated in the TAMs but did not participate in the TEQs (table 7.1). There were more female (70%) than male HCW, and the majority of HCW had a TB-specific work post (62%)(table 7.1).

Pilot study:

Results from the TEQ pilot phase demonstrated weak, non-linear agreement between the TAM and TEQ in all categories in the scatterplots (figures 7.S1A-C). The Bland-Altman plots from the pilot phase also showed poor agreement, bias (indicated by the V-shape of data points) and a large mean difference between the two measurements for total hours worked of -1.5 hours (95% CI: -6.8, 3.9) (figures 7.S2A-C). HCWs time on the TAMs

was on average -2.1 (95% CI: -2.8, -1.5) less than the pilot TEQ measurements (table 7.S2). Correlation of the TEQ with the TAM failed to meet the criterion validity threshold in the pilot phase, with correlation below 0.60 in all categories (table 7.S2).

Validation study:

The TAM and TEQ measurements indicated strong linear agreement in the scatterplots (figures 7.1A-C), and 7.2). The Bland Altman plot showed data points near the axis and close to zero, indicating no difference between the two measurements (figures 7.2A-C). TAM and TEQ measurements were improved when compared to the pilot TEQ.

Overall, HCW over-reported their time on the TEQs in all categories of work activities except other clinical activities and training or administrative tasks (table 7.2). The mean difference in reported time on the TEQ compared to the TAM, using a linear mixed model (LMM) to account for clustering, was less than 30 minutes for all categories except time on direct patient care and total hours worked, with a mean difference of -1.0 hours (95% CI: -1.3, -0.6), and -0.7 hours (42 minutes) (95% CI: -1.0, -0.4), respectively (table 7.2). These results were also improved compared to the pilot TEQ measurements.

Correlation of the interviewer administered TEQ with the TAM was above the criterion validity threshold of 0.70 in all categories of work activities (table 7.2). The percent of bias introduced by using the TEQ compared to the TAMs (reference standard) ranged from -14% to 50% for training/administrative tasks and active TB patient care, respectively (table 7.2). When stratified by country income setting (i.e. Canada vs. LMIC) correlation was higher in LMIC than Canadian sites for all categories of direct patient care activities (i.e. active TB, LTBI, non-TB)(table 7.3).

For each additional hour of time on the TEQ, the TAM estimate increased by 0.87 (95% CI: 0.8, 0.9) and 0.82 (95% CI: 0.7, 0.9) for total time and time on training and administrative tasks, respectively (table 7.4). For direct patient care, the proportion of HCW time on LTBI predicted by the TEQ was 0.55 hours (95% CI: 0.5, 0.6). Interactions

for use of the TEQ with covariates such as: sex, LMIC, HCW cadre and TB-specific job post were not statistically significant.

Relative to the TAM, the TEQ was : 1) statistically significantly larger than the TAM but within the predetermined limits of equivalence for total hours worked; 2) equivalent to the TAM for LTBI activities; and 3) statistically significantly larger than the TAM and the difference was not within the limits of equivalence for active TB activities (figures 7.3A-3C).

Variability: Across the 10 days of repeated TEQ measurements, there was significant variability shown at the site and individual HCW levels for all categories of work activities (table 7.5) as indicated by ICCs ranging from 0.07 (active TB patient care) to 0.32 (training and administrative tasks) (figure 7.S3).

Discussion:

The correlation of the TEQ responses with the TAM measurements across all seven categories of HCW activities achieved the threshold level to demonstrate criterion validity. Further, our results demonstrated that the process of piloting and refining the TEQs improved the validity of the TEQ as a measurement tool. Using numerous measures of agreement to assess validity (i.e. Bland-Altman plots, correlation and LMM), with similar results for each method provided strong evidence of the criterion validity of the TEQ. However, our results also demonstrated that there was bias introduced by using the TEQs, particularly for time on direct patient care activities, although this was the lowest in LTBI patient care. The descriptive analyses of the repeated TEQ measurements across 10 days of work documented substation within-subject variability due to the highly varied nature of clinical work.

Limitations

One disadvantage for our TEQ validation study was that there was not an already established set of standardized work tasks to compare the TAMs to the TEQ to assess performance of the TEQ for specific TB-related patient care. In other studies, such as those looking at job satisfaction levels, there are pre-tested and defined indices that can be used for any study to assess performance of a new tool such as the TEQ(19). Despite this limitation, the

TEQ performed well in the participating health facilities. However, the reporting categories chosen for the TAM and TEQ were specific to our study, they may not be relevant or generalizable to other clinical settings.

Since HCWs were being observed for the TAM components of the study, the Hawthorne effect cannot be ruled out as potentially impacting study results. HCWs may have changed their behavior to take fewer breaks during the TAM days or to spend more time on each patient encounter. But the break time was removed from analyses and there is no reason for HCWs would have spent more time with one specific type of patient, so increased patient time would be for all patients but in a non-differential manner.

The TEQ was an interviewer administered questionnaire that required HCW to recall the time spent on daily activities. As such, there is potential for recall bias. HCW who participated in the TEQs had already been part of the TAM study and therefore might have been more motivated to complete the TEQ because it was a less intrusive method for measuring time than the TAMs. However, HCW participation should not have had an impact on recall of their daily activities. And HCW were required to perform the TEQ daily to minimize recall bias that might arise after a longer recall period, such as waiting until the end of the week to report all five preceding days. In a routine clinical setting, however, it may be more challenging to ensure daily completion.

Another limitation of our study was that the bounds to test for clinical equivalence were not based on published clinical reference standards of a significant change in HCW time allocation. The limits of equivalence for each category were set by investigators, but they were established *a priori* and the investigators were not involved in the TAM or TEQ data collection, thus their responses should not have biased the results. However, if the investigators had set wider bounds (i.e. long acceptable differences in time) then the equivalence may have been shown for all categories of work activity, but if narrower bounds had been set, then there may not have been equivalence for any of the categories. This highlights the difficulty of equivalence testing in the absence of a true standard of acceptable difference between two measurement tools.

Strengths

A strength of this study was that a large number of HCW participated in both the TAM and TEQ measurements in the pilot and final phases, 86 and 125, respectively. We were able to capture a wide range of time allocations for HCW in both high-income (i.e. Canada) and LMIC settings among all HCW cadres (i.e. doctors, nurses, and other HCW). There are very few studies that have compared TAMs to a self-reported measure, one of which focused almost exclusively on nurses' time allocations(20). There have been calls for additional research(4) to validate approaches of self-reported data on work patterns for HCW due to discordant results from other studies, thus our study adds important research to the body of evidence for the validity of questionnaires and other self-reported measures of HCW time allocation(4). Including over 100 HCW in the final comparison of the TAM and TEQ was another key strength since most studies comparing two measurement techniques for HCW have fewer participants, typically no more than 30, due to cost and feasibility issues(21-23).

Another strength of our study was the comparison of the health measurement tool we developed (i.e. TEQ) to the reference standard (i.e. TAM) on the same day, allowing for direct comparison of the two measurement tools. It has been suggested that using multiple measurement approaches to assess validity is important in the development of new health measurement tools(14). We used multiple measures of agreement, which all showed consistent results, further supporting the finding that the criterion validity threshold was met.

Repeating TEQs over 10 consecutive days of clinical work was an additional strength of this study. The repeated TEQs enabled us to quantify the variability of HCW time allocation over two weeks, rather than just a single day.

Implications

Although TAMs are considered the reference standard for precisely measuring time on pre-specified categories of work activities, the human resource requirements (i.e. external observer) and cost implications make them challenging to implement in a programmatic setting. Our study aimed to demonstrate that a short, interviewer-

administered questionnaire (TEQ) performed at the end of the day among participating HCWs could perform sufficiently well to be considered as a cost-saving substitute for TAM measurements. Our results suggest that the TEQ administered at the end of the workday correlated well with the TAM for all categories of work activities and could be used in other clinical settings as a method of capturing HCW time allocation.

The simplicity and low-cost of the TEQ tool suggest that in routine clinical settings where a better understanding of HCW time allocation will support human resource planning and staffing, the TEQ could be implemented if there is a research assistant to follow-up with HCW and ensure the TEQs are completed daily. The TEQ could be a useful tool to repeatedly capture HCW time allocation over longer intervals, such as once weekly for three months. Yet more research is needed to determine how well the TEQ captures the variability of HCW time allocation over many months or even a full year, to determine if this could be used to estimate HCW staffing needs.

Conclusion

Quantification of HCW time allocation is challenging due to the variation in work activities performed each day, and from day-to-day. The use of a simple, low-cost TEQ could enable health facilities to quantify the overall, and specific work activities of HCW. Providing healthcare systems with detailed information on the time allocation of HCW job responsibilities will enable better human resource management and planning for staffing requirements.

Table 7.1: Characteristics for 132 HCWs who participated in the TAMs and time-estimation questionnaires (TEQs)

	Time-estimation questionnaire (TEQ)	
	YES	No
Sex	**(N = 125)**	**(N=7)**
Male	38 (30%)	1 (14%)
Female	87 (70%)	6 (86%)
TB specific role		
Yes	78 (62%)	1 (14%)
No	47 (38%)	6 (86%)
HCW category		
Doctor	70 (56%)	2 (29%)
Nurse	47 (38%)	5 (71%)
Other HCW	8 (6%)	0 (-)
Country		
Benin	6 (5%)	4 (57%)
Canada	38 (30%)	2 (29%)
Ghana	11 (9%)	0 (-)
Indonesia	30 (24%)	0 (-)
Vietnam[1]	40 (32%)	1 (14%)

Table 7.2: Comparison of time* (hours) from TAM vs. TEQ for 125 HCWs – Same Day

	TAM: Mean time, in hours, observed per HCW (range)	TEQ: Mean time, in hours, reported per HCW (range)	Mean Difference in time (hours)[1] TAM- TEQ (95% CI)	Percent Bias (Δ TAM-TEQ) TAM	Correlation coefficient[2,3]
Total Time Worked[4]	5.8 (1-11)	6.3 (3-11)	-0.7 (-1.0, -0.4)	12.0%	0.82
Time on Direct Patient Care	2.2 (0-7)	3.0 (0-9)	-1.0 (-1.3, -0.6)	45.4%	0.74
Time on Other Clinical Activity	1.4 (0-7)	1.4 (0-7)	0.1 (-0.2, 0.2)	-7.1%	0.80
Time on Training/ Administrative Tasks	2.1 (0-7)	2.0 (0-7)	0.3 (0.1, 0.6)	-14.3%	0.92
Direct Patient Care Activities[5]					
Active TB	0.8 (0-5)	1.1 (0-5)	-0.4 (-0.6, -0.1)	50.0%	0.75
LTBI	0.6 (0-4)	0.7 (0-6)	-0.1(-0.3, 0.0)	16.7%	0.81
Non-TB	0.8 (0-4)	1.1 (0-5)	-0.5 (-0.7, -0.2)	62.5%	0.84

[1]Mean difference in time (and 95% CIs) in each category from a linear mixed model which accounts for clustering at the health facility level

[2]Correlation was adjusted for the partial variance due to clustering at the health facility (site) level but did not change the coefficients.

[3]Note: All correlation coefficients were statistically significant at p-value <0.01

[4]Total time worked = Direct Patient Care + Other Clinical Activity + Training/Administrative tasks

[5]Direct Patient Care = time spent in direct contact with patients with Active TB + LTBI + Non-TB

*Note: Total time worked recorded on the TAM day included time on breaks but that time was removed from the analyses; HCWs were told not to include their break time for the interviewer-administered TEQ

Table 7.3: Comparison of time on direct patient care by reason for care and setting for 125 HCWs participating in TAMs and final TEQ

	N	TAM: Mean time, in hours, observed per HCW (range)	TEQ: Mean time, in hours, reported per HCW (range)	Mean Difference in time (hours) TAM- TEQ (95% CI)	Correlation coefficient*
Active TB					
LMIC	87	0.8 (0-5)	1.0 (0-6)	-0.2 (-0.4, -0.1)	0.78
Canada	38	1.0 (0-3)	1.3 (0-5)	-0.3 (-0.5, 0.0)	0.58
LTBI					
LMIC	87	0.2 (0-3)	0.2 (0-3)	0.0 (-0.1, 0.0)	0.85
Canada	38	1.5 (0-4)	1.8 (0-6)	-0.3 (-0.8, 0.0)	0.65
Non-TB					
LMIC	87	1.1 (0-4)	1.5 (0-5)	-0.4 (-0.6, -0.2)	0.81
Canada	38	0.2 (0-2)	0.4 (0-3)	-0.2 (-0.3, 0.0)	0.77

*Note: All correlation coefficients were statistically significant at $p<0.01$

Table 7.4: Linear mixed models (LMMs) for TEQ as a predictor of time measured with TAMs

Model	Proportion of TAM time predicted by TEQ	95% CI	ICC[1] site
Total Hours	**0.87**	**(0.8, 0.9)**	**0.63**
Other Clinical Activity	0.67	(0.6, 0.8)	0.35
Direct Patient Care	0.66	(0.6, 0.7)	0.57
Training/Administrative Tasks	0.82	(0.7, 0.9)	0.62
Direct Patient Care			
LTBI	0.55	(0.5, 0.6)	0.18
Active TB	0.63	(0.5, 0.7)	0.12
Non-TB	0.64	(0.6, 0.7)	0.28

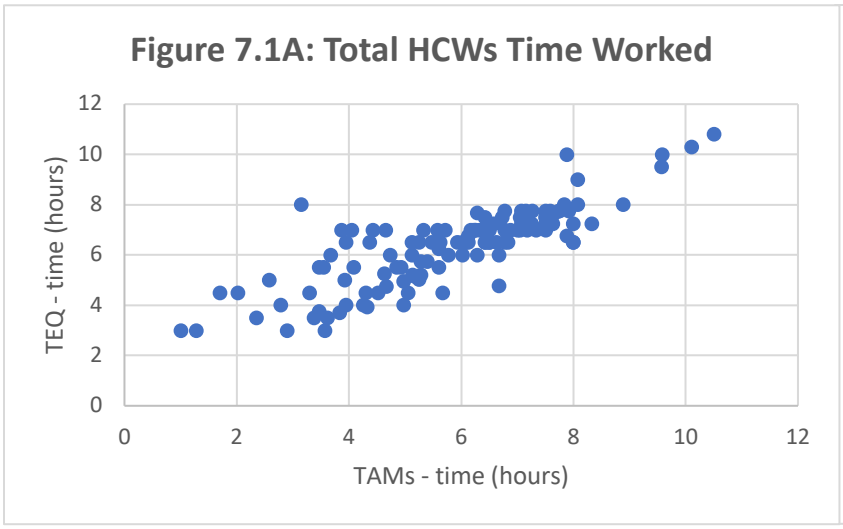
[1]ICC = Intra-class correlation coefficient (ICC) is a measure of variability between health facilities (site)

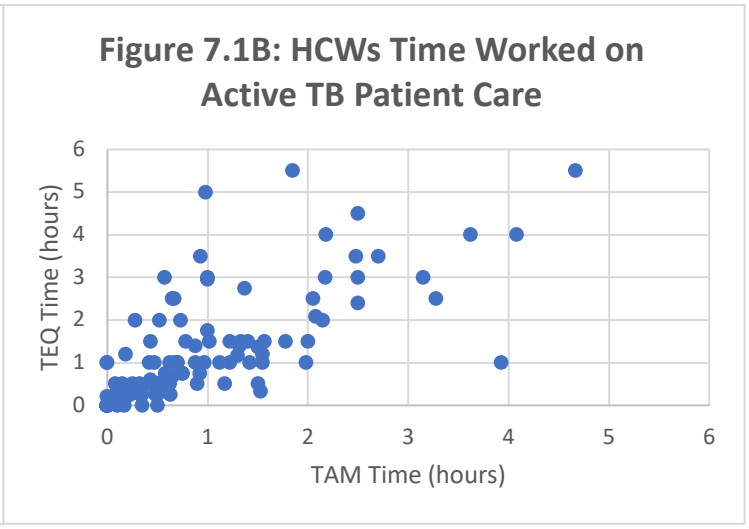
Table 7.5: Linear mixed model (LMM) for average HCWs time (hours) spent on each category of work activity across 10 days of TEQ of measurements

	Average Hours Worked per TEQ day (95% CI)	ICC[1] Site	ICC[2] HCW
Total Hours	5.3 (4.7, 5.8)	0.15	0.25
Other Clinical Activities	1.0 (0.7, 1.4)	0.23	0.27
Direct Patient Care	3.0 (2.6, 3.4)	0.10	0.29
Training/ Administrative Tasks	1.2 (0.7, 1.7)	0.32	0.28
Direct Patient Care			
ATB	0.8 (0.6, 1.0)	0.07	0.31
LTBI	0.4 (0.2, 0.6)	0.12	0.31
Non-TB	1.9 (1.4, 2.3)	0.22	0.28

[1]ICC = Intra-class correlation coefficient (ICC) is a measure of variability between health facilities (site)
[2]ICC = Intra-class correlation coefficient (ICC) is a measure of variability for individual HCWs across the 10 days of TEQ measurements

Figure 7.1: Scatterplots of time by category of work activity for TAMs compared to TEQs





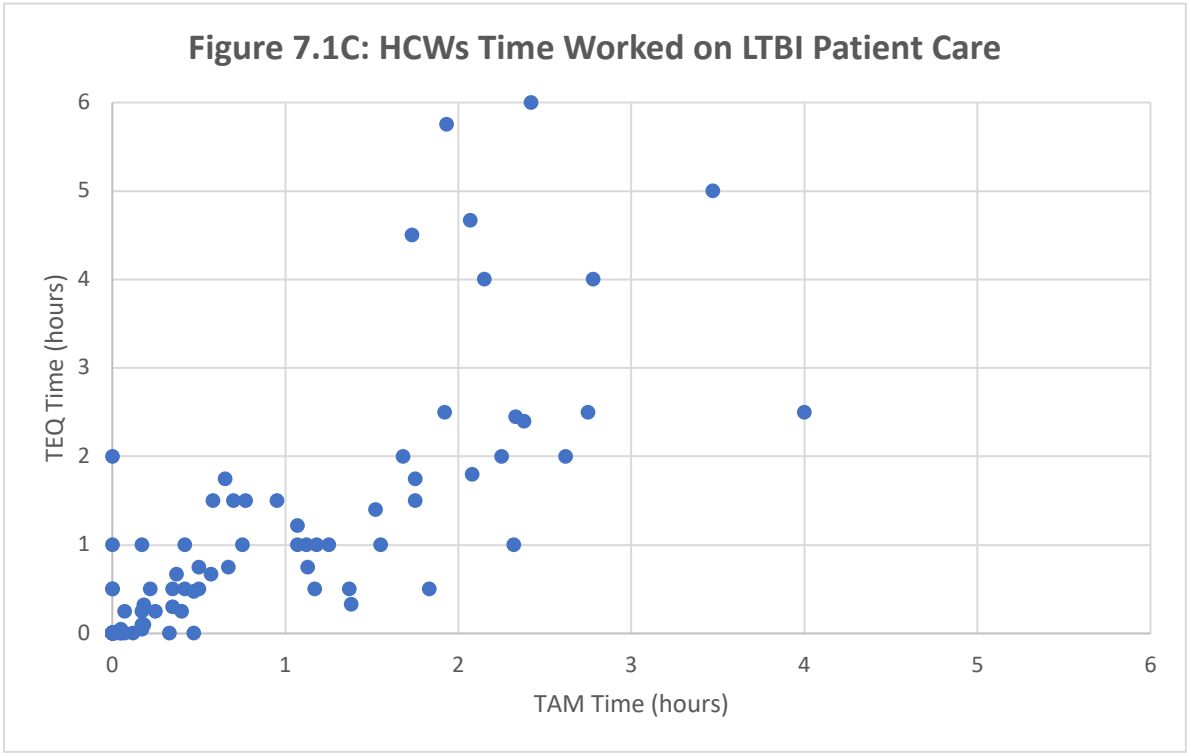
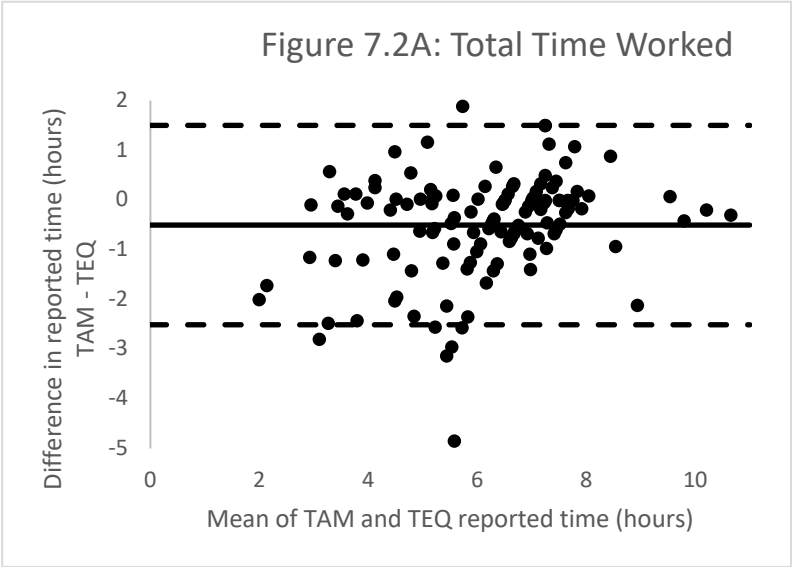
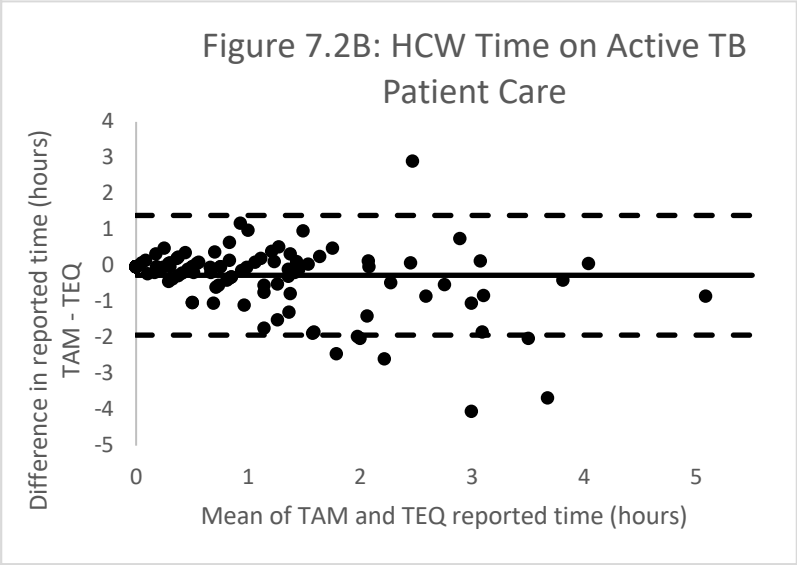


Figure 7.2: Bland-Altman Plots* of Difference Between TAM and TEQ Measurements of Time
*Note: *Mean difference is represented by the solid black line and the limits of agreement (+/- 1.96 standard deviation of the mean differences) are represented by the dashed line in each plot*





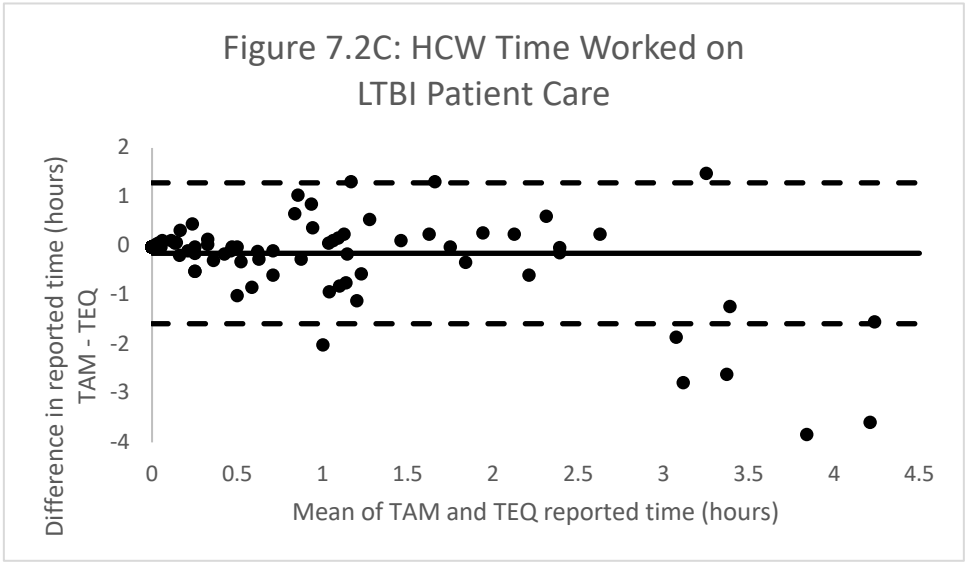


Figure 7.3: Mean difference (colored squares) and 95% confidence intervals for TEQ compared to TAMs for: A) Total hours worked on TAM day (blue); B) active TB (yellow); and C) LTBI (green). The equivalence bounds are indicated by dashed lines (by color for each category).

Figure 7.3A: Total Hours

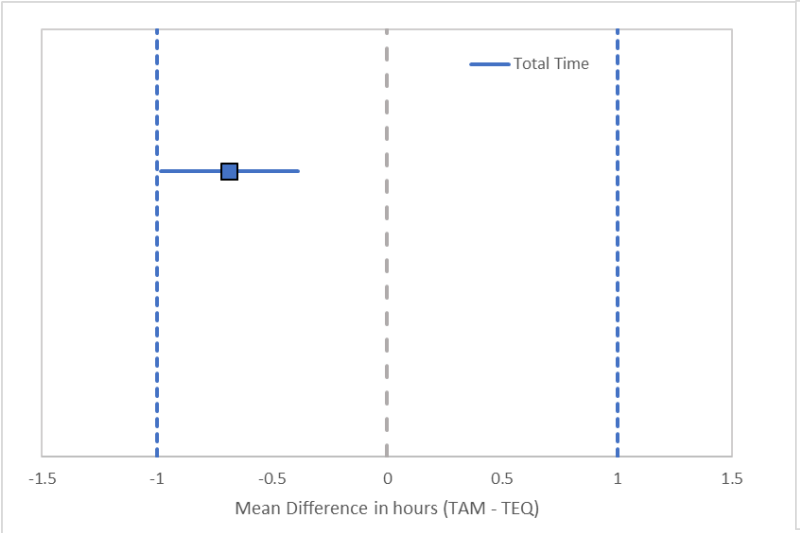


Figure 7.3B: Time (hours) on Active TB

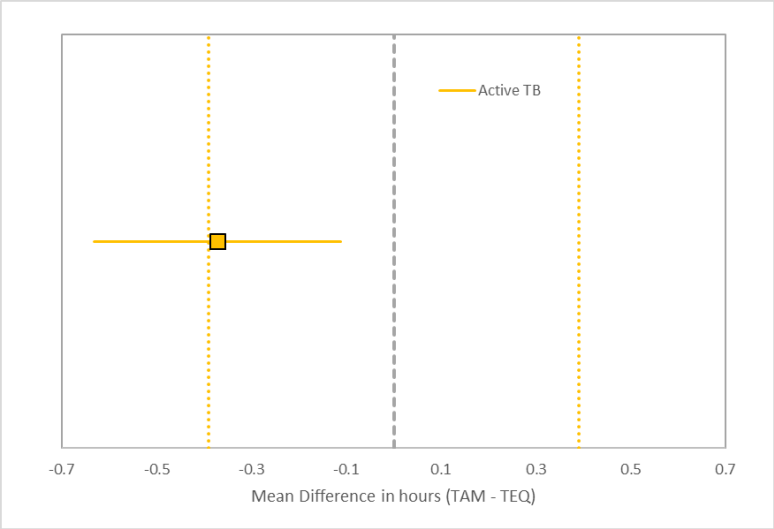


Figure 7.3C: Time (hours) on LTBI

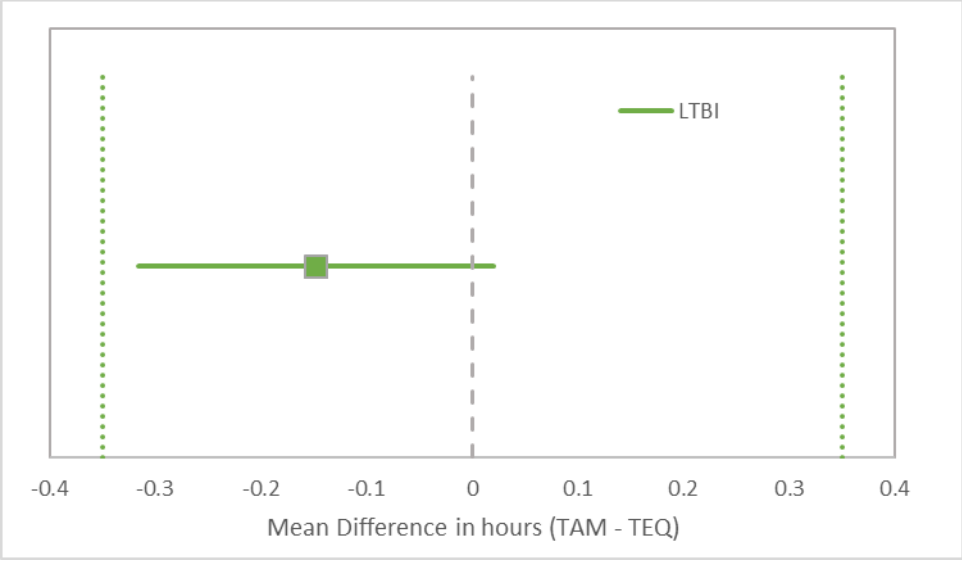


Table 7.S1: Characteristics of 86 HCWs who participated in the pilot TEQ

	Pilot TEQ	
	YES	NO
Sex	**(N=86)**	**(N=16)**
Male	21 (24%)	7 (44%)
Female	65 (76%)	9 (56%)
TB specific role		
Yes	66 (77%)	11 (69%)
No	20 (23%)	5 (31%)
HCW category		
Doctor	29 (34%)	2 (13%)
Nurse	48 (56%)	13 (81%)
Other HCW	9 (10%)	1 (6%)
Country		
Benin	16 (19%)	2 (13%)
Canada	40 (46%)	1 (6%)
Ghana[1]	0 (-)	13 (81%)
Indonesia	30 (35%)	0 (-)
Vietnam[2]	0 (-)	0 (-)

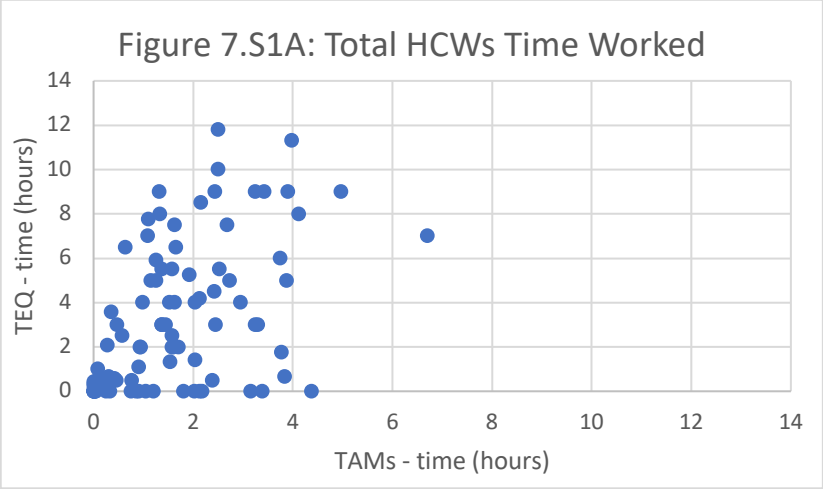
[1]In Ghana the pilot TEQ was not performed on any of the HCWs
[2]In Vietnam, HCWs did not participate in the pilot TEQ

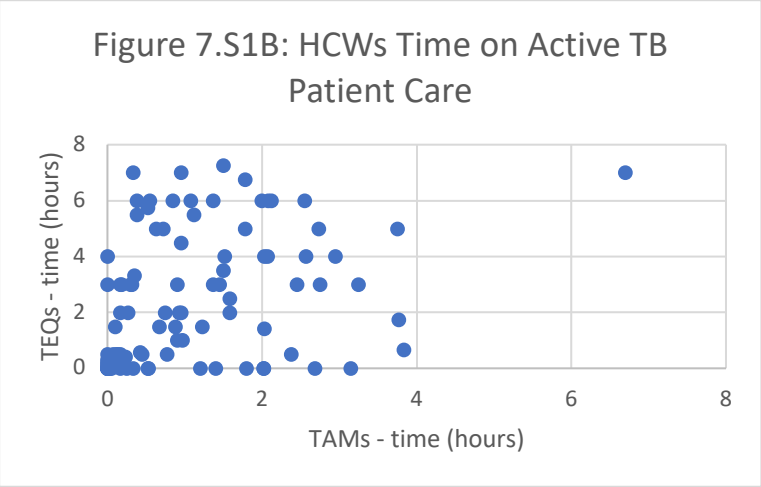
Table 7.S2: Comparison of time (hours) from TAM vs. pilot TEQ for 86 HCWs – Same Day

	TAM: Mean time, in hours, observed per HCW (range)	**TEQ: Mean time, in hours, reported per HCW (range)**	**Mean Difference in time (hours) TAM- TEQ (95% CI)**	**Correlation coefficient**
Total Time on All TB-related activities	1.6 (1-7)	3.7 (0-18)	-2.1 (-2.8, -1.5)	0.58
Active TB	1.1 (0-7)	2.8 (0-10)	-1.7 (-2.2, -1.3)	0.42
LTBI	0.5 (0-3)	0.9 (0-9)	-0.4 (-0.7, -0.2)	0.61

*Note: All correlation coefficients were statistically significant at $p<0.01$

Figure 7.S1: Scatterplots of time by category of work activity for TAMs compared to TEQs – Pilot TEQ phase
*Note: *Correlation coefficients for each category of activity are shown in Table 7.S2*





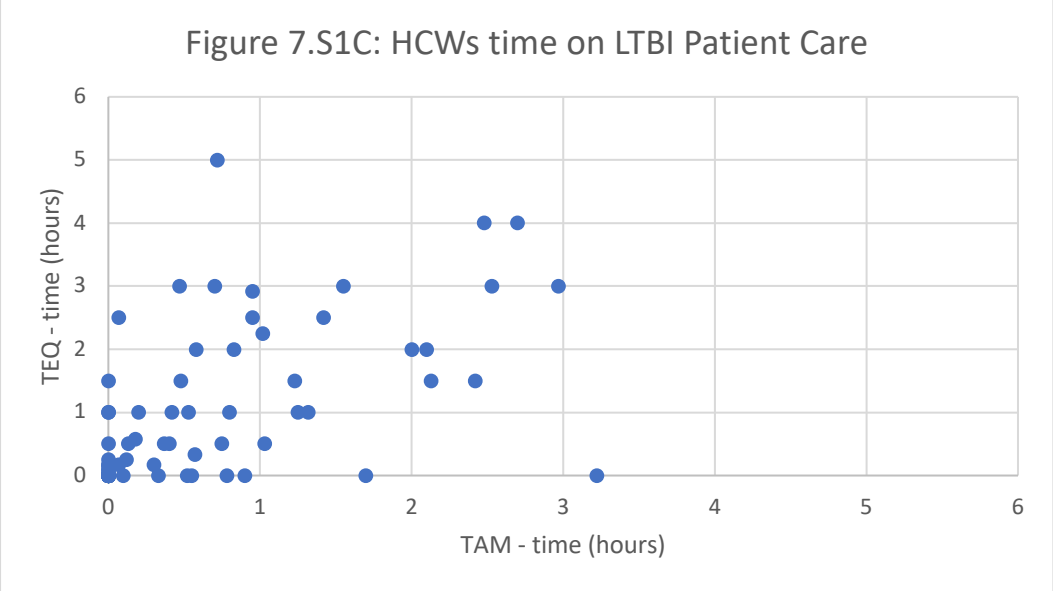
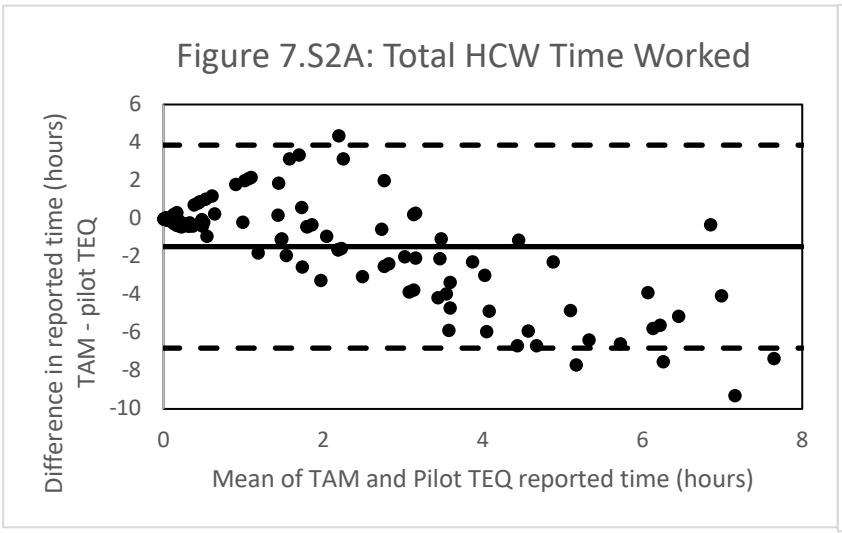
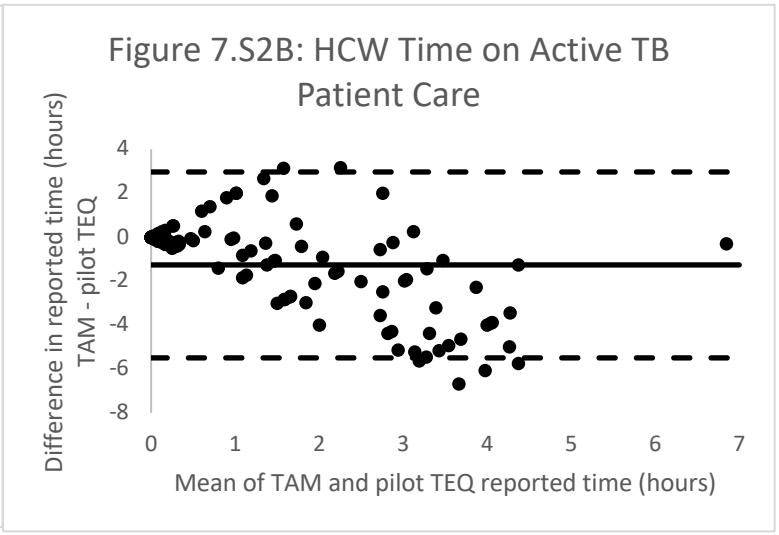
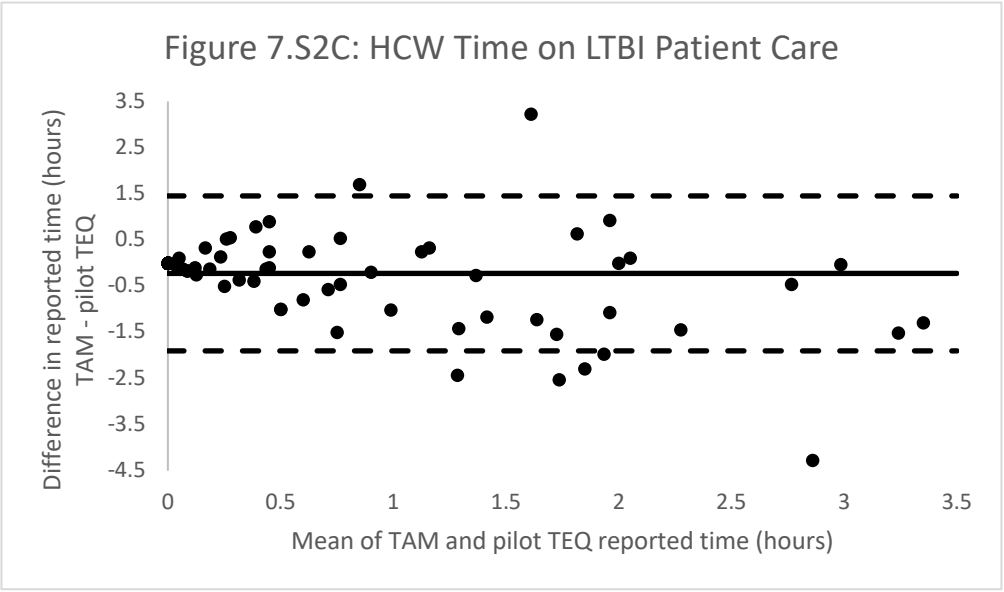


Figure 7.S2: Bland Altman plots* of the difference between TAM and TEQ measurements of HCW time – Pilot TEQ phase
*Note: *Mean difference is represented by the solid black line and the limits of agreement (+/- 1.96 standard deviation of the mean differences) are represented by the dashed line in each plot*







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Chapter 8 Discussion

8.1 Summary of Findings

The work presented in my doctoral thesis generally aimed to quantify the impacts on HCW time for scale-up of LTBI services, a key gap that was identified in the literature. In the first manuscript in my thesis (Chapter 4) we formally introduced the cascade of care framework for the patient care journey for LTBI. We identified the steps along the LTBI cascade of care where most losses occurred based on the available evidence in the published literature. This systematic review highlighted the need for interventions aimed at improving LTBI patient care and services by addressing gaps along the LTBI cascade of care.

The parent trial (ACT4) under which my doctoral research took place focused on evaluating and then finding solutions to address these gaps in the five participating countries. As part of this larger trial, my research was able to quantify the human resource needs required to provide improved LTBI care. My research captured the HCW time needed to perform work tasks at each step along the LTBI cascade (Chapter 5) as well as changes in their time allocated to patients with different health problems – notably LTBI and active TB – after improving LTBI services (Chapter 6). Thus, my research addressed the gap in the literature on the human resource needs to perform scale-up and expansion of LTBI-related patient care which the WHO has called for in its End TB Strategy(15).

My research further demonstrated that in countries with high numbers of household contacts, such as Ghana, health systems will need to make serious investments in healthcare staffing in order to have sufficient HCW available for the time required to contact, screen and educate all household contacts of people with active TB disease (Chapter 5). Since there has been limited data to-date on the impacts on HCW time allocation due to interventions to increase LTBI services, the data presented in my thesis provides evidence that scale-up will require many hours of HCW time which translates into additional staffing needs that must be quantified for each setting.

In the final manuscript of my thesis (Chapter 7), I was able to validate a simple, inexpensive tool to capture HCW time allocation (i.e. TEQ). The TEQ showed good performance based on high correlation with the reference standard TAMs, with consistent results across all categories of work. The findings from my research highlight the

importance of developing simple tools to quantify HCW time requirements to enable projections of staffing needs based on the local context.

8.2 Limitations

The main limitations were discussed in each of the manuscripts presented in this thesis, but there are a few that pertain to all the research that should be acknowledged here. Overall, the data were collected using TAM studies which have the potential for Hawthorne bias. There was no way to remove this bias (i.e. sensitivity analysis), it is simply a limitation of the methodology. We made every effort to inform HCW that the results from the TAM study were not given to health facility management and could not be used for reviews of their work performance. As noted elsewhere, the effect of the observer can be minimized but never eliminated since there is a natural human tendency to alter behavior to be more socially-desirable when under direct observation by someone else (29).

Interviewer-administered questionnaires that rely on recall by HCW regarding their daily activities are inherently subject to recall biases such as: 1) unintentional responder bias (i.e. HCW forget how much time was spent on certain tasks such as administrative work); and 2) socially-desirable recall of time allocation (i.e. HCW may report taking fewer breaks)(29). Furthermore, it is impossible for self-reported data to be as precise at quantifying time as TAM studies (i.e. reference standard). While the results from the TEQ had the inherent recall limitations of questionnaires, our study showed that by administering the questionnaires at the end of each workday, the information obtained compared well to the TAMs. An analysis of the percent bias (i.e. difference between two methods as a percent of the TAMs reference standard) showed a wide range particularly for direct patient care activities for active and non-TB patients. However, the percent bias was lowest among LTBI patient care activities which may be a result of increased HCW attention to LTBI patient care services following the intervention. These results highlight the difficulties of using tools based on recall, particularly during an entire workday. Further, we could not validate the TEQ over a longer period of time (i.e. additional nine days of TEQ measurements) due to the cost and feasibility issues of performing numerous TAM measurements.

Another limitation that applies to all manuscripts was that we were not able to recruit enough HCW to meet our sample size calculations since we could only include the HCW employed in each health facility. A pragmatic

limitation to our study was that there were not enough HCW employed across all study sites to perform the 280 TAMs needed following the intervention. Despite this limitation, our results demonstrated a significant change in HCW time allocations.

The results presented in this thesis were part of an intervention study to improve LTBI services which included extensive evaluation of the local cascade of care. Thus, changes in the proportion of HCW time spent on LTBI-related patient care activities occurred in a trial setting and may not be generalizable to other settings without dedicated resources to improving LTBI services. All health facilities that participated in the parent trial (ACT4) had previous experience conducting clinical research, so may have performed more efficiently than in non-research, programmatic settings. However, because it was a pragmatic trial, and the HCW participating in the TAMs were followed during typical workdays, the results ought to be fairly similar to other programmatic settings. Regardless, the results from these TAM studies demonstrate changes in personnel time that health systems and TB programmes may expect following improvements to LTBI-related service delivery.

8.3. Strengths

My doctoral research had a number of strengths which were discussed in each manuscript, but a few are worth highlighting here. First, although the TAM study was not able to conduct the almost 300 TAMs calculated for the sample size following the intervention, an important strength of this research is that the TAMs were conducted multiple times (three time points in total) and collected over 125 individual HCW observations at each time point, which is rarely feasible in TAM studies. And, the detailed HCW time estimates for all work tasks at each step along the LTBI cascade of care provided data to address a gap in the literature to inform costing and human resource planning for LTBI program scale-up.

Another strength of my doctoral research was that we demonstrated a statistically significant impact of the intervention of the parent trial (ACT4) on the HCW time dedicated to LTBI services, as well as the negative impact to time on active TB patient care activities in both high-income and LMIC. Linear mixed models were used to

account for clustering at the health facility-level, to ensure these results were not confounded by similarities among HCW at the same health facility.

My doctoral research quantified HCW time requirements at each step along the LTBI Cascade of Care, as well as overall changes in proportion of total time HCW spent on broader categories of work activities (i.e. direct patient care, other clinical activities, or training and administrative tasks). These results highlight the difficulty of translating precise time estimates into number of additional HCW needed to perform the work tasks. We were not able to quantify HCW time on indirect patient care activities related to LTBI, and therefore time estimates may have been an underestimate of overall HCW time needed for latent TB patient care. A key strength is that my research contributed initial estimates of HCW time needed for LTBI patient care activities and demonstrated the need for additional research in other settings to better understand and anticipate human resource needs for LTBI scale-up.

Finally, a key strength of the TEQ study was that we were able to recruit numerous HCW to participate in both the pilot and final TEQ measurements, as well as the same-day TAM. By conducting both TAMs and TEQs, we assessed the performance of a self-reported measure with data collection by an external observer, thereby addressing a gap in the literature particularly for TB-related work activities. Capturing HCW self-reported data over two full work weeks captured critical data on the variability of HCW work tasks across longer periods of time to better understand how HCW time is allocated.

8.4 Implications

There are a few key implications of the research presented in my doctoral thesis. First, there is likely to be an enormous increase in the numbers of people (primarily household contacts) accessing LTBI services globally in the coming years due to the push from WHO and the UNHLM-TB. In order to provide the needed services along the LTBI cascade of care, serious consideration and planning is needed at the local and national levels, namely, to ensure there are adequate staff employed in health facilities to perform this work. My doctoral research highlighted the importance of quantifying the human resource needs for better understanding the health system implications of

expanded services. This research also demonstrates that estimating the additional number of personnel needed to provide these services is an extremely complicated process.

One major challenge to providing HCW time estimates was the difficulty in quantifying time spent on indirect patient-care related work tasks (i.e. paperwork, forms, electronic charting, or consultations with other clinicians). Quantification of the average weekly work time on indirect patient care activities, along with all other types of patient care (i.e. diabetes, HIV, cancer, other infectious diseases, etc.) is needed for a comprehensive understanding of total staffing needs. And should be done over longer periods of time (i.e. multiple weeks or a month) to ensure extrapolations of HCW needs are not significantly underestimated.

We chose to report our estimates as a total number of HCW hours for all the household contacts of one person with active TB (i.e. index patient), a WHO-reported measure across TB programmes globally. The aim was to enable other TB programmes to estimate their local HCW needs following LTBI programme strengthening. We could have shown estimates as additional full-time equivalent (FTE) personnel, but since total work time was likely to be an underestimate, FTEs would then also seem unreasonably low. For example, in Canadian sites, the result when translating time (in hours) to FTEs was three additional FTEs for LTBI-related expansion. However, there were four ACT4 health facilities (sites) in four different cities across Canada. Clearly, if there was political supprot to expand LTBI services in Canada, it would not be feasible to only employ three HCW but rather a minimum of one additional HCW would be needed in each health facility. This illustrates the complexity of presenting our data in the most useful manner for planners and policy makers. Practical constraints and local health system considerations need to be accounted for in any personnel-related decisions, thus my doctoral research findings provide an initial guide to human resource needs but should be interpreted and applied in a logical, pragmatic manner for each specific context.

As discussed above, TB programmes should anticipate significant changes in the HCW time allocations on patient care activities following LTBI program expansion and scale-up, an important finding that was consistent across sites in all countries. By capturing the negative impacts of LTBI strengthening, my research demonstrated that TB programmes need to thoughtfully plan staffing requirements as they expand LTBI patient care to avoid

diminished services to other patients, particularly active TB patients. It is worth noting that time on active TB decreased less among HCW at intervention sites (although not statistically significant), which implies that a focus of the health system on improved care for related patient care services (i.e. both active TB and LTBI services as part of a robust TB programme) may ensure such patient care is improved overall.

Finally, an important implication of my doctoral research is that major investments in education and training for health systems will be required in order for such expansion of LTBI services to be possible. It is not simply a matter of hiring additional staff, particularly in high TB-burden countries where there is a dearth of HCW. Training and educating the next generation of nurses, doctors and other HCW will require strategic planning by local governments to prioritize the development of a pool of committed HCW.

8.5 Opportunities for Future Research

The TAM study demonstrated that TB programmes planning to expand LTBI services based on the push from WHO should anticipate increases in the number of HCW required to provide the LTBI-related services. However, the type and number of HCW needed for LTBI-related activities will depend on the staff organization at the local setting as well as the annual number of persons with active TB (i.e. index cases) cared for at each local health facility. The discussion above (see ***8.4 Implications***) highlights the difficulty of accounting for the varied nature of HCW workload to capture true estimates of overall HCW time and personnel needed for LTBI programme expansion.

The TAM study presented in my thesis (Chapters 5 and 6) provided some of the first estimates of HCW time requirements to perform all patient care activities along the entire LTBI cascade of care. My doctoral research highlights the need for additional studies to quantify HCW time requirements to enable more robust estimates across different types of health facilities (i.e. local and district-level facilities, teaching and private hospitals) and settings (i.e. low- and middle-income countries). Gathering data from other TB programmes in LMIC and high TB-burden countries would provide a better understanding of the work task components needed at each step to provide quality LTBI patient care as well as a more comprehensive picture of the impacts of LTBI scale-up globally.

There is also the need for additional research to verify the performance of an interviewer-administered questionnaire to capture data on HCW time allocation. Although use of TEQs was assessed and validated in the final manuscript (Chapter 7) of my thesis, there are other possible means of administering the TEQ in the programmatic setting. For example, conducting a TEQ for one week per month over the period of three months would provide more details on HCWs time allocation over a longer time frame. And while the TEQ results showed good correlation to the TAM reference standard, there is still the possibility of bias from the TEQ since HCW TEQ estimates of time on patient care, in particular, were consistently higher than the TAMs. More research is needed to better understand whether or not this overestimate is similar for HCW in other TB programmes and settings. And if so, then a means to correct for this overestimation (i.e. correction factor for TEQ) should be developed to enable the use of the TEQ to quantify HCW time and avoid unnecessary bias in HCW personnel time estimates.

8.6 Conclusion

My doctoral research focused on capturing the impacts on human resources in a number of health facilities in five countries to achieve improved LTBI services. This research has demonstrated the impact of interventions to increase identification, diagnosis and treatment of household contacts with LTBI on daily HCW work activities. My research also demonstrated the need for comprehensive assessments, both of HCW time requirements to perform specific tasks (i.e. patient care along the steps of the LTBI cascade of care), and to quantify the variability of HCW time allocation over longer time frames (i.e. weeks, months), in order to properly anticipate personnel-related needs for LTBI program expansion.

The global scale-up of LTBI services called for by the WHO and others will require programs to be thoughtful in planning human resource needs to expand LTBI care. This will require information about numbers of active TB patients (index cases), current staff time, and activities, and current functioning of the cascade of latent TB care to anticipate the human resource needs associated with LTBI expansion efforts. Providing LTBI patients with shorter treatment regimens may increase the acceptability of LTBI treatment and result in greater demand on TB clinics for LTBI services. My doctoral research has shown that it is critical for these human resource needs to be

examined and clearly quantified to anticipate the negative impacts to other patient care, such as for active TB patients. The TB community needs to be mindful of the resources and financial impacts this will have on the system. Yet the potential benefits and cost-savings of large-scale prevention efforts ultimately have the possibility to help end the TB epidemic globally.

Chapter 9 Appendices

9.1 Appendix 1 : Ethics Approval

Centre universitaire de santé McGill — McGill University Health Centre

Annual renewal submission

Date de dépôt du formulaire: **2017-11-02 11:51**
Déposé par: **VALIQUETTE, CHANTAL**
Date d'approbation du projet par le CER: **2015-11-27**
Identifiant Nagano: **15-291-MUHC**
Numéro(s) de projet: **2016-1712, 15-291-MUHC, eReviews_4963**
Formulaire: **F9 - 23803**
Statut du formulaire: **Approuvé**

Administration

1. **MUHC REB Panel & Co-chair(s):**
   Cells, tissues, genetics & qualitative research (CTGQ)
   Co-chair: Marie Hirtle

2. **REB Decision:**
   Approved - REB delegated review

3. **Renewal Period Granted:**
   From 2017-11-27 to 2018-11-26.

4. **Date of the REB final decision & signature**
   2017-11-26
   Signature

James Ellasus
MUHC REB Coordinator
for MUHC Co-chair mentioned above

9.2 Appendix 2: TAM Activity Code List

Description of Activities to be recorded for Clinical TAMs

Other activities:

1. Break
2. Other Clinical Activity
3. Training/Admin (including any paperwork not related to a particular clinical encounter with a patient)
4. Patient encounter – Non-TB

Patient encounter – Active TB related:

5. Patient encounter – Active TB
6. Patient encounter – Suspect active TB investigation including the medical evaluation and any diagnostic tests (i.e. Chest X-ray (CXR) of patients who present to the health facility/clinic for evaluation of symptoms and is considered a TB suspect)

Patient encounter- LTBI -related:

7. Identification and initial counselling for contacts or persons requiring LTBI testing for any other reason (including all activities such as phone calls, paperwork or patient education specific to the visit, home visits, interviews, etc.)
8. Place TST (or QFT). If there is a contact investigation, this includes meeting the contacts, initial teaching and any patient education related to the visit.
9. Read TST. And referral for medical evaluation
10. Conduct initial medical evaluation (history/interview, any patient education related to the visit and/or physical exam including: CXR, ordering/reading med evaluation related test)
11. Recommending and discussing LTBI treatment (including patient education and/or visit-related paperwork)
12. LTBI treatment follow-up visits including any follow-up/discussion and testing related to adverse events (also includes any follow-up done via phone calls).

Drop down lists included in Clinical TAM forms

Activity List (Master drop-down)
1. Break
2. Other Clinical Activity
3. Training/Admin
4. Patient encounter – Non-TB
5. Patient encounter – Active TB
6. Patient encounter – Suspect active TB
7. Identification/initial counselling for contacts/persons requiring LTBI testing
8. Place TST (or QFT)
9. Read TST (and referral for medical evaluation)
10. Conduct initial medical evaluation
11. Recommend and discuss LTBI treatment
12. LTBI treatment follow-up visits

9.3 Appendix 3A: Time estimation questionnaire (TEQ) Pilot

Retrospective, interviewer-administered questionnaire
TAM DAY VERSION

INSTRUCTIONS: At the END of the TAM day, please ask the HCW the following questions about their work schedule and activities TODAY.

1. Approximately how many hours did you spend today on **all TB-**related patient care activities?
   - ***Example response***: I worked 3 and a half hours in the morning today seeing patients with active TB, and their contacts, in the clinic.

   _____

2. Approximately how many hours did you spend today on **latent TB**-related patient care activities?
   - ***Example response***: I worked 2 hours today doing contact investigations and then placing TSTs for contacts of active TB.

   _____
   _____

3. Compared to this time one year ago (i.e. same month last year) has the amount of time you spend on **all TB**- related patient care changed?
   - No change
   - Yes – changed.
   - **If YES**, approximately how many more, or fewer, days (or half-days) per week do you spend in **all TB**-related patient care activities (active TB, latent TB, contacts)?
     - ***Example response***: I work one additional day in the TB clinic each week seeing TB patients giving them their medications.

   _____
   _____

4. Compared to this time one year ago (i.e. same month last year) has the amount of time you spend on **latent TB**-related patient care changed?
   - No change
   - Yes – changed.
   - **If YES**, approximately how many more, or fewer, days (or half-days) per week do you spend in patient care activities for LTBI patients?

     - ***Example response***: I work an additional half-day in the TB clinic each week doing contact investigations.

   _____
   _____

Please add notes or additional information on why the hours may have changed
Example notes: I was on maternity leave last year at this time last year

_____
_____
_____

9.4 Appendix 3B: Time estimation questionnaire (TEQ) Final

Time-estimation questionnaire (TEQ)

TEQ INSTRUCTIONS:

Choose one typical work week, for the HCW - no planned vacations.
At the END of each workday throughout that week, please ask the HCW the following questions about their work schedule and activities during THAT day. Fill in the responses (in hours) in the table on page 2.
This form should be administered in person by the RA on the first day. After that the RA can call the HCW and complete this by phone.

TEQ QUESTIONS (To be asked by the RA):

1. Approximately how many **TOTAL** hours did you work today on **all work-related activities** (i.e. not including any break time such as for personal phone calls, restroom, smoking break or lunch/coffee/tea time)?

2. Approximately how many hours did you spend today on **direct patient care** activities (i.e. time spent with all patients - HIV, LTBI, ATB, Non-TB - combined)? Direct patient activities include all in-person patient visits and telephone conversations with patients.

3. Approximately how many hours did you spend today on **other clinical work** activities (i.e. obtaining/reading/reviewing laboratory results or chest X-rays, writing in patient medical records/charts, patient related emails, patient scheduling, dictations, or consulting with other clinicians about patients)?

4. Approximately how many hours did you spend today on **training or administrative** activities (i.e. training others or being trained, supervising others or meeting with your supervisor, administrative tasks, or time spent in meetings)?

Responses to questions #2+3+4 should add up to the TOTAL HOURS worked in Question #1

5. Of the time you spent on all direct patient care activities, approximately how many hours did you spend today on **patient care for ACTIVE TB** (i.e. assessing cases of suspected ATB (sputum smear/culture), providing treatment (DOTS/injections), any follow-up visits for treatment/side effects, or telephone calls with ATB patients)?

6. Of the time you spent on all direct patient care activities, approximately how many hours did you spend today on **patient care for LATENT TB (LTBI)** (i.e. contact investigations (including telephone calls and home visits), placing/reading TST/IGRA, evaluation of TST/IGRA results, follow-up with any patients put on LTBI preventive treatment)?

7. Of the time you spent on all direct patient care activities, approximately how many hours did you spend today on **patient care for Non-TB** (patient care activities for HIV, Diabetes, asthma, cancer, or any other condition than active TB or latent TB)?

Responses to questions #5+6+7 should add up to the hours spent on DIRECT PATIENT CARE in Question #2.

	Example	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
1. Total hours worked today	**6.5**							*Not worked*
2. Direct Patient Care	4							
3. Other Clinical Activities	2							
4. Training/ Administrative Tasks	0.5							
5. Active TB patient care	2							
6. LTBI patient care	1							
7. Non-TB patient care	1							

1. Do not include any break time (i.e. pauses between patients, restroom, personal calls, smoking break or lunch/coffee/tea breaks)
2. Include all time spent in direct patient care (i.e. face to face medical visits (or telephone calls) with ALL patients (HIV, TB, non-TB)
3. Include all other clinical activities (i.e. reviewing laboratory results, CXR, dictations, charting, writing in medical records, consulting with other clinicians about a patient(s)
4. Include all time spent on supervision or training activities, emails/patient scheduling, or meetings
5. Include all time spent with patients (and telephone calls to patients directly) who have ATB or assessing patients suspected to have ATB (i.e. sputum smear, culture, providing treatment (DOTS or injections), follow-up visits to discuss medication or side effects)
6. Include all time spent with LTBI patients or patient care (i.e. contract investigations (including telephone calls), placing/reading TST or IGRA, evaluation of TST/IGRA results, medical evaluations or recommending preventive treatment and any follow-up visits)
7. Include all time spent with any other type of patients (i.e. HIV, diabetes, hypertension, asthma, etc.)

Please verify the following calculations:

Hours in box 2 + 3 + 4 = Total hours reported in box 1

- ***Example***: 4 hrs (#2 – patient care) + 2 hrs (#3 – other clinical) + 0.5 hrs (#4- training)
  = **6.5 hours worked in total (#1 above)**

Hours in box 5 + 6 + 7 = Total hours of direct patient care in box 2

- ***Example***: 2 hrs (#5 – ATB) + 1 hr (#6 - LTBI) + 1 hr (#7 – Non-TB)
  = **4 hours on direct patient care (#2 above)**

9.5 Appendix 4: TAM Study Sample Size Calculations

To account for clustering at the site level, the sample size was calculated by multiplying this sample size by the design effect

$$\mathbf{D_{eff}} = 1 + (m-1)p$$

Where:

- m = average cluster size = 13; and
- p = intraclass correlation coefficient (ICC) = 0.203

$$\mathbf{D_{eff}} = 1 + [(13-1)*(0.20)] = (3.4) * (42 \text{ TAMs}) = \mathbf{143\ TAMs}$$

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