Active case finding for TB cases in high burden, low HIV settings, Lima, Peru

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A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Doctor of Philosophy (Ph.D.)

Montreal, Quebec, Canada

April 2015

ABSTRACT (ENGLISH)

Globally, tuberculosis (TB) remains a leading source of morbidity and mortality, with an estimated 9 million new cases and 2 million deaths per year. Following 20 years of the World Health Organization (WHO) TB control recommended strategy, the Directly Observed Treatment Short-Course (DOTS), TB rates have continued their decline, however progress is still required to stem ongoing TB transmission. In 2012, WHO released recommendations on investigating contacts of person with infectious TB in low and middle income countries with the goal of reducing and controlling the spread of TB in the community in endemic areas and rapidly detect cases. Although active case finding strategies are increasingly cited as important to TB control and case detection within TB programs, there is currently limited evidence available on the use of these strategies in TB programs in endemic areas. This thesis aims to contribute a better understanding the role of active case finding for TB cases in the district of San Juan de Lurigancho (SJL) with amongst the highest TB and MDR-TB in Lima, Peru.

The first objective of the thesis was to examine the geographic clustering of primary multidrug (MDR) TB cases compared with drug sensitive (DS) TB in the district of SJL in order to prioritize certain areas for targeted active case-finding in the community. Data from case control studies and cohort studies were examined using simple cluster detection methods. The second objective of the thesis was to design the implementation and roll-out of an active TB case finding program across all health centers in the district of SJL. A pragmatic stepped wedge cluster randomized trial design for the roll out of a household contact evaluation program within a routine public health setting is presented. This innovative design is discussed in the context of its potential to provide higher quality evidence, and the strengths and

challenges of its use in the real world. The third objective was to estimate the cost-effectiveness of an active case finding program of adult household contacts of new infectious TB cases in comparison with the existing passive case finding program in order to detect co-prevalent active TB cases in the district of SJL. Theoretical costs and effects were considered in decision analytic models to estimate the cost-effectiveness of actively evaluating household contacts to detect TB cases in this setting.

The collective evidence from this thesis contributes to the larger discussion on the use of active case finding of TB cases in resource limited or constrained settings with a high TB burden. The thesis highlights specific evidence that will contribute to public health decision-making on the role of household contact tracing, its cost-effectiveness and the clustering of MDR-TB cases for targeted community interventions.

ABSTRACT (FRENCH)

Globalement, la tuberculose (TB) demeure une source majeure de morbidité et de mortalité, avec environ 9 millions de nouveaux cas et 2 millions de décès chaque année. Après 20 ans de la stratégie de lutte contre la tuberculose, inclus le traitement de cas de tuberculose avec observation directe (DOTS) recommandée par l´Organisation mondiale de la Santé (OMS), les taux de tuberculose ont commencé à diminuer lentement, mais plus de progrès est encore nécessaire pour eviter la transmission continue de la tuberculose. En 2012, l'OMS a publié ses recommandations sur l'enquête de contacts de personne avec tuberculose infectieuse dans les pays à revenu faible et moyen afin de réduire et de contrôler la propagation de la tuberculose dans la communauté dans les zones endémiques et de détecter rapidement les cas. Bien que le dépistage actif des stratégies sont de plus en plus recommandé et incorporé dans les normes nationales et internationales, il existe peu de preuve de la qualité et effet de ces interventions. Cette thèse vise à contribuer à une meilleure compréhension du rôle de la recherche active de cas de tuberculose dans le district de San Juan de Lurigancho (SJL) avec parmi les taux plus élevés TB et MDR-TB à Lima, au Pérou.

Plus précisément, le premier objectif de la thèse était d'examiner le regroupement géographique de multirésistance primaire (MDR) des cas de tuberculose par rapport aux médicaments sensibles (DS) tuberculose dans le district de SJL afin de prioriser certaines zones de recherche active des cas ciblés dans la communauté. Les données des études cas-témoins et des études de cohorte ont été examinés à l'aide de méthodes de détection de cluster simples. Le deuxième objectif était d'estimer le rapport coût-efficacité d'un dépistage actif des cas programme des contacts familiaux adultes de nouveaux cas de tuberculose infectieuse en comparaison avec le programme passif afin de détecter les cas de tuberculose active dans le quartier de SJL. Les coûts et les effets théoriques ont été pris en compte dans les modèles de décision d'analyse pour

estimer la coût-efficacité d'évaluer activement les contacts familiaux de détecter les cas de tuberculose dans ce cadre. Le troisième objectif était de concevoir la mise en œuvre et le déploiement d'un cas de tuberculose active trouver programme dans tous les centers de santé dans le district de SJL. Un protocol d´essai randomisé pragmatique avec implementation en groupes en stages est présenté pour un programme d'évaluation de contact actif dans un contexte de santé publique de routine. Cette conception novatrice est discuté dans le cadre de son potentiel à fournir des preuves de meilleure qualité, et les avantages et défis de son utilisation dans le monde réel.

L'ensemble des preuves de cette thèse contribue à la discussion plus large sur l'utilisation de la recherche active des cas de tuberculose dans les contexte avec ressources limitées et nombreux cas de la tuberculose. La thèse met en évidence des preuves spécifiques qui contribueront à la prise de décisions de santé publique. Cette thèse contribue à futur sur le rôle de la recherche des contacts de cas de tuberculose, son rapport coût-efficacité et le regroupement des cas de MDR-TB pour des interventions communautaires ciblées.

ACKNOWLEDGMENTS

First and foremost, I am tremendously grateful for the mentorship provided to me by primary supervisors, Dr. Timothy Brewer and Dr. Jay Kaufman. Dr. Brewer invested much time, energy and patience to facilitate my development as an independent researcher, epidemiologist and as a passionate public health practitioner. Dr. Kaufman provided invaluable comments throughout my research experience and I am thankful for his inspired discussions on every topic ranging from methodologic epidemiology to his vast knowledge and interest in local research work in Peru. Thank you also to my exceptional committee members at McGill University, for their advice and support at the outset of my field work Dr. Madhukar Pai, and Dr. Andrea Benedetti. For their time efforts and guidance at various times during my work, I wish to thank to Dr. Eric Latimer and Mr. Aman Verma.

I am equally indebted to Dr. Eduardo Gotuzzo and Dr. Carlos Seas of the Unidad de Tuberculosis (TB Unit) of the Instituto de Medicina Tropical "Alexander von Humboldt" at Universidad Peruana Cayetano Heredia (UPCH). I am very thankful to my friends, colleagues, and teammates at UPCH for their assistance, especially to Dr. Larissa Otero, Dr. Carlos Zamudio, Dr. Elsa Gonzalez and Dr. Cesar Ugarte. Sincere thanks to Marlene Rojas Pena, Dr. Oscar Mori and the Red de Salud de San Juan de Lurigancho, DISA Lima IV Este and the Ministerio de Salud in Peru for their ongoing support and collaboration. Sincere thanks to Dr. Kim Hoffman, Dr. Javier Ponce, Dr. Carlton Evans, Dr. Sumona Datta, Dr. Tom Wingfield and Ms. Thea Wingfield, for providing insights as expatriates conducting health research in Peru and for their camaraderie.

I thank my classmates for their encouragement during my doctoral studies, in particular Serene Joseph, Kate Zinszer, Carmen Messerlian, Daphne Ling, Alice Zwerling, Opal Huang, Melissa Bauer and Laura Thompson. I also wish to thank my dearest friends, Rena, Mohyna, Sonu, Janine and Rhea.

I would especially like to thank my parents and my sister Reena for their unwavering support throughout my studies. I dedicate this thesis to my grandmother, Hasumati Shah.

STATEMENT OF ORIGINALITY

All elements of this thesis dissertation and its manuscripts are considered original scholarship and represent distinct contributions of knowledge. This doctoral thesis sought to extend the existing literature in the areas of tuberculosis epidemiology and public health. This thesis examines several questions pertaining to the district of San Juan de Lurigancho, Lima, Peru, amongst the highest TB endemic areas of Peru. The manuscripts examine the clustering of primary MDR-TB cases in order to improve targeted active case finding, discuss the real-world challenges to implementing household contact tracing programs within a routine TB control program and examine the cost-effectiveness of actively finding cases of TB among household contacts of TB cases. I declare this doctoral thesis and each of the manuscripts to be of my own authorship with the input, advice and guidance of my advisory committee and contributing original and unique contributions to the literature and to fellow researchers and public health practitioners.

PREFACE AND CONTRIBUTION OF AUTHORS

I confirm that during my doctoral studies, as the primary author, I developed and have written all components of the thesis and each of the included manuscripts. I reviewed the literature and identified questions and gaps for further study, developed individual research questions within each of the manuscripts, conducted statistical and relevant analyses, considered the interpretation and significance of findings and drafted all manuscripts included in this thesis. I lead the circulation of manuscripts to co-authors, including incorporating feedback, submitting to journals and making revisions to all papers in preparation for publication. I received guidance from my primary supervisors Dr. Timothy Brewer and Dr. Jay Kaufman and from specific co-authors, who contributed expertise on topics ranging from epidemiology, biostatistics, public health, tuberculosis and on infectious disease prevention and control programs (detailed further below). The manuscript-based thesis contains distinct and original contributions to knowledge which are shared in peer-reviewed publications and also through knowledge translation efforts both locally in Peru, in Canada and internationally.

Manuscript 1. 'Geographic predictors of primary multidrug-resistant tuberculosis cases in an endemic area of Lima, Peru'

Manuscript 2. 'Implementation of a stepped-wedge cluster randomized design in routine public health practice: design and application for a tuberculosis household contact study in a high burden area of Lima, Peru'

Manuscript 3. 'Cost-effectiveness of actively evaluating household contacts of TB patients in a TB endemic setting in Lima, Peru'

Role of the PhD Student

In addition to the above mentioned responsibilities, I undertook the following tasks related to the specific work throughout the thesis. In Manuscript 1, I gained access to primary data

sources, cleaned individual datasets, merged and further developed the final study database presented in the paper, developed the analysis plan and undertook all related analyses and writing of the manuscript. In Manuscript 2, from the outset I identified the original primary research questions, developed and designed the pragmatic stepped-wedge design in the field including undertaking various collaborative meetings with the program manager of the National TB Program (NTP) of San Juan de Lurigancho district and local stakeholders at the health center level. I also worked on the development of the protocol which was included as the original CIHR grant submission protocol. I hired and trained the local teams, set up networks, and undertook activities related to the planning, design and implementation of the pragmatic stepped-wedge cluster randomized trial protocol in the field. In Manuscript 3, I developed the research questions, analysis plan, identified all input parameters required for analysis (from direct data sources and from published literature) and undertook all related analyses and writing of the manuscript.

Role of Co-authors

In all manuscripts, Dr. Timothy Brewer arranged for the overarching collaboration through his existing partnership with Dr. Eduardo Gotuzzo of the Institute of Tropical Medicine "Alexander von Humboldt" of the Universidad Peruana Cayetano Heredia (UPCH). These authors provided input into the overall approach, principal roles in obtaining funding and overall coordination. Dr. Jay Kaufman provided epidemiologic and statistical guidance throughout all manuscripts. Key collaborators at the UPCH were Drs. Carlos Seas who provided input into the drafting of all manuscripts, Dr. Carlos Zamudio and Dr. Larissa Otero who provided input on field methodologies in particular for Manuscript 2. In manuscript 1, Dr. Antonio Ciampi provided statistical advice, Mr. Howard Choi, Dr. Fiorella Krapp, and Dr. German Hernostra coordinated data collection and supervision of the field aspects and Dr. Jody

Heymann provided input during the design and writing stages of Manuscript 1. Dr. Lea Berrang-Ford provided input into the geographic analysis plan in Manuscript 1. Dr. Eric Latimer provided guidance on analysis plan in Manuscript 3.

STATEMENT OF FINANCIAL SUPPORT

Financial support of the doctoral student was provided through the following doctoral awards: Canadian Institute of Health Research (CIHR) Frederick Banting and Charles Best Doctoral Research Award, International Development Research Center (IDRC) Doctoral Research Award and the McGill University Provost Graduate Fellowship. Travel awards for data collection, dissemination and conferences were provided by the CIHR Michael Smith Travel Supplement and Department of Epidemiology, Biostatistics and Occupational Health GREAT Travel award. The costs of data collection, analysis, drafting of manuscripts, travel and associated expenditures for Manuscripts 2 and 3 were provided by a CIHR Operating Grant (#235353).

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LIST OF ACRONYMS

AFB	Acid Fast Bacilli
BCG	Bacillus Calmette-Guérin
CEA	Cost Effective Analysis
CIHR	Canadian Institutes of Health Research
DISA	Direccion de Salud
DOTS	Directly Observed Therapy Short Course (WHO strategy)
DST	Drug Susceptibility Testing
FIND	Foundation for Innovative New Diagnostics
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
ICER	Incremental Cost-Effectiveness Ratio
IDRC	International Development Research Center
IMT	Instituto de Medicina Tropical "Alexander von Humboldt"
IUATLD	International Union Against Tuberculosis and Lung Disease
LMIC	Low and Middle Income Country
LTBI	Latent Tuberculosis Infection
MDR-TB	Multi Drug Resistant tuberculosis
MGIT	Mycobacteria Growth Indicator Tube
MINSA	Ministerio de Salud de Perú (Ministry of Health of Peru)
NTP	National Tuberculosis Program
PAHO	Pan American Health Organization
PTB	Pulmonary Tuberculosis
SES	Socio Economic Status
TB	Tuberculosis
UPCH	Universidad Peruana Cayetano Heredia
WHO	World Health Organization
XDR-TB	Extensively drug resistant tuberculosis
ZN	Ziehl-Nieelsen stain

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CHAPTER 1 : INTRODUCTION

Globally, an estimated nine million TB cases and approximately two million TB deaths occur each year, with the vast majority occurring in low- and middle-income countries.[1] Since 1993, the Directly Observed Treatment Short Course (DOTS) strategy has been the key component of global TB control programs, focused primarily on the self-report of symptomatic persons to health care services for TB diagnosis and the appropriate allocation and completion of treatment regimens in order to stem community transmission.[2] In 2011, despite almost two decades of DOTS programming worldwide and the availability of cheap and effective treatment, TB continues to be a large source of morbidity and mortality.[3,4] The emergence of human immunodeficiency virus (HIV) and multidrug resistant TB strains (MDR-TB) are considered important drivers of the global TB epidemic, however only account for a proportion of all TB cases worldwide (approximately 13% and 3.5%, respectively, of new TB cases reported annually).[5,6] Delays to TB diagnosis, prolonged infectious periods and undetected secondary cases in communities continue to be challenges for current TB programs and contribute substantially to the propagation of the TB epidemic.[7,8]

Routine and comprehensive evaluation of close contacts, including household members, of infectious TB cases to identify secondary TB cases and latent TB infections (dormant TB infection) is considered essential for TB control in settings where TB prevalence is low, such as in Canada and the United States.[9,10] In contrast, active evaluation for TB cases in high TB burden settings is reserved primarily for groups at highest risk of progressing to TB disease including children under 5 years of age, contacts with known immunosuppressed states (e.g. HIV), and in high priority groups such as contacts of known drug resistant TB cases.[11] While approximately 50% of close contacts will have latent TB and 5 to 10% of contacts will develop active disease during contact investigation, routine evaluation of all close contacts for active TB

disease continues to be a low priority in most TB control programs in high burden settings.[12] This is due, in part, to the perceived need to focus on active TB case management alone.[7,13]

Recent evidence suggests that active case finding, or actively seeking smear-positive TB cases outside of clinic settings may substantially improve TB case detection rates and therefore contribute to overall reductions in TB prevalence and incidence in the community over time.[14–18] Based on the potential to strategically detect cases earlier through active case finding, recommendations have emerged for conducting contact investigations in high–incidence settings.[12,13,15,19,20] However, estimates of the effectiveness of active TB case finding for household contacts of TB cases in comparison to the passive system case detection in which symptomatic household contacts self-present for care, are not fully understood.[21] Additionally, the resource implications of TB program health facility staff actively seeking and evaluating contacts outside of clinic settings has not been evaluated in low and middle income countries. Given the potential for active case finding to reduce the TB burden, the cost-effectiveness of implementing active case finding strategies is an urgent priority for TB control programs.[21,22]

In 2012, the World Health Organization (WHO) released its first guidelines for the evaluation of household contacts in low- and middle-income countries (LMICs).[12] Given the important role of screening close contacts in TB control programs in high-income settings, the expansion to include screening of close contacts in LMICs seems straightforward. The WHO recommendations now include evaluating household and close contacts of all smear positive TB cases in LMICs, however currently there is limited or low quality evidence to support this decision.[12] Implementation and operational studies undertaken in LMICs have been identified as major gaps in existing literature and could provide important knowledge on the role of TB case finding in endemic areas.[23–25]

1.1 Research Objectives and Overview

1.1.1 Objectives

Overall Aim: The overall aim of this doctoral thesis is to examine the role of active case finding of TB cases within a routine TB control program in the TB endemic setting of San Juan de Lurigancho (SJL) district, Lima, Peru.

Specific Objectives:

1. To examine the geographic clustering of Primary MDR-TB cases compared with DS-TB in the district of SJL to prioritize areas for targeted active case-finding prevention and prevent the continued community spread of drug resistant TB cases. (Manuscript 1)
2. To design and implement an active case finding program for household contacts across all NTP health centers in the district of SJL. (Manuscript 2)
3. To discuss the strengths and challenges of using the pragmatic stepped wedge cluster randomized trial design in operational research for TB programs in endemic settings. (Manuscript 2)
4. To estimate the cost-effectiveness of an active case finding program of household contacts of new infectious TB cases in the district of SJL, in comparison with the standard passive case finding program. (Manuscript 3)

1.1.2 Thesis Overview

Following the introduction and description of the objectives of this thesis in Chapter 1, the subsequent chapters include the background and literature leading up to the specific manuscripts (Chapter 2), each of the three manuscripts (Chapters 3, 4 and 5, respectively) and

finally a discussion of the overall contributions of the work in this thesis including ongoing work currently underway in SJL, future directions and implications of this thesis to the literature, researchers and public health programmers (Chapter 6).

In Summary:

- Chapter 2 describes the background specific to tuberculosis, its epidemiology, and the prevention and control of tuberculosis. This chapter also describes the setting in which the work was undertaken.
- Chapter 3 includes the manuscript entitled ´Geographic predictors of primary MDR-TB cases in San Juan de Lurigancho district, Lima, Peru´. The chapter presents analysis of primary data from SJL district which examined the hypothesis of primary MDR-TB cases clustering in comparison to primary Drug Susceptible (DS-TB) cases within SJL district.
- Chapter 4 includes the manuscript entitled 'Implementation of a stepped-wedge cluster randomized design in routine public health practice: design and application for a tuberculosis household contact study in a high burden area of Lima, Peru´. The chapter presents a study protocol for a pragmatic stepped wedge cluster randomized trial of an intervention for active case finding of household contacts and discusses the strengths and practical challenges faced during implementation within a routine NTP program. Although the full study trial is currently ongoing in SJL District, the manuscript presents the study design and implementation phases with commentary on the strengths and challenges as experienced by the doctoral student from the outset of developing the collaboration to the full implementation of the active case finding intervention.

- Chapter 5 includes the manuscript entitled ´Cost-effectiveness of actively evaluating household contacts of TB patients in a TB endemic setting in Lima, Peru´. The chapter examines the cost-effectiveness of active case finding for household contacts in the SJL district compared to a routine passive case finding system within a WHO DOTS strategy.
- Chapter 6 follows with an overall discussion of the contributions and summary of the work, including suggestions for future directions of the work. The final conclusions discuss the overall significance of the findings and their usefulness to researchers and to public health programmers.

An overall reference list for all chapters of the thesis (including individual manuscripts) can be found at the end of the thesis document. Final appendices include relevant ethical approvals and supporting documentation.

CHAPTER 2 : BACKGROUND AND LITERATURE REVIEW

2.1 TB Burden

In 2012, the WHO reported approximately 9 million new cases of TB worldwide with 2 million deaths.[26] Over the last 50 years, the overall incidence of TB has gradually declined, attributed in part to availability and widespread use of antituberculosis treatment and to rising standards of living.[27,28] In many LMICs, and marginalized and impoverished populations within high income settings, TB continues to be a major cause of morbidity and mortality. [3,29,30] TB is considered one of the top 10 causes of death in LMICs and the second highest cause of death from an infectious disease behind HIV.[31,32] The global TB burden is concentrated in certain geographic areas. In some regions, such as in Sub-Saharan Africa, HIV is seen as a major contributor to the reemergence of TB disease, however this co-morbidity represents approximately 13% of all TB cases. Overall, more than half of TB cases are reported from India, China and the Russian Federation. In the Western Hemisphere, Haiti, Suriname, Bolivia, Guyana and Peru report the highest overall TB rates, upwards of 100 incident TB cases per 100,000 population per year.[26]

2.2 Tuberculosis (TB) Disease

2.2.1 Active TB Disease

Tuberculosis (TB) is caused by a bacteria called *Mycobacterium tuberculosis* (M. tbc). An estimated 70% of all TB cases are classified as pulmonary TB which affects primarily the lungs. Classic pulmonary TB symptoms include chronic productive cough, fever, weight loss, night sweats, loss of appetite and hemoptysis (bloody phlegm).[33] Extrapulmonary TB presentations can present in virtually any organ in the body, most commonly in the pleural space in the lining of the lungs (pleural TB), lymph nodes, kidney, joints, spine and brain.[33] Clinically, active TB symptoms can range from mild to severe and can result in death. Asymptomatic or subclinical

TB disease, without obvious clinical changes, is less frequent and of primary concern in HIV infected or immunosuppressed patients.[4,33]

2.2.2 Transmission and Pathogenesis

TB is spread by aerosol droplet transmission produced during coughing or breathing primarily from smear-positive (high bacillary load in sputum samples) pulmonary TB cases to other persons with whom they are in prolonged close contact.[34] Prolonged close contact is generally considered based on the proximity of persons to the infectious TB case, the duration of exposure and the environment of the contact (e.g. in enclosed rooms). Exposed persons may develop a latent TB infection (LTBI) which is an asymptomatic and dormant form of TB infection. In general, LTBI is not considered harmful; it cannot be transmitted and has no associated morbidity and the vast majority of LTBI cases will not progress to active TB disease in their lifetime (Figure 2.1)

TB pathogenesis is a complex process relying on the interaction between M.tbc and the human host immune response.[35] Following exposure to an infectious case of TB, the risk of progressing to active TB disease is considered highest within the first 18 months from infection, with an estimated 5% of initially infected persons progressing to active disease.[9] Of those with LTBI, an estimated 5% will progress to active TB at some point during the remainder of their lifetime (reactivation TB) (Figure 2.1). The varying responses to TB between human hosts and the overall immune response is still under completely understood, however several known risk factors are associated with a greater risk of progression to active TB including the following: HIV, diabetes, undernutrition or vitamin deficiencies, smoking, indoor air pollution, silicosis, alcohol, gender, age, renal failure, corticosteroid therapy and overcrowded living conditions.[33,36]

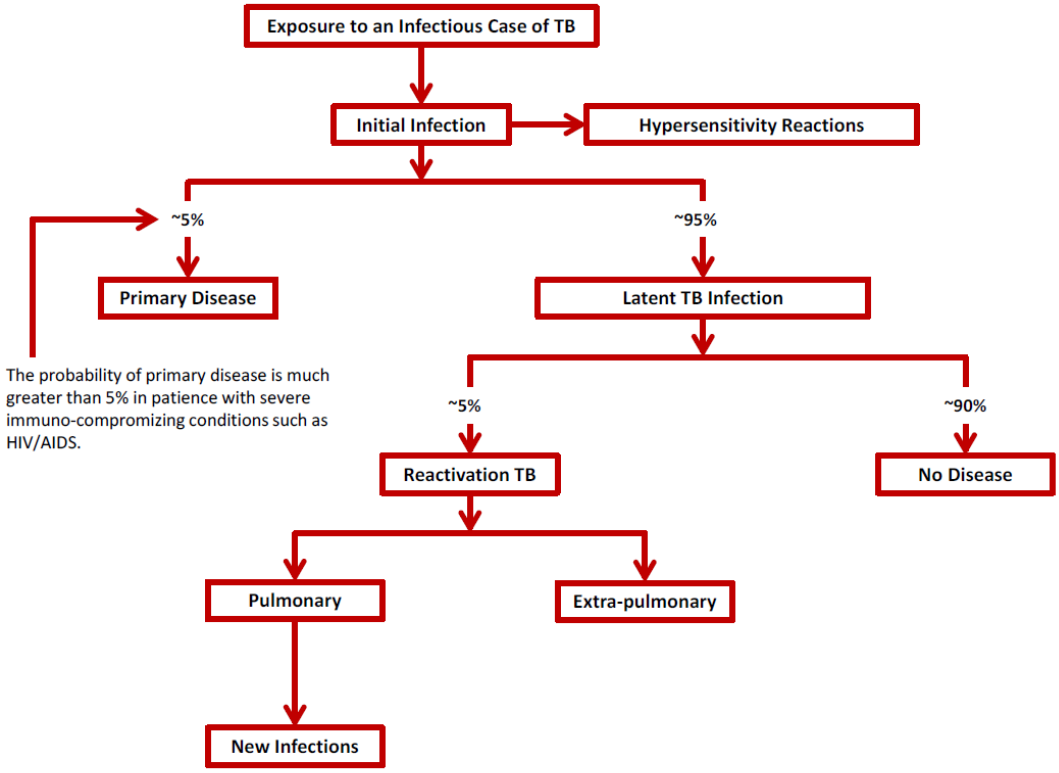


Figure 2.1: Pathogenesis of TB in the Human Host

(Source: Canadian TB Standards 6th Edition)[9]

2.2.3 Diagnosis of Active TB

Sputum smear microscopy followed by culture in liquid medium with drug susceptibility testing for first-line drugs is now considered a standard method for diagnosis of pulmonary TB.[4,37] In addition, chest radiography (X-Ray) and clinical evaluation play important roles in the suspicion and/or confirmation of both smear positive and smear negative pulmonary TB and extrapulmonary TB cases.[38] In recent years, more sensitive and rapid diagnostics are available and endorsed by the WHO for scale-up in LMICs, though most new diagnostic tests are relatively expensive and not yet universally used in TB endemic areas.[39,40]

Sputum smear microscopy

Sputum smear microscopy is a rapid, inexpensive and specific direct method used to detect acid-fast bacilli (AFB) from persons with active pulmonary TB. In brief, a person with a productive cough for greater than 15 days is asked to expel the sputum produced into a receptacle which is closed and labelled. The sputum is then tested by Ziehl-Neelsen (ZN) staining and observed under microscope. Despite its known lower sensitivity than other currently available methods, ZN sputum smear microscopy remains the cornerstone of diagnostic algorithms in local health centers as they are inexpensive, easy to perform in low resource settings and require minimal technical training.[41,42]

Infectiousness

The terms sputum smear positive and sputum smear negative are used within TB programs as a categorization of the quantity or load of acid fast bacilli (AFB) in sputum smear samples observed under microscopy. The bacillary load in sputum samples is considered a marker for infectiousness in active TB cases, such that TB cases with higher bacillary loads (AFB counts) are classified as sputum positive which may lead to more secondary infections and active TB cases amongst their contacts. Secondary cases of TB can be attributable to transmission from sputum smear negative cases, however sputum smear positivity are considered the main source of transmission in the community and remain the top priority for TB control programs in managing spread.[42–44] In addition to bacterial burden (smear positivity), the following factors are also considered important in estimating the probability of transmission from TB cases to other persons: cavitary and upper lung zone disease, laryngeal disease, amount and severity of cough in the source case, duration of exposure, proximity to the source case, crowding and poor room ventilation, delays in diagnosis and/or ineffective treatment.[9]

2.2.4 Tuberculosis Treatment

Standardized first-line anti-tuberculosis regimens include isoniazid (INH), rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA) for a minimum of 6 months (2 months daily intensive phase of all four drugs followed by 4 months continuation phase of INH and RIF typically two to three times weekly). For drug sensitive TB cases, this regimen is considered effective and inexpensive although the adherence and completion to an appropriate treatment first-line regimen is crucial to ensure high cure rates and to avoid the development of drug resistant TB strains. Many TB programs include a form of directly observed therapy which involves the direct observation, by a TB control program nurse, to ensure all doses of the treatment are consumed by the patients. Any patients who miss any of their treatments are actively followed up.

2.2.5 Directly Observed Therapy Short Course (DOTs)

The Directly Observed Therapy, Short Course, also commonly referred to as DOTS, is a core component of the WHO STOP TB Strategy. First introduced in the early 1990s, DOTS aims to provide a standardized approach to TB control and has been adopted in numerous national TB programs.[45,46] Initial mathematical models suggested that if DOTS programs were able to detect at least 70% of infectious cases and reach cure rates of 85%, declines 5 to 10% per year in TB would be achieved.[47] Globally, drug sensitive TB rates appear to be declining, albeit gradually and too slowly to meet the Millenium Development Goals.[48,49] Updated modeling studies and programmatic experience now suggest that vigorous improvements to case detection, beyond those currently within DOTS passive strategies, are essential to reach substantial reductions in TB incidence.[50,51]

Table 2.1: Basic components of DOTS strategy

(Source: World Health Organization (WHO))

a. Political commitment with increased and sustained financing
b. Case detection through quality-assured bacteriology
c. Standardized treatment, with supervision and patient support
d. Effective drug supply and management system
e. Monitoring and evaluation system, and impact measurement

2.2.6 Multidrug resistant TB

Multidrug resistant tuberculosis (MDR-TB), which is resistant to the two first line drugs INH and RIF, has emerged as a critical threat given that two of the most important first-line drugs are no longer adequate for treatment.[6,52] Acquired MDR-TB refers to patients with an initially drug sensitive strain who are exposed to inadequate or incomplete first-line treatment regimens and develop drug resistant TB strains. While second-line treatments are available, these are more costly, have longer regimens (minimum of 18 months), are more complicated to administer (including injectable drugs), and are associated with greater adverse reactions.[53] An added concern is the continued propagation of those who have acquired MDR-TB disease to others in the community.[54,55] Primary MDR-TB refers to newly diagnosed TB patients, with no history of TB treatment or previous TB episodes and suspected to have been infected with a strain resistant to at least INH and RIF. While MDR-TB represent a small proportion of the overall TB burden (3.5% of new TB cases[26]), the growing number of MDR-TB cases and

specifically the increasing proportion that are considered primary MDR-TB cases is an urgent priority to TB control programs globally.[56,57]

2.3 Case Finding

2.3.1 Passive case finding

Passive case finding refers to the current strategy within the WHO DOTS program. The program receives and diagnose persons with symptomatic TB who self-present for care.[1] Enhanced case finding refers to various modifications of the passive system, relying primarily on extensions of passive case finding, such as education or advertising or including incentives for presenting to clinics for evaluation.[22] Previously, passive case finding was considered sufficient for TB control programs in LMICs based on the assumption that symptomatic TB cases would eventually seek care and be captured by the health care system.

2.3.2 Active case finding for TB cases

Active case finding, also called intensified case finding, refers to strategies of actively searching for TB disease in a defined population, which require more intensive efforts on the part of health services, often involving screening endeavours outside of clinics.[21,22] Active case finding in LMICs refers to case finding strategies in defined populations which can range from community-based activities such as door-to-door campaigns, annual community-based surveys and mobile vans with screening services. More targeted case finding activities in specific high-risk groups include screening HIV patients and evaluation of household contacts with a known recent exposure to smear positive TB cases.[14,15,21,58,59] In contrast to passive case finding, active case finding implies a provider initiated effort to actively seek TB cases or those at-risk for having TB, outside of health facility settings. In particular, active case finding seeks TB suspects who may not self-present to health facilities in a timely manner. Currently, there is no

single standard approach to active case finding.[21] Depending on the setting, active case finding is used with various frequencies (adhoc, periodically (annual or bi-annual) or routinely (weekly or monthly)), using various diagnostic tests (smear microscopy, radiology, rapid diagnostic tests), and in different target populations (household contacts of TB cases, community wide screening programs).[14,60,61]

2.3.4 Active case finding literature

Mathematical modelling studies have suggested that active case finding may have benefits in high burden countries.[17,22,62] Borgdorff *et al (2002)*, in a review of the interventions to reduce tuberculosis mortality and transmission in LMICs, reported that active case-finding could potentially offer large benefits if cure rates were above 70% (and not below) and the impact of active case finding is influenced by the frequency of screening and the sensitivity of the screening method. A comprehensive historical examination of active case finding literature conducted in 2005, identified 106 primary studies from low-, middle- and high-income countries from the past 80 years which reported a wide range of active case finding strategies, and of which approximately 17 were conducted specifically in household contacts. The authors of the review specifically highlighted the gap in active case finding strategies undertaken in areas with DOTS programs with high cure rates in order to generate new evidence from active case finding interventions when there is availability of comprehensive treatment.[22] Overall, it appears that active case finding could contribute to improved case detection rates and in the prevention of deaths in addition to the benefits of passive case detection (Figure 2.2). However, in 2011, Fox *et al* carried out a systematic review of active case finding strategies in contacts of people with tuberculosis and reported that there was insufficient data from randomized controlled or quasi-randomized controlled trials to evaluate the effect of active case finding for TB among contacts of patients with confirmed TB disease in comparison to a

routine passive program.[21] The review identified only one RCT, which met inclusion criteria, though was not specifically aimed at measuring the effectiveness of active case finding alone.[16,63,64]

The systematic review did highlight a few landmark studies in active case finding endeavours. Amongst them, Corbett *et al* (2010), conducted a cluster RCT of a community based screening programme of symptomatic individuals, comparing active case finding at 6 month intervals using a mobile van to active case finding using door-to-door strategies the suburbs of Harare, Zimbabwe.[58] The mobile van strategy detected almost twice as many active TB cases and active case finding had an impact in reducing the overall prevalence from 6.5 per 1000 to 3.7 per 1000 persons in the area. Though this strategy did not consider the baseline routine case finding program as a comparator, nor direct exposure to a known TB case, it highlighted the role of community wide strategies to active case finding in a given geographic area.

Since Fox *et al* (2011) published their systematic review, a few additional studies have emerged which use a cluster randomized trial design, are conducted within a National TB program, and use routine passive case finding a comparator.[65,66] Fox *et al*., published their research protocol published describing a cluster RCT of an active screening program, in Hanoi, Vietnam, across 70 district in 8 provinces (rural and urban) where the intervention arm includes the evaluation of all household contacts of patients with smear-positive pulmonary tuberculosis on four occasions over a two-year period.[66] Eang *et al.* (2012) reported on a cluster randomized trial of active case finding amongst contacts and neighbourhood contacts of TB patients in Cambodia. Active case finding detected slightly fewer patients, these were significantly more likely to be

older patients and overall the active case finding strategy was found to be a cost-effective strategy compared to passive case finding alone.

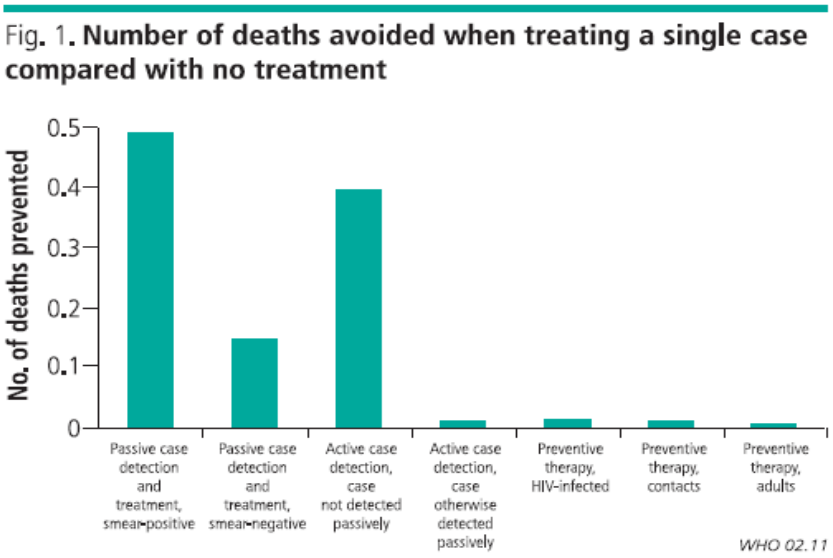


Figure 2.2: Number of deaths avoided when treating a single case with passive case detection and active case detection[67]

2.3.5 TB case detection in household contacts

A conventional contact investigation involves systematically identifying those individuals exposed to infectious (primarily smear-positive) TB cases, evaluating these contacts for recent latent M. tbc infection or active TB disease, and treating them immediately to interrupt further transmission.[68,69] Household contacts of smear-positive TB patients are at greatest risk for acquiring M. tbc infection and disease because of their duration and proximity of contact in enclosed spaces.[68,70,71] In 2008, a systematic review and meta-analysis of contacts of active and LTBI cases in low- and middle-income countries (LMICs) found that the yield of active TB was 4.5% (95%CI 4.3-4.8) and latent TB infection 51.4% (95%CI 50.6-52.2) of all household contacts

investigated.[13] In 2011, an updated systematic review and meta-analysis commissioned by the World Health Organization Expert Panel found a prevalence of active TB among household contacts was 3.1% (95% CI 2.1-4.5).

Amongst observational studies, Bayona *et al.* (2003), evaluated household contacts of MDR and XDR-TB and found secondary TB cases in 8% of close contacts over a 4-year period, which was estimated as a risk of 1300 per 100,000 person-years of contact follow-up at the time of the publication.[19,20] In Lima, Becerra *et al.* (2005) found almost 9 times more active TB cases in a cross-sectional screening of households of all TB cases in comparison to passive case finding.[15] Calvalcante *et al.* (2010) conducted a cluster randomized trial of active case finding in Brazil and reported a greater reduction in overall TB incidence in 5 years when compared with the passive DOTS program.[16] These studies highlight both the risk of household contacts as secondary TB cases and the need for active case finding amongst household contacts to improve TB case detection. Nevertheless, the large majority of studies have been observational, with only a few trials with a randomized or quasi-randomized design that have been published. [65,72] Additionally, even fewer studies have measured the effectiveness of active case finding for household contacts within the routine context of the current TB control program in comparison to the current DOTS passive case finding strategy.[21]

The existing research on screening household contacts or active case finding in LMICs use dedicated research teams that run in parallel to the routine TB program. Evidence generated from operational research studies is needed to understand the feasibility and effectiveness of active case finding for household contacts within established DOTS programs. Concern regarding undetected cases circulating in the community have prompted many TB control

programs in endemic countries to consider aggressively seeking TB cases outside of the clinic setting.[15,58,73–75] However, in addition to effectiveness and operational issue, very few if any existing studies have reported the operational costs or cost-effectiveness of any active case finding activities.

2.3.6 Cost-effectiveness of TB case finding

Cost-effectiveness analysis (CEA) is a tool increasingly used in health care and public health to support evidence-based decision-making.[76] The approach compares relative costs and effects (or outcomes) of two or more strategies. These strategies can range from clinical interventions, for example, comparing Drug A to Drug B, or comparing a new screening strategy with the standard of care. The referent or baseline comparator can be any comparator of interest and often this is the routine standard of care currently in use and the purpose is to understand whether the introduction of a new strategy is considered cost effective.

Cost-effectiveness analysis is a crucial component of decision-making for program and policy makers to assess the allocation of resources.[22] In low TB burden settings, active case finding amongst close contacts of active cases is considered cost-effective, as is the evaluation of latent TB infection (LTBI).[13] In contrast, in TB endemic settings the cost-effectiveness of screening for LTBI is considered limited due to higher LTBI prevalence, low predictive value of latent TB infection tests, lack of adherence to prophylactic regimens and the number of infected contacts that require to be treated to prevent a single case of TB.[15,77]

Data on cost-effectiveness for active TB case finding in TB endemic settings and on case finding for high-risk contacts are limited, despite current recommendations of intensified case

finding of high-risk contacts.[78–80] A systematic review of intensified case finding for TB in HIV-positive patients and their household contacts found that none of the 78 studies they identified reported cost or cost-effectiveness data.[81,82] Generally, active case finding is considered more resource intensive than passive case finding of TB, with the added operational costs, the number needed to screen to detect a single case, and the additional burden on laboratories.[83] To date, only very few of the active case finding studies of evaluating household contacts in high burden, low resource settings have included cost-effectiveness analyses and particularly, the incremental cost-effectiveness ratio comparing case finding methods.[65,84]

Active case finding necessarily involves added costs to the system, therefore understanding the cost-effectiveness around this strategy is needed. In 2014, modelled estimates reported active case finding in India, China and South Africa was considered highly cost-effective in short term and longer term models, even if costs were over US $1,000 to detect and treat and active TB case.[85] Yadav *et al* compared an active case finding strategy to a routine passive case finding program in Cambodia (a TB endemic country with relatively low HIV prevalence). The authors reported that a reduction in mortality from 14% to 2% would result in a cost per DALY averted of $330, and found overall that an active case finding program is highly cost-effective.[65]

2.4. World Health Organization Contact Tracing Recommendations

In 2012, the WHO released comprehensive guidelines on the evaluation of household contacts in LMICs. These guidelines were prompted by numerous requests from managers of many national TB programs from LMICs in order guide national TB strategies.[12] Prior to these

guidelines, routine evaluation of household contact of all smear-positive pulmonary TB was not considered as part of a core component of a DOTS program.

The WHO recommended the following new guideline:

Recommendation 1

It is recommended that contact investigation be conducted for household and close contacts when the index case has any of the following characteristics:

- has sputum smear-positive pulmonary TB,
- has multi-drug-resistant TB (MDR-TB or extremely-resistant TB (XDR-TB) (proven or suspected),
- is a person living with HIV or • is a child <5 years of age

Although the WHO reported to having made this important recommendation based on decades of knowledge of TB control programs from high-income countries, they also reported the existence of "very low-quality evidence" to support this recommendation and the need to generate further evidence specifically from operational studies and from LMICs.[12]

2.5 Study Setting

2.5.1 Peruvian National TB Program

Peru has one of the highest TB rates in the Americas and has a long standing history of DOTS programming that consistently meet WHO operational standards.[22] Since the early 1990s, TB DOTS have been widely implemented across all government health care centers in all districts in the country. Currently, the National TB Program (NTP) is overseen by the Ministry of Health of Peru (Ministerio de Salud del Perú, (MINSA). The NTP is responsible for National Guidelines and provision of public health indicators reported to the WHO, including clinical, public health and laboratory surveillance data. Peru is considered one of the successful

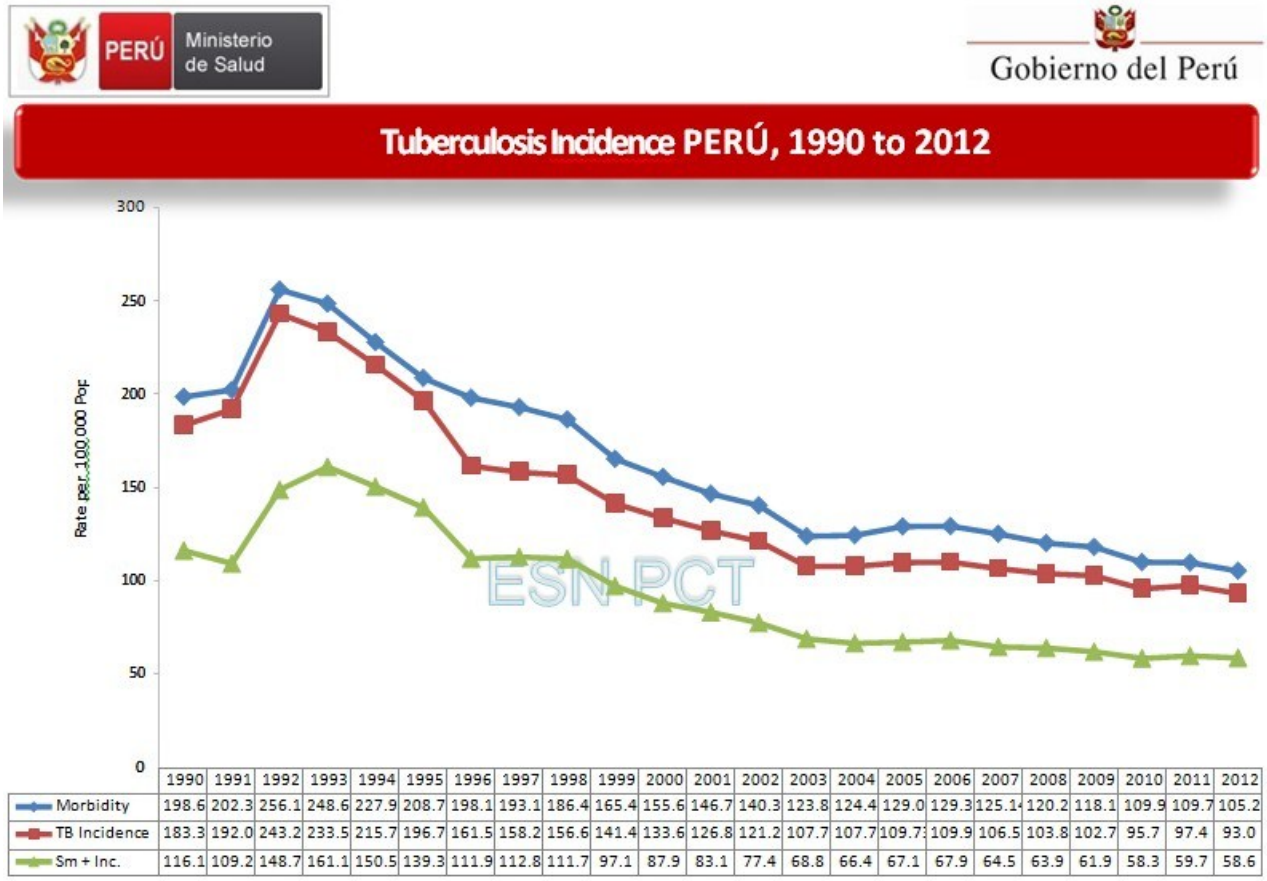
examples by the WHO in their ability to scale-up DOTS and to consistently meet the performance indicators, such as high TB treatment cure rates.

2.5.2 DOTS in Peru

DOTS refers to both a TB treatment program (including the direct observation of short-course therapy for treatment) and the first component of WHO's global STOP TB control strategy adopted by many NTPs globally, including in Peru. Since the early 1990s Peru has had a well performing DOTS program that has consistently met and surpassed WHO operational performance indicator targets, including the ≥ 85% cure of detected cases. Despite high-quality DOTS, the goal of TB elimination in Peru remains elusive. In addition to new diagnostics, therapeutics and the current passive detection of TB cases using sputum microscopy, improving the routine evaluation of household contacts of TB cases is considered a priority. Gradually incidence rates of pulmonary TB are estimated to have decreased by almost 6% annually due to high cure rate and case detection rates. Additionally, an estimated 70% of deaths were averted and attributed to the success of the DOTS program between 1991 and 2000.[86]

Conversely, DOTS in Peru is subject to limitations. While overall TB rates are declining, the rates are not declining quickly enough to meet elimination targets. Overall national incidence rates are decreasing, although there are high risk areas in Lima where TB rates are four times higher than that of the national average (400 per 100,000 in select sub districts of Lima).[87] MDR-TB has emerged as a major issue in Peru, reporting amongst the highest MDR-TB rates globally (approximately 5% of all new TB cases are MDR-TB). There are multiple hypotheses as to why MDR-TB has emerged and why rates of primary MDR-TB are on the rise within a

well-functioning DOTS program, primarily related to inadequate 1st line treatment regimens and delays to initiating appropriate treatment.[88]



	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Morbidity	198.6	202.3	256.1	248.6	227.9	208.7	198.1	193.1	186.4	165.4	155.6	146.7	140.3	123.8	124.4	129.0	129.3	125.1	120.2	118.1	109.9	109.7	105.2
TB Incidence	183.3	192.0	243.2	233.5	215.7	196.7	161.5	158.2	156.6	141.4	133.6	126.8	121.2	107.7	107.7	109.7	109.9	106.5	103.8	102.7	95.7	97.4	93.0
Sm + Inc.	116.1	109.2	148.7	161.1	150.5	139.3	111.9	112.8	111.7	97.1	87.9	83.1	77.4	68.8	66.4	67.1	67.9	64.5	63.9	61.9	58.3	59.7	58.6

Figure 2.3 TB incidence in Peru from 1990 to 2012, Ministry of Health of Peru data[89]

2.5.3 Current routine program status

Identification of TB cases hinges on the identification of persons suspected of having TB. In addition to sputum smear microscopy, radiography and clinical evaluation, symptom screening is considered a primary tool for TB case detection programs and is considered to be efficient and of high yield for TB detection in settings where resources are limited.[90] In the Peruvian NTP, the cornerstone for diagnosing pulmonary TB is cough of greater than 14 days duration.

In SJL district of Lima, Otero *et al.* (2010) found a smear positivity rate of 12.4% among all patients presenting to clinics with cough greater than 14 days, while those presenting with less than 14 days cough had a significantly lower smear positivity rate of 3.2%.[14,22,91–93]

2.5.3 District of San Juan de Lurigancho (SJL)

The proposed doctoral research will be undertaken in the district of San Juan de Lurigancho (SJL) in Lima, Peru, the most densely populated and the largest district of Eastern Lima. The 2007 Peruvian Census estimated SJL's population to be 900,000.[94] In 2010, over 1,800 new cases of TB were notified across the district clinics.[1] The Peruvian Ministry of Health operates the DOTS program through the district level (DISA) National TB Control Programs (NTP) in 34 health care facilities within the district (20 community health stepped-wedges (CHCs), 14 health posts) and one large central hospital.[95] Each DISA NTP site has a designated TB program office with a dedicated room where TB medication, follow-up visits, management of data and records, and counseling occur. The district has a successfully run DOTS TB treatment program with an overall cure rate of 92% rate and a case detection rate of 93%, which is based on passive case detection.[87] Unlike the TB epidemic in Sub-Saharan Africa, HIV is not considered the primary driver of the TB epidemic in Peru as the HIV rates among TB cases are <3%.[96] In Peru, the most densely populated and poorest districts of Lima are those with the highest TB burden. SJL has one of the highest TB burdens in all of Peru (incidence rate of 170 per 100,000 and up to 400 per 100,000 in high risk areas).[87,89] Low socioeconomic status (SES) including poor living and working conditions, crowding and poor ventilation are all considered risk factors for TB infection.[87]

Currently, active evaluation of all household contacts for active TB is a recommended component of the routine TB program in Peru, although it is rarely undertaken. The routine public health system in the district does involve the passive report of household contacts for care, whereby household contacts of TB cases are encouraged to present for screening. However, in 2010 in SJL district, less than 60% of household contacts presented for evaluation to district clinics.[87] The proportion of household contacts that are in fact evaluated in the passive case finding strategy is likely lower than the reported 60%, given the omission of missing data when there have been no contacts identified or evaluated (null reports) from the official indicator on household contacts.

The cost-effectiveness of active case finding for household contacts as part of the routine TB program has not been examined in LMICs and has not been undertaken previously in Peru. Several cross sectional and cohort studies in Peru have resulted in recommendations for the expansion of case finding for household contacts in Peru, although the cost-effectiveness remains a critical need for local decision makers and practitioners.[15,19,20]

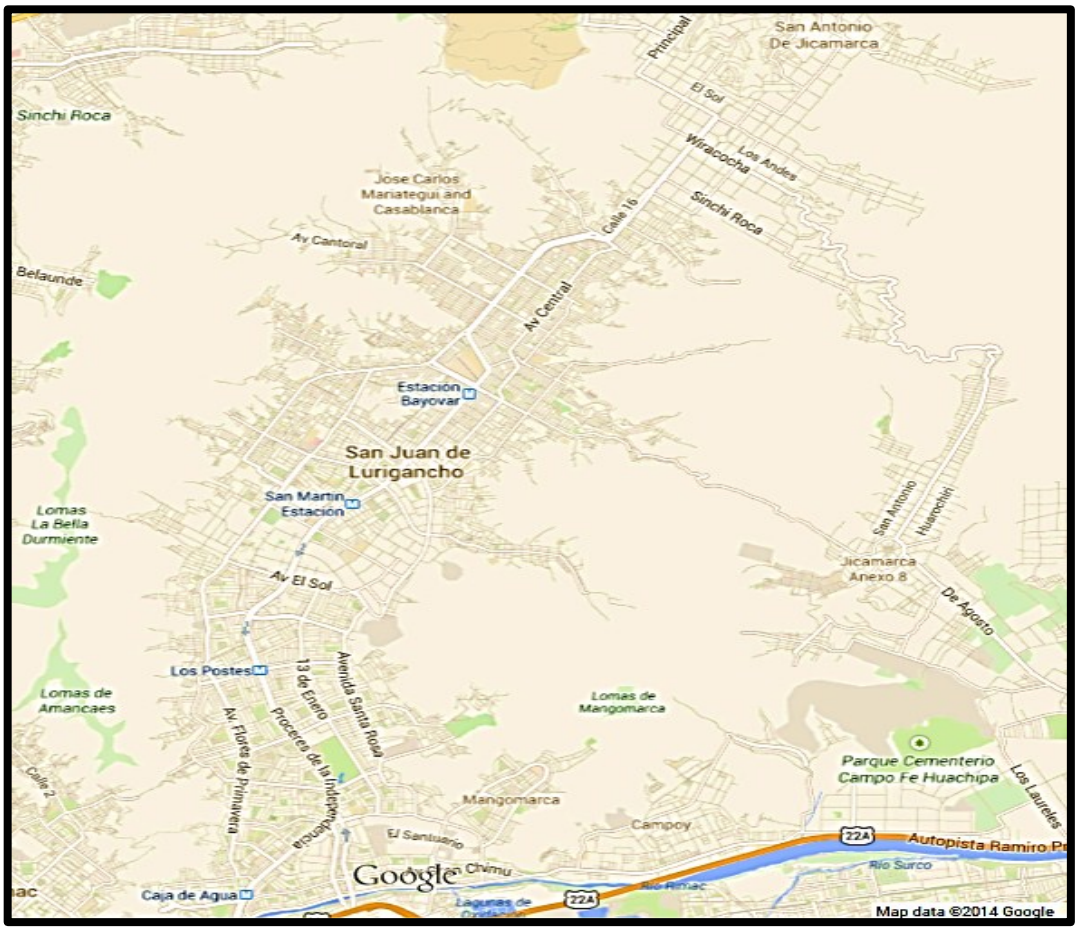


Figure 2.4: Map of San Juan de Lurigancho District, Lima, Peru (Source: GoogleMaps)

2.6 Summary of Thesis Rationale

In high-income countries, each case of TB is treated with priority and investigated thoroughly, where resources are available.[9,79,97] In addition to overseeing adherence to treatment, extensive contact tracing efforts are often undertaken amongst close contacts and, where necessary, extended to casual contacts. Location-based screening is also considered depending upon the understanding of transmission surrounding a given case of TB. This includes households, workplaces, social venues, and in institutions where cases have occurred, for example shelters, schools, hospitals or prisons.

Conversely, in the majority of LMIC with TB endemic areas, TB control program activities are primarily limited to TB case management through the DOTS strategy once the cases have been passively detected. This approach is dependent upon the assumption that symptomatic patients will eventually self-report to health clinics and will be detected through clinical diagnosis, sputum smear microscopy and enrolled into TB treatment. Numerous studies have shown that this approach alone is unlikely to stop TB transmission in the community and also unlikely to significantly affect the rate of TB decline.[46,98–100] In spite of the technological advances of new rapid diagnostics with greater sensitivity, quickly identifying TB cases in the community is now considered key to achieve TB elimination goals.[12] There remains a substantial gap in published literature in the evaluation of the effectiveness of case finding within community and amongst household contacts that occurs within routine DOTS programs in LMICs.

CHAPTER 3 : Geographic predictors of primary multidrug-resistant tuberculosis cases in an endemic area of Lima, Peru

3.1 Preface

MDR-TB is a growing concern worldwide and its ongoing spread from person-to-person in the community is an urgent priority due to the resources required to manage and treat a case of MDR-TB. There are also concerns regarding the lower cure rates among MDR-TB patients, longer treatment regimens and higher number adverse events under treatment then for DS-TB treatment. Given this, targeted interventions for primary MDR-TB are of urgent concern for national TB programs. The identification of focal 'hotspots' associated with more drug resistant cases is considered an important priority to better understand transmission and also to identify areas to target urgent case detection methods.[101] In SJL, the common risk factors of primary MDR-TB, such as drug use, imprisonment or previous TB treatment are not present suggesting that the spread may be occurring more widely in the community.[56] In SJL, primary MDR-TB cases have been found to have differing epidemiologic risk factors to that of DS-TB and acquired MDR-TB cases.[87,102]

The first manuscript of this thesis examines clustering of primary MDR-TB cases in the district in order to identify priority areas for active case finding of TB cases in the community. We present geographic analyses in order to examine the hypotheses that primary MDR-TB cases cluster within certain areas of the district, and potentially around key *apriori* selected central locations.

3.2 Manuscript: Geographic Predictors of Primary Multidrug Resistant Tuberculosis Cases in an Endemic Area of Lima, Peru

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This manuscript has been published in the International Journal of Tuberculosis and Lung Disease (IJTLD)(Published Nov, 2014)[103]

SUMMARY ABSTRACT

Setting: Peru reports amongst the highest multidrug resistant tuberculosis (MDR-TB) rates in the Americas, with a growing proportion of MDR-TB or resistant strains in previously untreated tuberculosis (TB) cases.

Objective: Identifying clusters of primary MDR-TB, compared with drug susceptible tuberculosis (DS-TB), could help prioritize public health interventions. We examined the clustering of primary MDR-TB case residences and their proximity to high risk locations in San Juan de Lurigancho district, Lima, Peru.

Design: Enrolled primary MDR-TB and primary DS-TB cases were interviewed and their primary residence at the time of diagnosis was recorded using handheld GPS devices. Kuldorff's spatial scan statistic was used for cluster detection (SaTScan™v9.1.1). Identified clusters were visualized in QGIS (v1.8.0). The following *a priori* selected cluster centers were tested: a health center with the highest TB and MDR-TB rates (Clinic X), a hospital and two prisons. Regression analyses examined predictors of primary MDR-TB cases compared with DS-TB cases.

Results: A statistically significant cluster of primary MDR-TB cases was identified within a 2.29 km radius around Clinic X. Proximity to Clinic X remained a significant predictor of primary MDR-TB in adjusted regression analyses.

Conclusion: We identified a "hotspot" of primary MDR-TB cases around Clinic X in a TB endemic area. Causes of this clustering require investigation, however targeted interventions to this high risk area should be considered.

INTRODUCTION

The emergence of multidrug-resistant tuberculosis (MDR-TB) strains, resistant to first-line drugs isoniazid (INH) and rifampicin (RIF), is a major threat to tuberculosis (TB) control worldwide. The World Health Organization (WHO) Standardized Directly Observed Treatment Short-Course strategy aims to prevent the development of MDR strains in drug-sensitive tuberculosis (DS-TB) patients entering treatment.[55,104,105] Once acquired, the propagation of MDR-TB in the community is not easily managed by TB programs. As a result, primary MDR-TB, or resistant strains in new untreated TB cases, now represents an increasing majority of all MDR-TB cases globally, both in human immunodeficiency virus (HIV)-positive and HIV-negative TB endemic populations.[106] The focused investigation of primary MDR-TB cases examines the community transmission of drug resistant strains.

Peru consistently meets WHO performance indicators for treatment completion with standardized first-line regimens, but is still a global "hotspot" of MDR-TB transmission.[106,107] In 2012, 5% of all reported TB cases in Peru were MDR-TB, of which approximately 40% were primary MDR-TB.[106] Further, household and workplace exposure to TB or MDR-TB cases were found to predict primary MDR-TB even compared to DS-TB, suggesting that transmission of primary MDR-TB is occurring in the community and no longer restricted to high risk populations, such as prisoners, drug users or the homeless.[102]

Within TB endemic districts of Lima, identifying local clustering or MDR-TB hotspots could help focus intervention efforts. Spatiotemporal analysis from 4 districts of Eastern Lima between 2005-2007 found an aggregation of MDR cases specifically due to increased clustering

of primary MDR-TB disease.[108] We examined geographic clustering and predictors of primary MDR-TB within the district of San Juan de Lurigancho (SJL), Lima.

MATERIALS AND METHODS

SJL district is one of the poorest and most densely populated urban areas of Lima (Pop.density:8,400/km^2), with amongst the highest TB and MDR-TB burden in Peru (2012 TB incidence:187 per 100,000,7% of new cases are MDR-TB).[89,109,110] DS-TB and MDR-TB case data were assembled from two mutually exclusive research studies recruited from all existing Ministry of Health National TB Program (NTP) designated areas in SJL district's 33 primary health centers and one hospital.

Enrolment

Eligible NTP patients were recruited by study personnel and informed written consent obtained from all study participants. Demographic and socioeconomic data were collected in structured questionnaires. Study personnel used handheld Global Positioning System (GPS) devices to record the latitude, longitude and altitude at the front entrance of each case residence located.

1245 TB cases were included from a population based cohort study conducted in the district clinics between May 2004 and March 2006 (Study A).[111,112] An additional 140 TB cases were included from a case-control study April to August 2008 from the same district clinics (Study B).[102] MDR-TB and DS-TB patients were acid fast bacilli (AFB) smear-positive pulmonary TB patients, ≥18 years old, and enrolled in treatment with the NTP of a SJL health center. At the time of the original studies, the NTP did not routinely perform sputum culture and drug susceptibility testing (DST), therefore DS-TB was defined as TB patients who became AFB

smear-negative within 2 months of a standard first-line TB treatment regimen and no report of relapse or failure at the time of interview. In Study A, all consecutive NTP registered DS-TB cases were eligible for enrollment in the study and DS-TB cases were further confirmed with research study DST results to INH, RIF, ethambutol and streptomycin. In Study B, a random sample of all NTP registered DS-TB cases were selected from a database representative of all cases across SJL district and their medical records reviewed for eligibility.

MDR-TB cases were defined as AFB smear-positive patients with laboratory proven resistance to first line drugs INH and RIF. All consecutive MDR-TB patients were considered eligible for participation in the study. Primary cases were defined as newly diagnosed cases without history of previous anti-tuberculosis treatment. In Study A, primary MDR-TB cases was additionally considered if treatment history was greater than 5 years prior to the current episode. Mono-resistant (resistant to only one of the tested first-line drugs and not meeting the MDR-TB definition), pan-resistant (resistant to all tested first line drugs) and extensively drug resistant cases (XDR-TB) were excluded in baseline analyses. In sensitivity analyses, patients with mono-resistant TB were added to the DS-TB group, while pan-resistant and XDR-TB patients were combined with MDR-TB cases.

Spatial Analysis

Kulldorff's spatial scan statistic (SaTScan™,v9.1.1) was used to detect clusters of primary MDR-TB cases compared with DS-TB cases, using a Bernoulli model and a standard circular scanning window.[113,114] An unfocused scan tested each case as a centerpoint, while a focused scan used a selected location as the centerpoint around which it scanned for potential clusters. A focused spatial scan around the following SJL locations reporting the highest TB rates in the

area were tested: a central large hospital (Hospital A), a health center with the highest TB rate (Clinic X), and 2 large prisons (Prisons A and B). SaTScan increases the likelihood ratio required for reaching a *p value*<0.05 as multiple scans are conducted. SaTScan cluster detection results were visualized in QGIS software (v1.8.0).

Logistic regression analysis examined geographic and demographic predictors (Tables 1 and 2) of primary MDR-TB compared with DS-TB (Table 3). The Euclidean distance (in kilometers) between patient residences to high TB rate locations of interest were included in analysis, as was the main district roadway and elevation of case homes (in meters from sea-level) and all individual level variables (Table 1). The adjusted regression model included variables significant at p=0.20 in bivariate analyses and forward selection was used to build the final model. Statistical analyses were performed in R statistical software.[115]

Ethical Statement

Ethical approvals were granted by the Human Ethics Research Boards of the McGill University Health Center (Montreal, Quebec, Canada), University of Alabama at Birmingham (Birmingham, Alabama, United States of America), Universidad Peruana Cayetano Heredia (Lima, Peru) and Direccion de Salud Lima IV Este (Lima, Peru).

RESULTS

Of 1385 patients, the following patients were excluded from analysis: 210 cases with missing DST results, 206 cases with mono-resistance to one first-line drug (non-MDR), 4 XDR-TB cases, 37 non-primary MDR-TB cases and 12 DS-TB reporting TB treatment within the past 5 years and 62 cases missing GPS data (Figure 3.1). The final study dataset contained 104

primary MDR-TB cases and 750 DS-TB cases. The mean age of cases included was 30.6 years and 58.4% were male, 50% unmarried, and 58.9% cohabiting with greater than 5 persons. Nearly half of participants reported no formal employment at the time of diagnosis, 60% of all participants earned less than 50 US Dollars per month and less than 5% reported ever having been to prison (Table 3.1).

Case residences were distributed across the district, with a third each of participants living within 2 km, 2-4 km away and greater than 4 km away from the high incidence area comprised of Clinic X with the highest TB rate in the district and the nearby hospital (Hospital A). The vast majority of participants (94.4%) lived within 2 km of the major roadway that crosses the entire length of the district and less than 20% of participants lived within 2 km of one of the large prisons located in the district (Table 3.2)

In SaTScan analysis of clustering around Hospital A, Clinic X, Prisons A and B, a significant cluster of primary MDR-TB cases compared with DS-TB cases was detected around Clinic X (radius=2.29km,p=0.037 Figure 3.2 : Location Map of Primary MDR-TB cases, DS-TB Cases, High TB rate locations of interest and significant cluster zone in San Juan de Lurigancho district. (Figure 3.2)). In the unfocussed SaTScan analysis, the largest cluster identified was comprised of 56 primary MDR-TB cases and nearest to the location of Clinic X, although due to adjustments for multiple testing this did not reach statistical significance (p=0.183).

In bivariate analyses, primary MDR-TB cases were significantly more likely than DS-TB cases to be younger than 35 years old, living within 2 km of both Clinic X and Hospital A and earn 51-100 US Dollars compared with those earning less than 50 US Dollars per month (Table 3.3).

Neither elevation, nor distance of residence to main roadway or to either prison was significantly associated with primary MDR-TB compared with DS-TB. In the final model adjusted for age and sex (Table 3.4), patients living within 2 km of Clinic X had twice the odds of primary MDR-TB compared with patients living greater than 4 km from this center (AOR:2.10, 95%CI[1.29-3.51]) (Table 3.4). In sensitivity analysis, the strength of the association between living near Clinic X and primary MDR-TB remained when poly-resistant cases were included along with MDR-TB cases and compared with DS-TB patients including mono-resistance to first-line drugs plus or minus streptomycin.

DISCUSSION

We detected a significant clustering of primary MDR-TB cases in the 2 km area surrounding Clinic X in the Northern part of SJL district by focused spatial scan statistics and logistic regression models (cluster radius=2.29 km, p=0.037(Figure 2),(AOR:2.10, 95%CI[1.29-3.51])(Table 3.4). Clinic X was selected *a priori* for analysis because of TB and MDR-TB rates nearly 4 times the national and local SJL district TB incidence.

The observed clustering of primary MDR-TB might be explained by several hypotheses. Firstly, nosocomial exposure of visiting non-infected patients to MDR-TB within Clinic X could explain the clustering of cases. There is no evidence that Clinic X was specifically located due to high TB and MDR-TB rates in the area, rather primary health facility placements are based on population density. In general, SJL health centers are well-ventilated, including open air waiting rooms (without roof covering or with open doors and windows to facilitate air flow) and NTP consultation rooms are physically separated from general

admission, which should potentially reduce transmission within health center.[116] The approximately 2 km radius surrounding Clinic X encompasses a significant portion of the catchment areas of at least eight distinct neighbouring health centers (denoted as a shaded zone in Figure 3) and TB patients must attend the health center of their primary residence, suggesting that primary MDR-TB is not limited to contact with Clinic X alone. Nonetheless, infection control practices such as wearing masks and isolation of infectious TB and MDR-TB patients should remain a priority.

In the community, primary MDR-TB cases have been significantly associated with higher self-reported exposures to TB cases in the household and the workplace than even DS-TB cases.[102] In Lima, a large proportion of secondary cases in households of MDR-TB also had MDR-TB and a DST that matched the index case.[20] Housing and neighborhood characteristics such as poverty and crowding have long been associated with clustering of TB cases, and in our data this result appears consistent for DS-TB patients.[117–119] However, we found primary MDR-TB cases were significantly more likely to be living with fewer than 2 people at the time of diagnosis. Further investigation is needed to understand the role that population density and household crowding has in the spread of primary MDR-TB in SJL.

Social mixing outside of households, such as in bars, cafes, schools and workplaces, has an important role in TB transmission.[120,121] Community socializing could contribute to the high rates of primary MDR-TB around Clinic X which treats mobile patients. As prisoners do not have the same mobility, this could potentially explain lack of cases clustered near the prisons. Of note, in these data, primary MDR-TB cases were significantly younger than DS-TB cases

which could signal social networks of younger primary MDR-TB cases or venues frequented by younger persons in the community.[122,123]

In addition, biological, social and environmental factors could also explain the clustering of primary MDR-TB around Clinic X, though further data confirming these hypotheses are needed.[124,125] While detailed strain typing was unavailable, the strain virulence could be a consideration, as could host characteristics of the population in the area.[126] HIV co-infection rates in SJL are relatively low (1.3%, personal communication Larissa Otero) and not considered the primary driver of MDR-TB in this area. On the other hand, human T-lymphotropic virus type 1 (HTLV-1) patients in this population have high rates of TB co-infection and are associated with higher grade AFB on sputum smear suggesting higher infectiousness.[127] Though HTLV-1 rates in SJL´s primary MDR-TB cases remains unknown, the district receives migration from known HTLV-1 endemic Andean regions.[127,128] Finally, environmental factors such as humidity, population density and crowding all favour TB transmission, and along with air quality studies require further investigation among primary MDR-TB cases in SJL.[119,129]

No clustering of primary MDR-TB cases was detected around district prisons, where TB is in epidemic proportions, suggesting that living nearer to the prison is not a risk for primary MDR-TB. Nor was any clustering detected along the main roadway, which was a proxy measure for the use of mass public transport (such as buses and collective mini buses) previously associated with risk of TB transmission in Lima.[130] However, in our study population, over 90% of patients lived within 2 km of the roadway, and only 5% of patients lived near the prison limiting these analyses.

Our findings are subject to limitations. Selection of primary MDR-TB cases from certain areas of the district would have biased recruitment to the original studies, however all MDR-TB cases across the district were sought for study inclusion and were no different than DS-TB cases in the length of time living in the district or in their current household.[102] We limited analyses to purely spatial cluster analysis using Kulldorff's spatial scan statistic, a common approach to identifying disease clusters (or hot spots). While the statistic considered geography, it did not account for variation in times of infection or patients' dates of symptom onset, therefore it is possible that TB cases that cluster geographically are epidemiologically unrelated.

SaTScan adjusts the likelihood ratio for *p* values for the multiple scans it conducts to avoid falsely detecting clusters (false positives). A drawback of this conservative approach is that the likelihood required to be statistically significant increases as more data are included, resulting in a loss of power. Therefore, if many scans are conducted, there is a chance that even a sizeable cluster could be missed (Type II error or false negative).[131] This adjustment may explain the large cluster which in an unfocussed scan including 105 primary MDR-TB cases (therefore 105 tests), did not reach statistical significance, though was significant during specific *a priori* defined focused scans. Finally, genotyping data were unavailable to determine if cases represent a single primary MDR-TB strain from a single common source or widespread community transmission of various strains. Strain type data would provide additional valuable information, however even in the absence of genotyping information it is possible to undertake important public health actions based on these epidemiologic and geographic data.

We identified a "hotspot" or cluster of primary MDR-TB which could help target interventions, such as preventing nosocomial spread of MDR-TB, evaluation and monitoring of close contacts of patients with MDR-TB and active case detection using both intramural and extramural strategies.[37,132,133] While further investigation could identify causes for the clustering of primary MDR-TB cases, prioritizing and ensuring active prevention efforts in the 2 km surrounding Clinic X could be a first step towards controlling MDR-TB in the district.

ACKNOWLEDGEMENTS

Funding Sources

The data and analysis included in this manuscript were supported by funding from the Canadian Institutes of Health Research (CIHR), the Royal Victoria Foundation, the Gorgas Memorial Foundation Career Development Research Grant Award. The authors wish to thank the ongoing collaboration and cooperation of the Direccion de Salud Lima IV Este and the Red de Salud de San Juan de Lurigancho (Ministry of Health, Peru). Lena Shah was supported by a CIHR Frederick Banting and Charles Best Doctoral Research Fellowship, a CIHR Michael Smith Travel awards and the International Development Research Center (IDRC) Doctoral Award.

Author Contributions

HC, FK, CZ and GH coordinated data collection and supervision of the field aspects of the project. EGH; TFB, CS, GH and S.J.H. designed and wrote the original studies included in this manuscript and advised on the current analysis. LS, LBF and TFB devised the analysis plan. JK and SJH advised on the analysis plan. JK and AC advised the statistical analysis. LS, JK and TFB oversaw the writing of the current manuscript. EGH, HC, FK, CS and SJH reviewed drafts of and edited the manuscript.

Conflicts of Interest

None declared.

Table 3.1: Study Population Demographic Characteristics

	Frequencies Total n=854	%
AGE		
Age (mean,sd)	30.6 [s.d.11]	Range (18, 73)
Age (median)	27.5	
SEX		
Female	355	41.6
Male	499	58.4
CIVIL STATUS		
Single	427	50.0
Co-Habiting	248	29.0
Married	107	12.5
Divorced	63	7.4
Widowed	9	10.0
HOUSING STATUS		
Rented	126	14.8
Family Home	351	41.1
Owns	367	43.0
*Invasion or Squatters**	9	1.0
Missing	1	0.1
NUMBER OF ROOMS IN DWELLING		
0-2 rooms	233	27.3
3-4 rooms	279	32.4
5+ rooms	341	40.0
Missing	1	0.3
NUMBER OF PERSONS LIVING IN DWELLING		
0-2 persons	96	15.1
-4 persons	209	26.0
5+ persons	549	58.9
MPRISONED PRIOR TO DIAGNOSIS		
No	806	94.4
Yes	47	5.5
Missing	1	0.1
WORK STATUS AT THE TIME OF DIAGNOSIS		
Employed	352	41.1
Unemployed	424	49.6
Student	73	8.5
Retired	4	0.5
Missing	1	0.1
INCOME (monthly in USD)		
0-50 USD	525	61.5
51-100 USD	128	15.0
101 -300 USD	166	19.5
301+ USD	32	3.7
Missing	3	0.3

*Refers to overtaking abandoned housing or self-constructed housing built without the landowner's permission

Table 3.2 : Proximities of study patients´ primary residence to a priori selected points of interest.

	Hospital A*	Clinic X **	Prison A ǂ	Prison B	Main Thoroughfare Roadway	Elevation of patients home (in meters)
	Distance (in kilometers) from TB patients´ place of residence at the time of diagnosis to:					
Mean, [sd]	3.10, [1.93]	3.40, [2.40]	3.48, [1.50]	3.36, [1.34]	0.95, [0.68]	294, [176]
Median	2.82	2.80	3.45	3.22	0.84	280.8
Range	0.06 – 8.51	4.9 - 9.7	1.94 – 8.95	0.10 - 8.21	0.01-4.76	1 - 616
Number of participants´ residences, (%):						
≤ 2KM	293, (34.3)	302, (35.4)	147, (17.2)	128, (15.0)	806, (94.4)	854, (100.0)
2 to 4KM	315, (36.9)	251, (29.4)	414, (48.5)	477, (55.8)	43, (0.05)	0, (0.0)
≥4 KM	246, (28.8)	301, (35.2)	293, (34.3)	249, (29.1)	5, (0.05)	0, (0.0)

Note: Hospital A is the single large Ministry of Health tertiary care hospital serving SJL district; Clinic X is the health center with the highest TB rate in the district (incidence >350 per 100,000); Prison A and Prison B are the two prisons located in SJL with TB rates estimated at above 5000 per 100,000; the main thoroughfare roadway is the main route for the use of mass transit, a previously identified predictor of T B transmission in SJL district, elevation was included for areas in the hills where aggregations of cases could exist.

Table 3.3 : Bivariate Logistic Regression Models For Prediction of MDR-TB

	Odds Ratio	95 % CI	P Value
AGE			
>35 years	Ref		
<35 years	1.68	1.02 - 2.91	0.051
SEX			
Female	Ref		
Male	0.81	0.54 -1.22	0.312
CIVIL STATUS			
Single	Ref		
Co-Habiting	0.78	0.48–1.24	0.305
Married	0.50	0.21-1.01	0.073
Divorced	0.77	0.31 – 1.65	0.527
Widowed	0.76	0.04-4.27	0.802
HOUSING STATUS			
Rented	Ref		
Family Home	1.21	0.65-2.35	0.563
Owns	1.10	0.60 -2.13	0.792
Invasion	NA	NA	NA
NUMBER OF ROOMS IN DWELLING			
5+ rooms	Ref		
3-4 rooms	1.52	0.93-2.50	0.098
0-2 rooms	1.49	0.88-2.50	0.134
NUMBER OF PERSONS LIVING IN DWELLING			
5+persons	Ref		
3-4 persons	0.846	0.50-1.38	0.513
0-2 persons	0.886	0.43-1.68	0.725
WORK STATUS AT THE TIME OF DIAGNOSIS			
Employed	Ref		
Unemployed	0.83	0.54-1.28	0.397
Student	1.06	0.48-2.13	0.885
IMPRISONED PRIOR TO DIAGNOSIS			
No	Ref		
Yes	0.15	0.004-0.891	0.035*
INCOME (monthly income in US Dollars)			
0-50 USD	Ref		
51-100 USD	0.43	0.19-0.86	0.028
101 -300 USD	0.83	0.47-1.39	0.489
301 + USD	1.18	0.39-2.93	0.737
ELEVATION (meters)			
<250 meters	Ref		
250 – 350 meters	1.61	0.99-2.68	0.059
>350 meters	1.48	0.81-2.69	0.194
PRISON 1			
≥4 KM	Ref		
2 to 4KM	0.87	0.56-1.38	0.558
≤ 2KM	0.79	0.42-1.45	0.468

PRISON 2			
≥4 KM	Ref		
2 to 4KM	1.44	0.89 -2.38	0.144
≤ 2KM	1.01	0.49 -2.02	0.972
CLINIC X			
≥4 KM	Ref		
2 to 4KM	1.17	0.66-2.07	0.582
≤ 2KM	2.06	1.26 -3.43	0.004
HOSPITAL A			
≥4 KM	Ref		
2 to 4KM	1.08	0.62 -1.90	0.779
≤ 2KM	1.77	1.06 – 3.03	0.033
MAIN THOROUGHFARE ROADWAY			
>1 KM	Ref		
≤ 1KM	1.01	0.67 -1.54	0.956

Note: Total N = 854 ; 750 DS-TB, 104 MDR-TB
NA = Too few counts per cell to converge
**Fisher's exact test is presented due to low cell counts; only one MDR-TB case had been previously imprisoned.*

Table 3.4: Adjusted Final Logistic Regression Model

	Adjusted Odds Ratio	95% CI	P Value
AGE			
>35 years	Ref		
<35 years	1.74	1.05 -3.02	0.040
CLINIC X			
≥4 KM	Ref		
2 to 4KM	1.21	0.69- 2.15	0.501
≤ 2KM	2.10	1.29 -3.51	0.004
SEX			
Female	Ref		
Male	0.848	0.56-1.29	0.440

Note: Full model included age, sex, civil status, income, elevation and Hospital A, number of rooms in dwelling and number of persons in dwelling. Backward selection was used to select the final model.

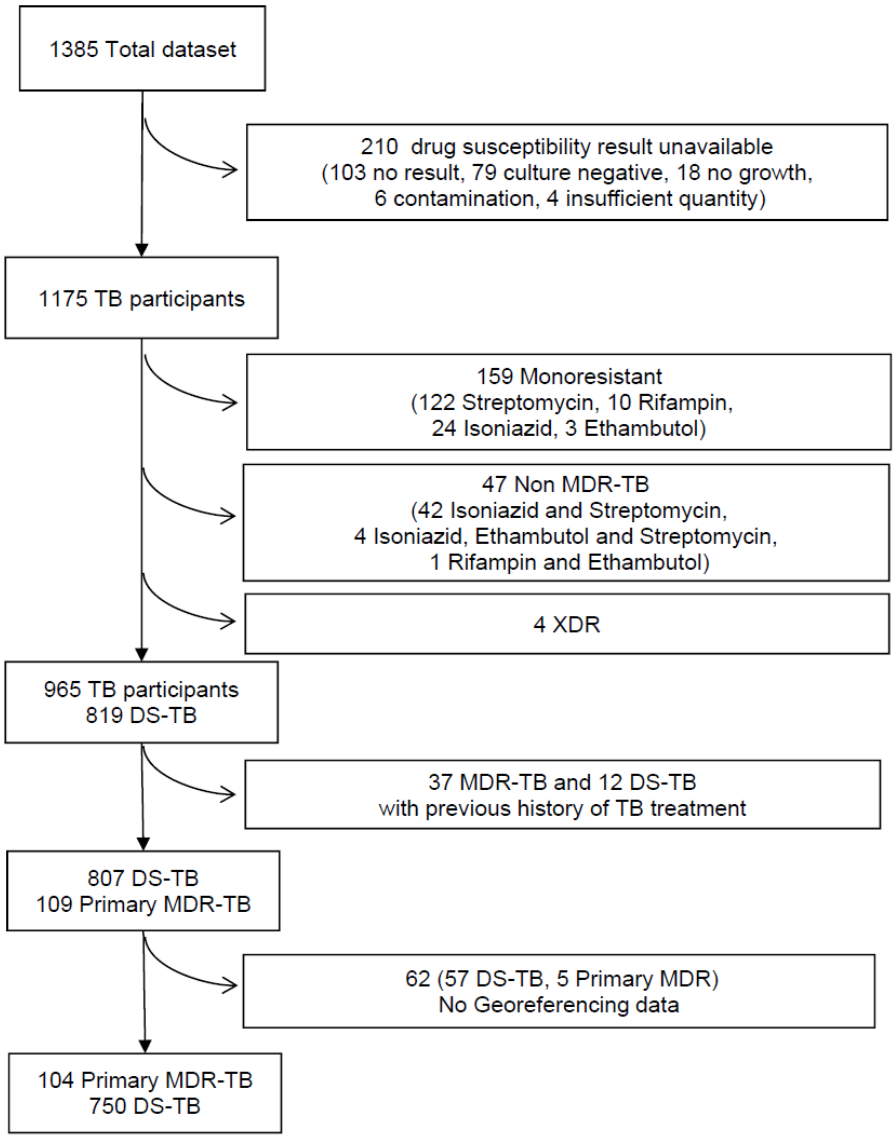

Figure 3.1 : Flow Diagram of Study Population

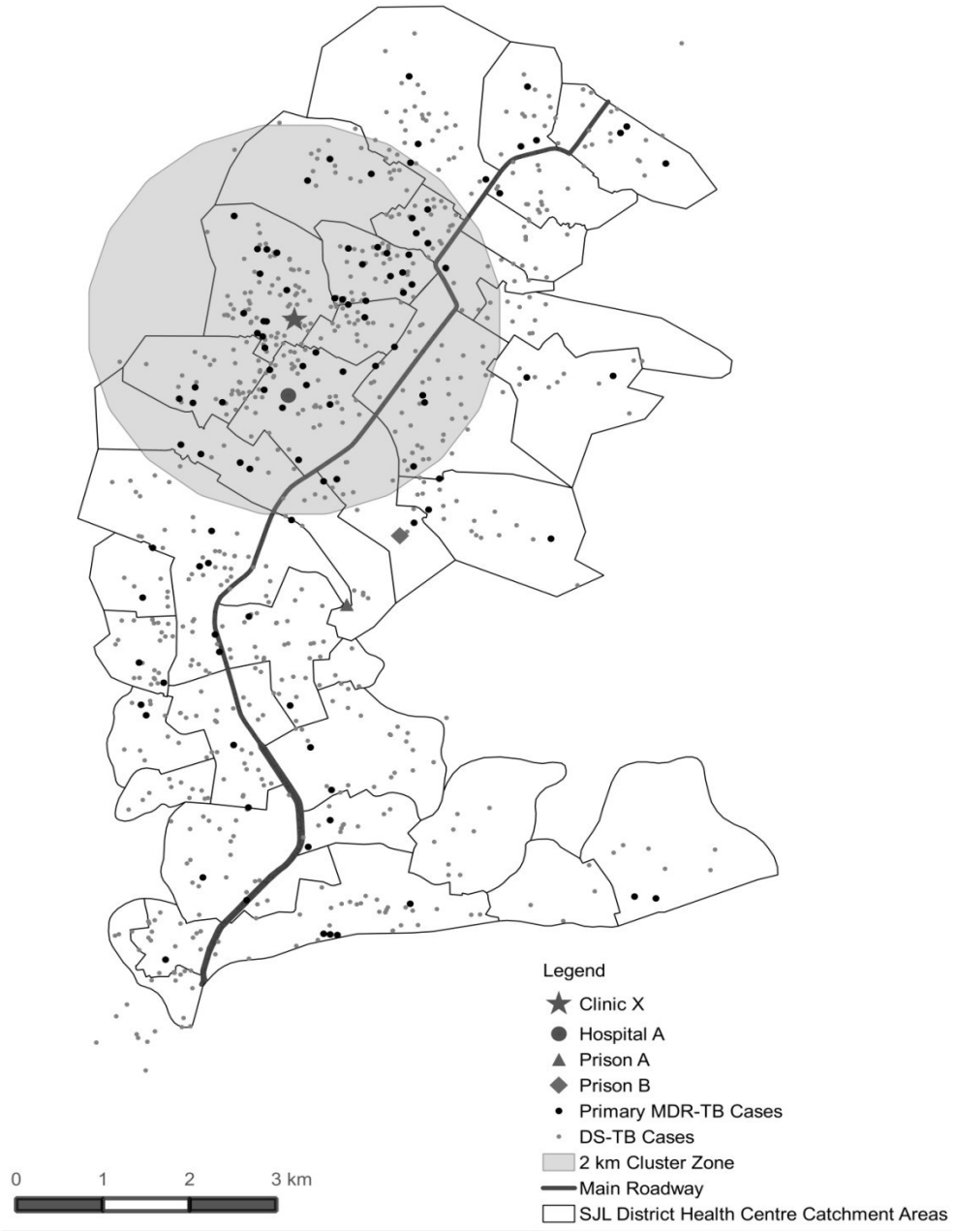

Figure 3.2 : Location Map of Primary MDR-TB cases, DS-TB Cases, High TB rate locations of interest and significant cluster zone in San Juan de Lurigancho district.

*Footnote: The 2 km grey shaded area represents the approximate location around clinic X with clustering of MDR-TB cases and the area within which a higher expected number of primary MDR-TB cases was found compared to Drug sensitive TB cases. Source: Kulldorff's space-time scan statistic (*SaTScan™,v9.1.1*) for space-only cluster, 50% maximum window using a Bernoulli model, N=348 in this cluster (58 MDR-TB cases) (P=0.037). Case data presented have a small random error to protect patient confidentiality. Map plotted QGIS software (v.1.8.0. Lisboa). Total MDR-TB cases n=104, DS-TB cases n=750.*

CHAPTER 4 : Implementation of a stepped-wedge cluster randomized design in routine public health practice: design and application for a tuberculosis (TB) household contact study in a high burden area of Lima, Peru

4.1 Preface

In the previous chapter, the investigation of clustering of primary MDR-TB cases in the community was presented. Until recently, the priority of active case finding was for high risk groups, such as MDR-TB patients. The previous study attempts to better understand clustering of primary MDR-TB with the potential goal of targeting active case finding activities in the community to those areas at highest risk. In addition, systematic introduction of active case finding for household contacts as a risk group is also in need in SJL. Very few NTP programs have published any evidence from within their programs on the ability and feasibility to integrate systematically active case finding for household contacts exposed to smear positive TB cases in LMICs. More importantly, amongst those that have undertaken active case finding as part of the program, few have used the routine programmatic NTP staff as opposed to the dedicated research teams.

4.1.1 Project background and timeline

The following manuscript describes the development and implementation of an operational research design of an active case finding strategy for household contacts of new TB cases within a routine NTP DOTS program in SJL district, Lima, Peru. Currently, the field work for the described study is underway and the analysis of this study will be available in 2015. In 2011, during the planning of this doctoral research, it became apparent that previously unrecognized considerations in the study design would need to be included, in order for the project to succeed. The stepped wedge design was agreed upon as a study design as it met the urgent needs of SJL district to roll out active case finding strategies, this was identified as a

local interest by the TB program manager. The stepped-wedge design provided a systematic approach to implementation to provide a potential opportunity to study the implementation and generate new data from a higher quality research design. This study received CIHR funding in April 2012 and the study teams were hired in October 2012. During this time, gaps in baseline training were identified and in January 2013 a large three day training for all TB staff in the district was set up on the basic operational aspects of the program. On March 1st 2013, the first group of health centers initiated the active case finding program, followed by additional centers every four months until the last group of health centers was trained and had implemented the intervention in March 2014 until June 2014. Data extraction is paper-based and contact data is recorded in health centers in case report and NTP forms within patient charts in 34 health centers. The efforts required to access information from health centers, to extract data from patient charts, and to enter data into electronic database is tremendous. Currently, the data from November 2013 and February 2014 are still being extracted from health center clinic charts and summarized in study case report forms. While the results from the pragmatic stepped-wedge cluster randomized trial will not be made available until 2015, the protocol for the study is being submitted as an independent contribution to the literature and includes a discussion of the advantages and challenges experienced during the design and implementation phases of this research project. The novelty of the study design and the scarcity of operational research studies that examine household contact tracing in an endemic area further support the inclusion of the study protocol as a separate manuscript in this dissertation.

4.2 Manuscript: Implementation of a stepped-wedge cluster randomized design in routine public health practice: design and application for a tuberculosis (TB) household contact study in a high burden area of Lima, Peru

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This manuscript is submitted to Implementation Science

SUMMARY ABSTRACT

Objectives: We designed a pragmatic stepped-wedge cluster randomized controlled trial in order to evaluate provider-initiated evaluation of household contacts (HCs) of smear positive tuberculosis (TB) cases within a routine TB program in Lima, Peru.

Methods: National TB program (NTP) officers of San Juan de Lurigancho District (Lima, Peru) and university-based researchers jointly designed a pragmatic stepped-wedge cluster randomized trial design in order to implement an active case finding (ACF) program for all HCs of smear-positive TB cases in 34 district healthcare centers. Randomization of times to intervention initiation was stratified by health center TB case rate. Once initiated, ACF was provided by NTP staff and integrated into routine TB program practice.

Results: This study protocol describes the currently ongoing pragmatic stepped-wedge cluster randomized trial of household contact evaluations within a passive routine TB program. In order to develop this collaborative study, multiple planning meetings were required to develop the appropriate networks and in order to understand the structure and operations of the NTP at the health center level. Working with routine TB programmatic staff identified the corresponding advantages and challenges of this study design in practice and within existing TB programs in a developing country context are also discussed.

Conclusions: The stepped-wedge design is a useful modification of pragmatic cluster randomized trials. There are many practical features of the stepped-wedge design that make it suitable for use during the implementation of a new public health intervention in a resource limited setting. NTP and researcher partnerships in the use of stepped-wedge designs to evaluate the large-scale roll-out of TB interventions under routine programmatic conditions in endemic settings may improve the evidence base for TB control globally.

INTRODUCTION

Randomized controlled trials (RCTs) are considered the 'gold standard' study design to determine the efficacy of health care interventions.[134] High quality RCTs require particularly stringent study contexts in order to optimize their internal validity. For many public health interventions, particularly those deployed in low-resource settings, efficacy findings from rigorous research contexts do not necessarily align with those observed under the conditions and contexts in which the intervention is to be operationalized.[135] Pragmatic RCTs were initially conceived to allow for the inclusion of a more realistic study environment, for example including the intervention´s study population. Nevertheless, these studies are limited in their ability to approximate the true real-world effectiveness of a public health intervention once it is assimilated into routine public health practice or implemented on a large-scale across populations.[136]

In practice, public health interventions are rapidly deployed on the basis of weak or limited pre-existing trial data if they are believed to be of more benefit than harm.[137,138] This decision to undertake a large-scale roll-out of a new public health intervention requires a corresponding investment of public resources. Depending on the intervention, this could range from costs of increasing public health staff and introducing training, to costs of programmatic materials including diagnostic tests or disease treatments. In order to examine the contextual effectiveness and to appropriately support evidence-based public health decision-making, public health interventions should be evaluated as they are implemented.[139]

The stepped-wedge design of the cluster randomized controlled trial (CRCT) has recently emerged as a variant of the RCT for use in pragmatic contexts.[140,141] In a classic parallel

CRCT, a commonly used design for community intervention effectiveness trials, groups of individuals or clusters (e.g. health centers) are randomly assigned to either the intervention or control arm for the entire study period.[142] In the stepped-wedge design, clusters are randomly assigned to start the intervention at different times (unidirectional cross-over trial) and by the end of the follow-up period all clusters have initiated the intervention.[140,143–145] Use of the stepped-wedge CRCT design has risen exponentially in recent years.[146] In the past three years (from 2011 to 2014), published protocols using the stepped-wedge design have quadrupled compared with previous years (pre-2011). These studies range from large scale clinical or hospital based interventions to public health programs targeting specific populations.[147–157] The integration of a staggered initiation time of the intervention in the stepped-wedge design is considered particularly useful, if withholding the intervention is not considered equitable, and for when it is difficult logistically to simultaneously initiate an intervention over a large population.[145,158]

In 2012, the World Health Organization (WHO) released its first comprehensive recommendations for investigating contacts of person with infectious tuberculosis (TB) in low- and middle-income countries (LMICs). These new guidelines are in response to slow declines in TB rates and the increasing concern of TB drug resistant strains spread in areas with well-established WHO Directly Observed Therapy, Short Course (DOTS) programs. DOTS focus primarily on the adequate treatment and management of TB cases once they self-report for diagnosis. Previously, the recommendations to screen close contacts in LMICs was for select high-risk groups such as children < 5 years old or individuals co-infected with human immunodeficiency virus (HIV).

The WHO introduced a new recommendation for LMICs which includes screening all household contacts of all smear positive pulmonary TB cases.[12] A substantial gap in evidence remains given the low quality of the existing data to support the integration of contact tracing to routine TB programs from LMICs. In recognition of this limitation, the WHO recommendations also call for stepped-wedge designed studies to study implementation of household and close contact tracing activities and operational research data to help further guide future recommendations.[12]

Currently, very few published studies using a stepped-wedge design have been undertaken in the context of infectious disease programs, or for interventions embedded within routine public health systems in LMICs. Amongst these, even fewer have shared information on the design, implementation, strengths and practical issues encountered in undertaking the stepped-wedge design in this context.[149] The evaluation of a given public health intervention, when it is embedded into local health infrastructure, would provide invaluable information regarding its effectiveness.[136] We designed a pragmatic stepped-wedge CRCT for active case finding among household contacts of index TB cases in comparison with the detection of secondary TB cases using the routine passive detection of TB cases. The advantages and challenges of implementing the stepped-wedge design are also discussed.

STUDY DESIGN

Background

TB is caused by the pathogen *Mycobacterium tuberculosis* which is spread primarily when a smear-positive (i.e. high bacillary load in sputum samples) pulmonary TB case coughs or exhales aerosolized droplets which are then inhaled by their close contacts. Household contacts

(HCs) of smear-positive TB patients often are at greater risk for acquiring TB infection and disease than the general community because of their duration and proximity of contact to the infectious case. [68,70] Once infected, exposed persons either develop latent TB infection (LTBI) or may progress to active TB disease either soon after exposure (primary TB) or at some later point during their lifetime.

DOTS refers to both a TB treatment program (including the direct observation of short-course therapy for treatment) and the first component of WHO's global STOP TB control strategy adopted by many National TB programs (NTPs) globally, including in Peru. Since the early 1990's Peru has had a well-performing DOTS program in that it has consistently met and surpassed WHO operational performance indicator targets including the ≥ 85% cure of detected cases. Despite having a high-quality DOTS program in place, the goal of TB elimination in Peru remains elusive. In addition to new diagnostics, therapeutics and the current passive detection of TB cases using sputum microscopy, expanding case finding activities is of particular interest where the basic core NTP program is well-functioning, such as is the case in Peru.

In 2013, Peru reported an average TB incidence of 99 per 100,000 population, which is amongst the highest in the Americas. Unlike the TB epidemic in Sub-Saharan Africa, HIV is not a primary driver of the epidemic in Peru (HIV rates among TB cases are <3%).[159,160] In 2010, over 1,800 new cases of TB (170 per100,000 population) were identified in San Juan de Lurigancho (SJL), Northern Lima's most densely population and largest district (population: 900,000, area: 131.25 km^2. [95] In SJL, nearly 30% of health centers reported an incidence ranging from 200 to 400 per 100,000 population.[87]

The Peruvian Ministry of Health operates the National TB Program (NTP) in SJL through 34 health care facilities (20 community health clinics (CHCs), 14 health posts) and 1 hospital.[96] The NTP DOTS program, including TB treatment, follow-up visits, management of clinical and programmatic records and counseling occur within a designated outpatient TB program office within each of these health care facilities. The routine public health system in SJL includes the passive reporting of household contacts of TB cases who present for symptom screening. In 2010, over 60% of eligible household contacts presented to district clinics for evaluation.[87] In each health center, typically a physician, nurse and nurse's aide are responsible for the TB program activities. In smaller health centers with fewer TB cases, the staff is responsible for multiple public health programs within the center, while in larger centers with numerous TB cases, full-time staff are allocated to the TB programs.

Intervention Arm

The active evaluation of household and close contacts is considered a priority for control programs in TB endemic LMICs in order to stop ongoing transmission.[12] The SJL district NTP initiated a population-based strategy entitled "*Familia saludables de contactos de tuberculosis*"or "Healthy Families of TB Cases", an ACF program to evaluate all HCs of TB patients through visits to the residences of index TB cases (Table 1). In the intervention arm, The DISA NTP proposes the *Familia Saludables de contactos de TB* program which includes visits by a TB program nurse to households of all newly diagnosed smear positive TB cases enrolled in DOTS treatment within a DISA NTP clinic. During the home visit NTP staff evaluate all household contacts for symptoms of active TB. Any person reporting cough for over 14 days will be asked to provide a spot sputum for microscopy and referred to the clinic

for chest x-ray and clinical evaluation. All household contacts less than 16 years old are referred to the health center for chest x-ray, pediatric clinical evaluation and initiation of treatment for active or latent TB as required. Counseling including TB infection control practices and importance of diagnosis and treatment completion for TB cases is provided to household members. (Table 4.1, Figure 4.3)

Control Arm

In the control arm, passive case finding is used, which is the presentation of a symptomatic HC for evaluation for TB at a NTP clinic. This approach is standard for TB control programs in most LMICs with high rates of TB. Previously in SJL, when household visits were used for TB related activities, they were primarily used to verify the jurisdiction of residence of the case and to capture any TB patients who were missing doses of their TB treatment.

Stepped-wedge Design

Following a baseline pre-intervention data collection period, the 34 healthcare centers (excluding the hospital) were randomized to receive the *Familia Saludables de contactos de TB* program in groups of 8 or 9 clinics at four-month intervals (Figure 4.1). While waiting to roll-over to the ACF home visitation intervention program, clinics continued with their standard of care routine passive DOTS program. A total of 20 months was required, including the four month baseline pre-roll-out period, plus each of the four cross-over time points, until full implementation across all centers was reached.

Participants

Index TB cases in SJL are included if they are less than 16 years old, sputum smear-positive and have reported having at least one HC upon questioning. All TB HCs identified are included if they meet the program HC definition and are not currently under TB treatment.[161] Patients diagnosed outside of the Ministry of Health NTP, such as those imprisoned, institutionalized or attending private clinics, are excluded unless referred and registered into the Ministry of Health NTP DOTS program.

Randomization and Stratification

Randomization of health centers was stratified by TB incidence rate to achieve a balance of TB burden in clusters crossing over to the intervention arm at each time period (step). Clinics were categorized into one of following TB rate strata: less than100/100,000 population, between 100 to 200/100,000 population, and greater than 200/100,000 population. These strata were determined by examining the distribution of TB rates and calculating approximate rate tertiles. Health centers within strata were randomized to the time of intervention initiation using a random number generated sequence in R Software.(Table 4.2)

Blinding

Study investigators, DISA NTP TB program staff, TB cases and their household contacts were not blinded to the initiation of the intervention. Clinics were notified one month prior to their cross-over date to initiate planning. To minimize potential ascertainment bias, TB disease was determined by laboratory diagnosis.[162] While the intervention and control arms were integrated into routine public health practice, there was potential for some behavior differences given our supervision of health centers, simply from staff knowing their work is monitored. Data collection in all clinics is initiated several months prior to the initial rollout of the

intervention to reduce biases incurred from study research team observing practices during the intervention period.

Prevention of Contamination

Health center TB program staff were trained to prospectively enroll newly diagnosed TB cases beginning on the first of the month they initiate the intervention period. During cross-over, there was a risk of contamination from the time the study staff began intervention training until the time of initiation of the new program. Training and monitoring was scheduled as closely as possible to the intervention start date to minimize this effect (within the two weeks). Contamination between clinics was therefore considered to be minimal given that, as cases and contacts are required to initiate TB treatment within the clinic catchment area of their primary residence, which is primarily for administrative reasons. There are circumstances where TB cases may be diagnosed in other clinics within the district or in other districts; however these cases are referred to the designated clinic of their primary residence prior to treatment initiation or shortly thereafter.

TB Diagnosis

Throughout the study both cases and contacts were diagnosed using existing local NTP diagnostic practice. This routine practice includes symptom screening, sputum smear microscopy, radiography, clinical evaluation and where available, culture-confirmation and drug susceptibility testing. Though alternative rapid TB diagnostic methods are in the process of being integrated into Peru's NTP, they are not in use in SJL.

Power Analysis

The specified level of power for a population in a stepped-wedge design is less than that of a parallel randomized trial, although standard normal deviates must be increased by an inflation factor.[63] Accounting for the stepped-wedge design and the varying cluster sizes within the sample, with a fixed number of clusters (n=34 health centers), a power of 90% would be a able to detect a difference of 3-4% as significant. Based on previous studies, this is sufficient power to determine an effect that would be of clinical and programmatic importance.[13,20] The primary outcome is the rate of TB among household contacts of TB patients, yields in % positive for TB by total number of contacts evaluated, and the secondary outcome is the number of contacts tested per index case.

Current status

This pragmatic stepped-wedge CRCT is currently underway across SJL health centers, Lima, Peru with funds from the Canadian Institutes of Health Research and is registered in the Clinical Trials.gov database NCT02174380. Ethical approvals were granted by the Human Ethics Research Boards of the McGill University Health Center (Montreal, Quebec, Canada), Universidad Peruana Cayetano Heredia (Lima, Peru) and Direccion de Salud Lima IV Este (Lima, Peru).

RESULTS

This pragmatic stepped-wedge CRCT protocol is among the very few undertaken in an operational TB program in a LMIC.[163] The following discussion highlights the strengths and

challenges of using this design in the implementation of an intervention within a public health program under real-world conditions (Tables 2 and 3).

Strengths of the stepped-wedge design in evaluating public health interventions.

The stepped-wedge design is particularly useful in this study due to the impending rapid and widescale roll-out of this public health intervention. In SJL, there exists a need to evaluate how the local public health context influences intervention effectiveness. The design also allows the generation of new data from a provider initiated ACF program in HCs integrated into the routine public health program in a TB endemic area, for which there is limited pre-existing effectiveness data.

During planning stages, the partnership of NTP programmers with local and international researchers was formed with the common goal of estimating the added benefit of actively evaluating HCs of TB cases for disease compared to the existing DOTS TB strategy of symptomatic individuals self-reporting for evaluation (standard of care). NTP programmers highlighted the importance of a rapid intervention rollout in order to meet annual programmatic targets and to demonstrate public health action across all health centers in their jurisdiction. Typically, less than half of the health centers included in this study would be included in many RCT designs.[141] Researchers emphasized the need to plan study design aspects such as random assignment, sufficient study sample size in intervention or control arms and supervision of health workers to ensure high quality implementation and sound data management. The stepped-wedge design was identified as the design most aligned with various

stakeholder needs, including the introduction of randomized cross-over times and flexibility in order for programmers to oversee a controlled implementation across all health centers. [164]

The stepped-wedge design is appropriate for logistical constraints that prohibit implementing a new program across numerous centers and settings simultaneously.[140,145] The systematic staggered implementation has numerous advantages in resource-limited settings when the goal is to integrate the intervention into existing programmatic activities. A unique feature of the current protocol is the use of routine NTP program staff. Unlike dedicated research study staff, the use of routine NTP nurses and physicians adds a complexity given that this intervention of household contact tracing is conducted in context of numerous other responsibilities of the health center staff. Public health interventions are complex and context dependent, as they are integrated within the infrastructure of existing health systems, dependent on local political, socioeconomic and cultural perspectives of the population and its public health practitioners.[139] TB programs are further impacted by complex treatment management protocols for active TB cases, a high burden of cases in endemic areas and numerous administrative programmatic activities (e.g. reporting forms, indicators, record keeping). Therefore effective implementation requires planning, high quality training and active monitoring. These factors are better achieved when a manageable number of sites are initiated at a given cross-over time point as in the stepped-wedge design.[165]

In the context of the current study, health center NTP staff were substantially more motivated and engaged in training and preparation for the intervention once it was known that all centers would receive an increase in workload and undergo the same intensive training, monitoring and evaluation processes. The randomized allocation of centers to the cross-over time point

also eliminated preferential assignments due to either health centers' performance evaluations or other subjective criteria.

Challenges of the stepped-wedge design in evaluating public health interventions.

While the staggered intervention initiation times increase the flexibility and pragmatic usefulness of the stepped-wedge design in practice, this requires understanding of the methodological complexities involved. For example, the determination of the number of clusters, number of steps and time frame for rollout must all be predetermined and require special consideration. If the composition of clusters to be randomized to each cross-over time point are unbalanced, this could result in skewed increases or decreases in the measured outcomes. For example, if all high TB rate centers were to cross over at the first time point and all low TB rate centers cross over at the last time point this could result in a skewed numbers of secondary TB outcomes in HCs observed earlier and for a longer time period of the study. A simple stratification for the randomization of health centers by TB rate at each cross-over time point, is used in the current protocol to account for TB burden and as a proxy for the corresponding size of clinics to evenly distribute centers across the various wedges.[87,95]

Blinding of the intervention assignment is not possible, which is a common challenge for most stepped-wedge designed studies. In the current protocol, health centers awaiting cross-over might increasingly anticipate their likely cross-over time based on the number of health centers that have already initiated the intervention. Additionally, the public health intervention is undertaken by health center staff, who along with patients, know whether or not they have initiated the intervention. In our study, contamination between clusters, though theoretically

possible, is not a major concern, since TB patients and their HCs must attend the health center of the catchment area to which their primary residence is registered.

The selection of a stepped-wedge design is considered optimal in the context of logistical, feasibility and resource challenges. There is, however, limited evidence to suggest the stepped-wedge design of a population-based implementation requires fewer research or programmatic resources to undertake adequately given the increased length of time to undertake the study. In the current study, resources were required for monitoring the full implementation, to improve data quality, and the repeated measurements for the entirety of the study. Any research data related to the stepped-wedge design in the current study, requires manual patient chart review, extraction and entry into electronic relational databases, for which corresponding study infrastructure are essential. Although the costs implicated apply to all operational studies to be undertaken in this or similar contexts, the overall stepped-wedge in an operational setting requires supervision and resource planning to ensure that this can be done throughout the study period.

In a successfully operating DOTS TB program, several challenges are encountered when evaluated ACF within routine Ministry of Health TB operations (Table 4.3). These issues range from high staff turnover, health care worker strikes, outbreaks in other disease areas, and authorization requirements for data access. These substantial issues lead to interruptions of activities which are not encountered in standard research studies. The stepped-wedge approach using NTP personnel provides an evaluation of intervention effectiveness within actual programmatic conditions and therefore, will be more representative.

Adherence or fidelity to the program and whether the intervention, in its intended form, is systematically applied by staff within a health center is a distinct challenge particularly in pragmatic trials where actual program staff are undertaking the new intervention as part of their normal duties[139]. From an analytic perspective, intention to treat analysis (ITT) is generally the preferred analytic strategy for CRCTs, which considers outcomes based on the random allocation to the intervention arm, regardless of what happened subsequent to assignment. In practice, if there is no reported difference in effectiveness between intervention and control arms, conclusions need to consider to what degree the ineffectiveness of the intervention itself is the cause or if the low adherence of implementers to the intervention is the more likely explanation. In addition, per protocol analyses, which consider actual adherence to the intervention, will also be examined in our study.

Concluding Remarks:

Stepped-wedge designs provide an important option for public health researchers and practitioners to generate intervention effectiveness data that otherwise would remain unmeasured. Typically, stepped-wedge designs are justified when feasibility, logistics and/or limited resources are important practical considerations. Furthermore, the stepped-wedge design is of high quality given the randomization process, offering a sound option for operational research. An additional benefit of the stepped-wedge design is the greater chance of a successful and sustained implementation given the focused waves or wedges of implementation. Overall, there is no indication that a stepped-wedge design requires fewer resources than other designs; the design requires resources over a longer period of time, yet involves smaller resources for training and monitoring at any given time point during the study. Finally, fidelity or adherence to the intervention needs to be considered during

implementation and in the analysis, in order to correctly interpret null or negligible findings of effect.

The currently ongoing study will provide invaluable evidence on contextual factors that would not have been possible in traditional study designs. The findings of this study will have implications for the selection of interventions and allocation of resources in TB programming for Peru, and will be a major contribution in the field of TB prevention and TB contact tracing in LMICs.

Funding Source

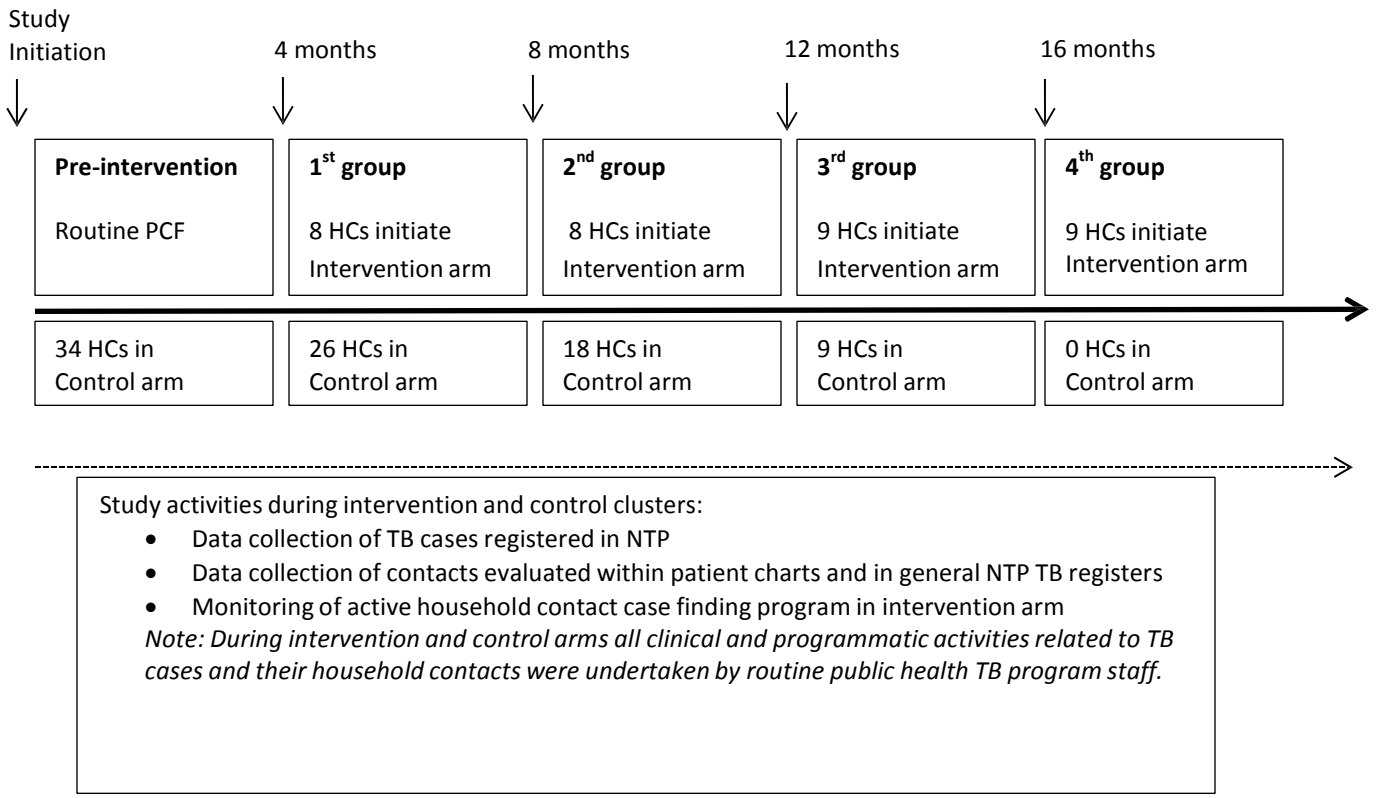
Funding for the described study protocol is provided by the Canadian Institutes of Health Research (CIHR) Operating Grant. Additional travel for the primary author was provided by the CIHR Michael Smith Travel Supplement and the International Development Research Center (IDRC) Doctoral Research Award

Figure 4.1 - Stepped-wedge implementation table

Time points

Groups	*1*	*2*	*3*	*4*	*5*
1	*0*	*1*	*1*	*1*	*1*
2	*0*	*0*	*1*	*1*	*1*
3	*0*	*0*	*0*	*1*	*1*
4	*0*	*0*	*0*	*0*	*1*

0= Routine program (PCF); 1= Initiation of the Familia Saludables ACF program; Groups = 8 clinics per group; Time points = 4 month intervals



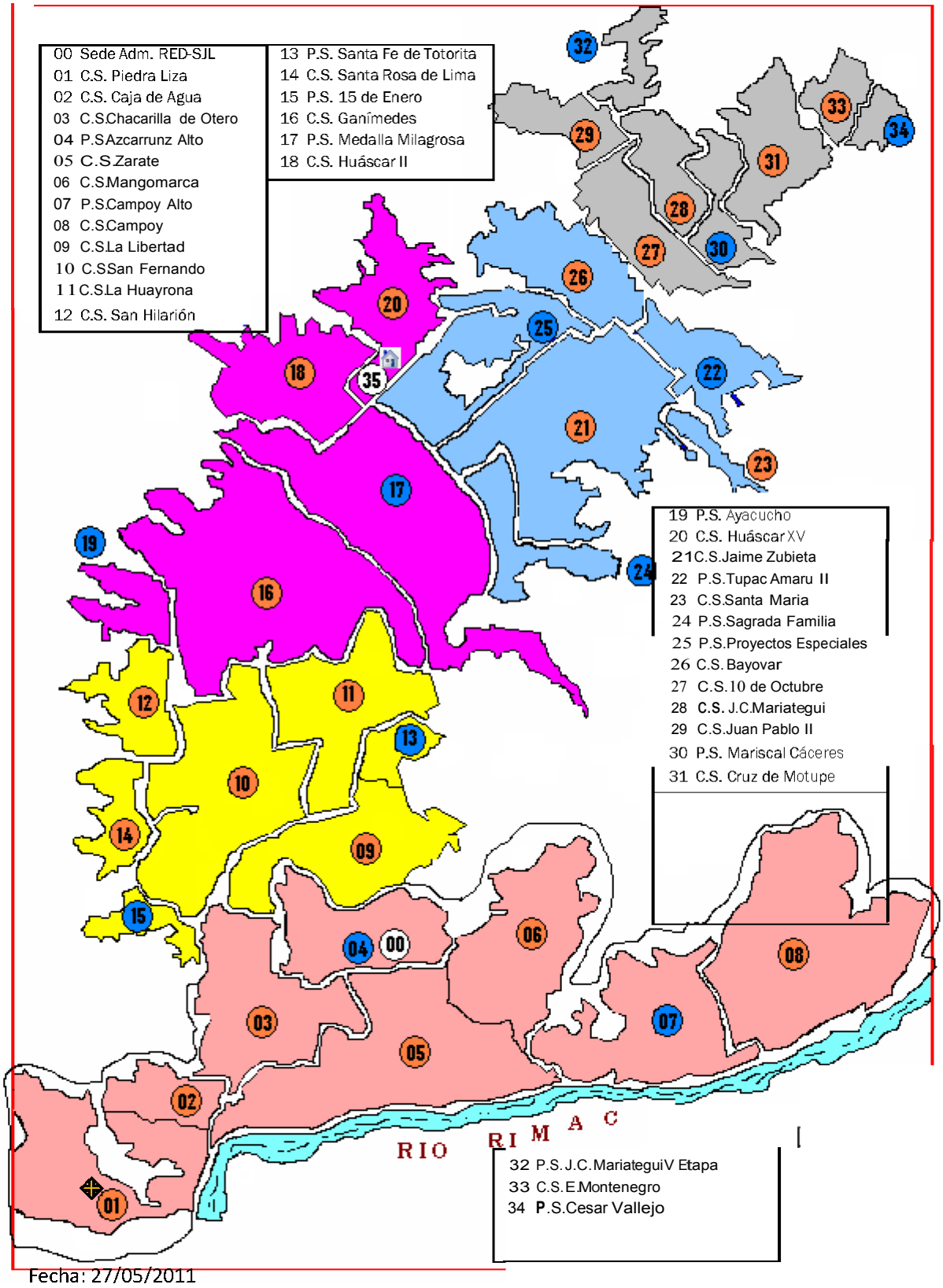


Figure 4.2 **Health centers and catchment areas of SJL district**

Table 4.1: Definitions of cases, contacts, intervention and comparator arms.

STUDY DEFINITIONS	
TB case	A definite TB case is defined as an individual with newly diagnosed smear-positive or culture positive TB. Smear-negative individuals meeting NTP clinical guidelines for TB (cough >14 days duration with or without the presence of chest pain, fever, haemoptysis (blood in sputum), night sweats or fatigue and/or weight loss)[161,166] were classified as probable cases.
Household Contact	Household contact is defined as living and sleeping at the same dwelling/property as the respective index case at the time of diagnosis, sharing kitchen and bathroom facilities [69,161,167].
Routine practice comparator	Passive case finding is the current NTP DOTS program of symptomatic persons voluntarily self-reporting to the health system for diagnosis of TB and initiation of chemotherapy [22]. Newly diagnosed and retreated smear positive TB cases enrolled in DOTS treatment at SJL NTP clinics are asked to name their household contacts and encouraged to tell household members ≥15 years with cough >14 days to self-report to the clinic for evaluation. All children <15, with or without symptoms, are encouraged to attend clinic for evaluation for latent or active TB (as per DISA NTP guidelines). TB evaluation at clinics includes sputum smear microscopy, chest x-ray and clinical evaluation.
Intervention – active case finding of household contacts – Familia Saludables de contactos de TB Program	The DISA NTP proposes the *Familia Saludables de contactos de TB* program which includes households visits of all newly diagnosed TB cases enrolled in DOTS treatment within a DISA NTP clinic. During the home visit NTP staff evaluate all household contacts for symptoms of active TB. Any person reporting cough for >14 days will be asked to provide a spot sputum for microscopy and referred to the clinic for chest x-ray and clinical evaluation. All household contacts ≤15 years are referred to the health center for chest x-ray, pediatric clinical evaluation and initiation of treatment for active or latent TB as required. Counseling including TB infection control practices and importance of diagnosis and treatment completion for TB cases is provided to household members. The ACF home visit is to be repeated at three times, within a month of the time the index TB case initiates treatment, at 3 months and at 6 months.

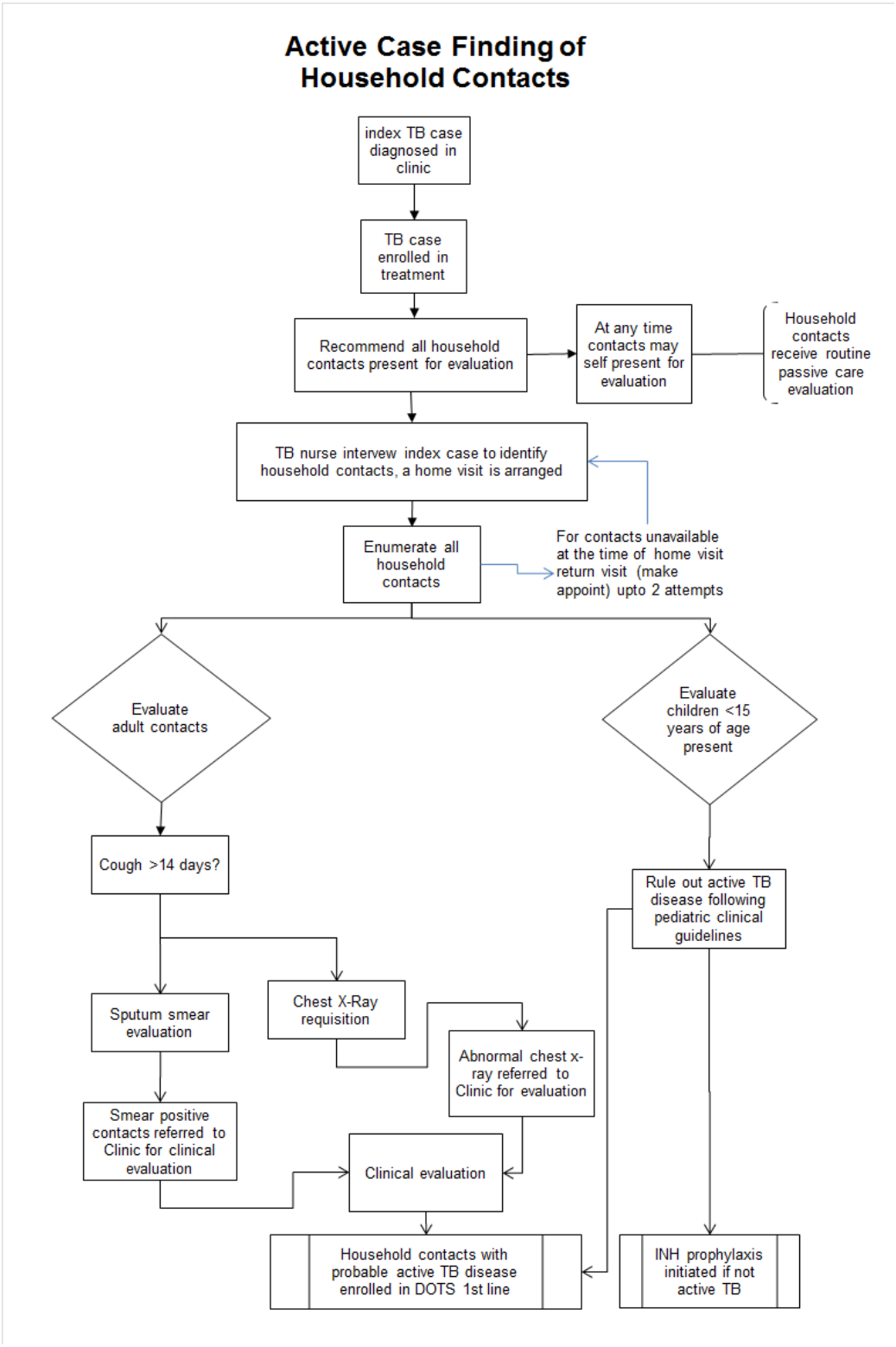


Figure 4.3 : Diagram schematic of the active case finding program implemented in SJL district

Table 4.2 Randomization of Health Centers to Steps

	STEP 1	TB Rate	STEP 2	TB Rate	STEP 3	TB Rate	STEP 4	TB Rate
	Azcarrunz Alto	under 100	Proyectos Especial	under 100	Mangomarca	under 100	Zarate	under 100
	Ayacucho	under 100	10 de Octubre	under 100	15 de Enero	under 100	Santa Rosa	under 100
	J.C.Mariategui V Etapa	under 100	Chacarilla de Otero	100 to 200	La Libertad	under 100	La Huayrona	under 100
	Piedra Liza	100 to 200	San Fernando	100 to 200	Ganimedes	100 to 200	Medalla Milagrosa	100 to 200
	Santa Fe de Totoritas	100 to 200	Montenegro	100 to 200	Bayovar	100 to 200	Sagrada	100 to 200
	Jaime Zubieta	over 200	Campoy Alto	over 200	Cesar Vallejo	100 to 200	Mariscal Caceres	100 to 200
	Santa Maria	over 200	San Hilarion	over 200	JCMariategui	over 200	Campoy	over 200
	Juan Pablo II	over 200	Huascar II	over 200	Caja de Agua	over 200	Cruz de Motupe	over 200
					Tupac Amaru	over 200	Huascar XV	over 200
TOTAL	8		8		9		9	
START DATE	MARCH 2013		JULY 2013		NOV 2013		MARCH 2014	

Under 100= TB incidence less than 100 per 100,000 population; 100-200= TB incidence between 100 and 200 per 100,000 population; over 200= over 200 per 100,000 population

Table 2. Key advantages and challenges related to public health implementation in a stepped-wedge pragmatic CRCT

Study Feature	Advantages	Challenges	Implications in current protocol
Stepped or staggered implementation	• Allows for the incremental introduction of the intervention or program • Flexible design that can be modified for amount of steps and clusters based on need or manageability. • Higher quality evidence than observational and non-randomized pretest-posttest designs • All centers are intervention and controls	• Multiple training and initiation must be undertaken at each step (or cluster cross-over) • Multiple measurements and resource intensive throughout the entire study period during cross-over initiation and throughout all steps. • Higher complexity in biostatistical analysis	• The phased initiation is crucial to undertaking implementation across all 34 health centers all of which require individual training and monitoring which would not have been feasible in a full roll-out or even a parallel CRCT.
Implementation in routine conditions	• The stepped-wedge study design allows for all partners to reach their specific goals and obtain the evidence they need from their perspective. • The design can be used to provide real world evidence of effectiveness by using a staggered implementation when a full population based intervention is planned. This allows for evidence that may not exist otherwise.	• Routine public health in LMICs is subject to many fiscal, political and programmatic pressures, however methodological rigour is still required in this design and should be adhered to at least during the study period. • Researchers desire randomization, unbiased allocation of health centers • Data quality needs for research design may be above daily programmatic requirements (data quality control)	• The stepped-wedge pragmatic RCT is the most suited so all partners could benefit from high quality evidence, yet pragmatic utility: • Researchers had identified the major gaps in available high quality research evidence for the routine systematic evaluation of household contacts of TB cases within the context of resource constrained TB endemic areas. In parallel, SJL district local NTP programmers had identified the urgent need to implement a program to actively evaluate household contacts of TB cases undergoing treatment; there is local programmatic concern of cases that were linked through familial or household contact, and the underperformance of their current passive approach for achieving screening of household contacts.
Overall Design	• Easy to integrate design, a modification of existing RCT and CRCT • RCT experts and methodologists widely available	• Methodological complexities to power and analyses of stepped-wedge designs • Fewer experts with technical and practical experience using stepped-wedge designs • Unlike traditional individual randomized controlled trials and cluster randomized	• Many of the authors of stepped-wedge design papers have contributed to the use and the methods for this design. On the other hand every study has its individual specific needs and we required specialized guidance in terms of the overall framework of the roll-out, the frequency

		controlled trials, less is formally taught in research training and in operational training on the design and requirements for methodological rigour. • The nomenclature is complex and could be confusing to stakeholder. Several terms have been used for the same design modification, including implementation trial, randomized start or staggered start trial, delayed designs, step or stepped-wedge designs amongst others [143,144]	and duration of steps • Because of its relatively recent use, published literature including many of the published stepped-wedge trial protocols in peer reviewed literature were relied upon
Longer trial length	• Focuses on smaller subset of the intervention groups at time • Improves adherence by allowing for intensive monitoring and supervision of groups • Improves quality of training including smaller size of training groups and ability to integrate peer to peer support and hands on training in the field	• Population based intervention implementation requires programmatic and research, throughout the duration of the entire study. • Longer trial period is also associated with increased intensity and duration of labour	• As it is phased in, the monitoring, supervision and training can be improved and also any major problems, political, technical or resources can be identified to improve the implementation. • There are great challenges to sustaining monitoring efforts, in practice far more training and monitoring and supervision is required then initially estimated. • Research components can increase burden and the longer duration can lead to exhaustion for researchers, programmers and local health care staff.
Sample size/Power	• The stepped-wedge CRCT is considered to have higher power and precision with fewer clusters and increasing number of steps	• In reality, the power, number of clusters and relative sample size is far more complex • The potential required power depends both on local requirements or existing fixed numbers of centers or patient populations.	• Achieving sample size and power in the design are not the major issue, however the study is limited to a fixed number of clusters and number of TB diagnosed cases within the NTP that occur during the study period

Table 4.3 : Project specific challenges in evaluation of program or intervention implementation in a LMIC TB control program in a real world public health context

Practical Challenges	Description
Staff Turnover	Staff turnover is extremely high, at minimum annually and additionally on an *ad hoc* basis (unplanned). • This involves re-training new staff on basic TB DOTS program in addition to re-orienting new staff to the intervention and provision of additional on the job training
Baseline Training and Experience	The intervention assumes basic operational knowledge and functioning in the TB program. • A wide range of experience and training is observed amongst TB program staff, and this makes introducing training on the intervention challenging given the assumption of thorough knowledge of the basics NTP DOTS program and ability to operate this underlying program well. • Routine programmatic supervision is highly variable. Given high burden of load and limited staffing resources, typically only reported problems are addressed within daily program activities. In the case of the intervention implementation, one on one peer mentoring was offered to health centers in addition to group training to support TB nurses with less experience, to answer questions regarding procedures related to identifying, locating, evaluating household contacts and the corresponding reporting.
Timing of training	The timing of the pre-intervention cross-over training sessions requires adjustment based on local needs. • Initially training was designed to be offered in advance of the cross-over, however if this is too far prior to the prospective admission of the next TB case, it results in having to redo training, for example *ad hoc* in situ additional training once the first few TB cases were actually enrolled into treatment in the NTP program and eligible for the home visits and evaluation of contacts. • TB program and public health staff are extremely busy and require special permissions to attend any offsite training related to the new intervention. Each step involves a minimum of 8 health centers with 2 TB staff from each invited for training. Therefore 16 formal invitation letters and permission approvals for classroom based training are required at each cross-over time point.
Outbreaks or unexpected health issues (e.g. health campaign/ interventions in response to urgent health events or political priorities)	During public health disease outbreaks, all public health staff are mobilized and reduced or basic TB program activities are maintained. • Without warning, infectious disease outbreaks can occur and result in de-prioritization of routine public health efforts and suspension of non-essential programming for varying periods of time. Although a dengue outbreak has not yet occur during the study period, the primary challenge in our setting is the preparedness for a potential dengue outbreak and the allocation of any extra staffing hours to instantaneous door to door dengue prevention campaigns
Staffing Strikes	Public health staff may undergo general strikes • To date, during the study period, two separate two-month long physician strikes, a one-month nursing strike and a two-week nursing aide strike have occurred. This results in interruptions to regular TB program activities, including any intervention related activities, and is reduced to only the provision of basic DOTS treatments.
Authorizations for data extraction	Official authorizations are required to access public health data • Administrative level ethical approvals were required • Individual health center level approvals for chart access are also required from each of the 34 health centers. If there is

	staffing change of any of the TB program staff, or the chief medical office of the entire health center, a new original approval letter addressed by name to that individual is required. • In order to have a source document available at the research site, that allows for quality control, a photo or a photocopy might be needed.
Data quality	Use of actual chart data • Data quality is variable by health center • A high degree of missing data • Good quality on basic DOTS required data is high, for example treatment allocation, sputum smear result • Contacts are monitored in index patient´s chart, however names are often misspelled and scanning electronic databases is subject to error.

CHAPTER 5 : Cost-effectiveness of actively evaluating household contacts of TB patients in a TB endemic setting in Lima, Peru

5.1 Preface

The previous manuscript presented the design of a pragmatic stepped-wedge cluster randomized trial, which examined the implementation of an active case finding program within a routine TB program in SJL District. The advantages and challenges of using this design in practice and undertaking active case finding within a routine program were also described. An important aspect of operational research and the scale-up of an intervention is its cost-effectiveness. Therefore, in order to complement the operational research component of the implementation of active case finding, the last manuscript of this thesis aims to estimate the cost- effectiveness of active case finding for household contacts of TB cases within a routine TB program.

In LMICs, the cost-effectiveness of different aspects of TB programs has previously been considered, for example, in determining the cost-effectiveness of diagnostics (e.g., introducing culture confirmation or use of rapid diagnostics), treatment delivery strategies (e.g., variations of DOTS), and treatments (e.g., effective treatment regimens and delivery for DS-TB and for MDR-TB patients).[39,93,111,168–171] These studies have informed guidelines in countries like Peru have provided evidence for the introduction of second-line MDR-TB treatment as well as the introduction of new diagnostic tools. To date, however, the cost-effectiveness of active case finding programs for household contacts have not been evaluated in Peru.

Clearly, active case finding will cost more than the passive case finding system, given the added resources that are required. These resources include the labour costs and time for NTP

program physicians and nurses to actively seek and evaluate contacts in to detect active TB. In Peru, standard NTP programmatic costs for smears, cultures, diagnostic tests, anti-tuberculosis treatments and laboratory costs including overhead have been considered in cost-effectiveness studies and values for these estimates are available through published sources.[93,111,172] The costs of active case finding programs, including the time required for evaluating household contacts by personnel, are not standardly measured in NTP programs and are subject to the local context of the case finding program. Evaluating added direct cost measures informs the current gaps in knowledge and the literature and the results may be of use to NTP programmers and local decision makers.

5.2. Additional Methodological overview

5.1.2 Decision Analytic models

Decision analysis is a form of analysis increasingly used in the economic evaluation of health–care interventions.[76] Decision analytic models are now widely used in evaluating the cost-effectiveness of public health interventions particularly for cross-sectional screening programs.[39,82,173] Decision trees, which are represented as branched structures, are the most commonly used structure to represent decision analysis. Each branch represents an event and its alternatives and a sequence or linkage of these events is used to display the complex decision process or series of events. The advantages of decision analytic models are that they are straightforward, simple and produce transparent models with visual interpretation of the complex scenarios such as when evaluating public health interventions.[76] Complex disease dynamics that account for transmission, reinfection or transitional states can be considered; however, they likely require different types of models such as Markov models or individual sampling models, which are useful to model repeated events and to follow events over longer

time periods.[76] Therefore, the selection of the model (decision tree or any other structure) and the various branches of the model must be guided by the research question, the perspective (e.g. patient or societal), the time horizon, available measures of costs and benefits and the overall scope of the study.

Input parameters

For each branch of the decision tree, an associated probability is identified. The probabilities are selected from published studies, where available from systematic reviews or meta-analyses of high quality research studies, or from primary data. The probabilities are then assigned to each branch of the decision tree. The best estimate for each probability, also referred to as the base case parameter, and a range of values for the parameters are also included in order to account for potential variability the value of the estimate which is then examined during sensitivity analyses. The terminal end of each branch is allocated the cumulative cost across the events occurring within that branch, as well as the effects. The effects are the final outcomes of interest, including number of cases detected, or deaths averted. Quality adjusted life year (QALYs) and the disability adjusted life year (DALYs), which provide a composite approach to valuing health outcomes, are also widely used effect or outcome measures in cost-effectiveness analyses.

Disability Adjusted Life Years

The disability adjusted life year (DALY) is a metric used to estimate the years of life lost or lived with disability. In the 1990's DALYs were introduced by the World Bank and the World Health Organization (WHO) to estimate the global burden of disease attributable to a range of disease and injuries.[76] As a measure of health outcome, it includes two main components, the

duration of a lifetime lost due to premature death (years of life lost; YLL), and the reduction in quality of life due to a disability (years of life with a disability; YLD). The disability weight, also known as the utility weight, reflects the severity of disease and is represented on a scale from 0 to 1, with 0= "perfect health with no disability" and 1= "dead". Disease specific disability weights are estimated and periodically updated in the Global Burden of Disease (GBD) report lead by the WHO.[174–176] The advantage to using DALYs is it provides a standardized metric to compare health conditions. Nevertheless, there are limitations and in particular the development of the disability weights have been criticized for their generalization of certain weights across all populations, which are based data from a few select groups.[174] More recently, the GBD surveys were undertaken in different countries (including the United States and Peru) to reflect various contexts, demographic groups and education levels. Despite the controversies surrounding the use of DALYs, the WHO has used this measure to estimate the cost-effectiveness of a range of interventions, in particular in LMICs. [76,177]

DALY= YLL + YLD

YLL = # of deaths * standard life expectancy at age of death (years)

YLD= $I * DW * L$

I= # of incident cases

DW= disability weight

L= mean duration of disease until remission or death

Figure 5.1 Formula for calculating DALYs

In summary, there are three types of input parameters which are required to estimate the cost-effectiveness: the probabilities at each transition point in the tree or chance of the event occurring, the costs and the effects (outcomes).

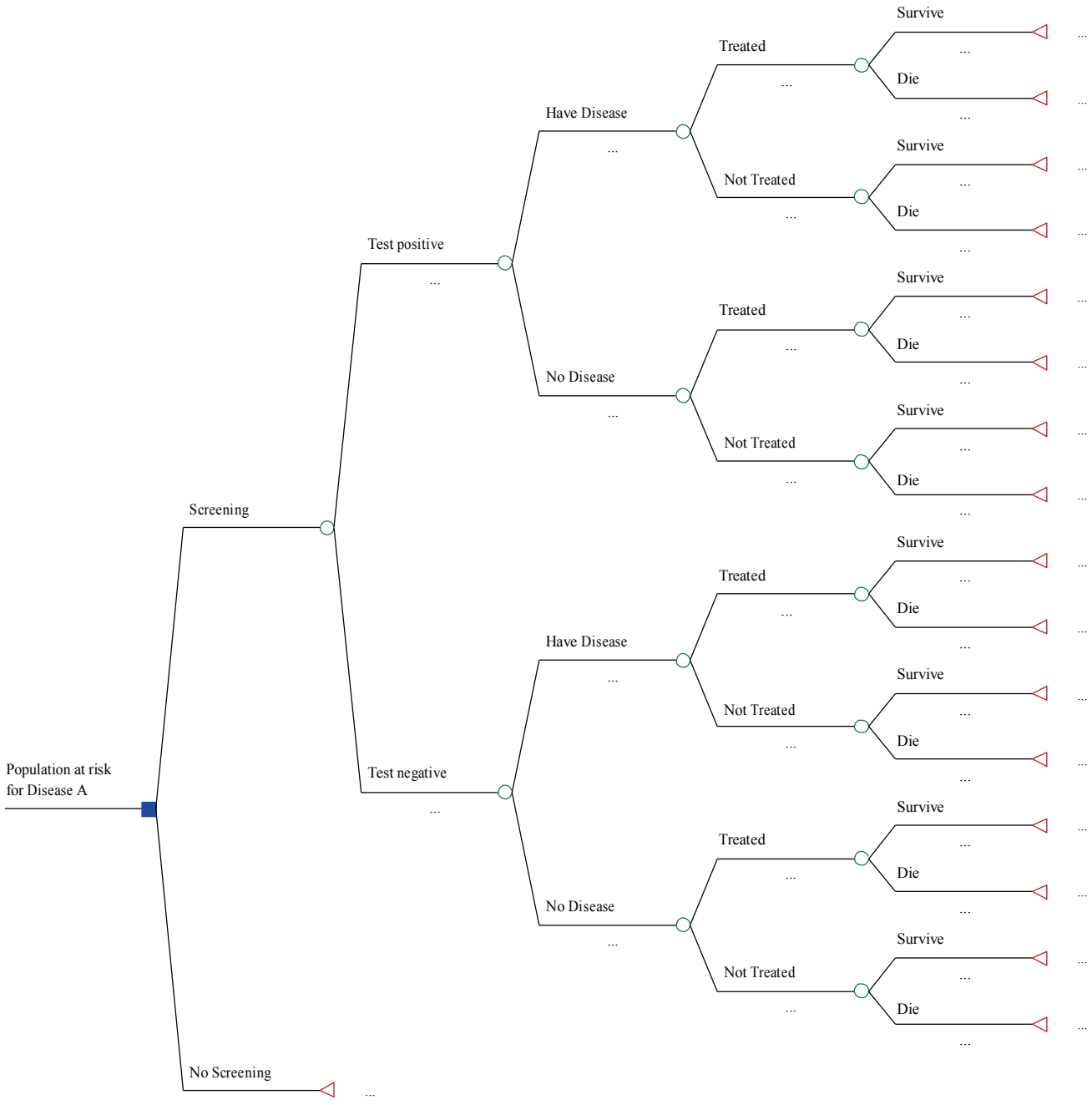


Figure 5.2 Sample of a Decision tree

Note: Circles where branches diverge represent "chance nodes", probabilities at each circle node juncture must sum to 1. Triangles at the far right of all branches represent "terminal nodes" or endpoints of a given series of branches at which the costs and effects will be assigned

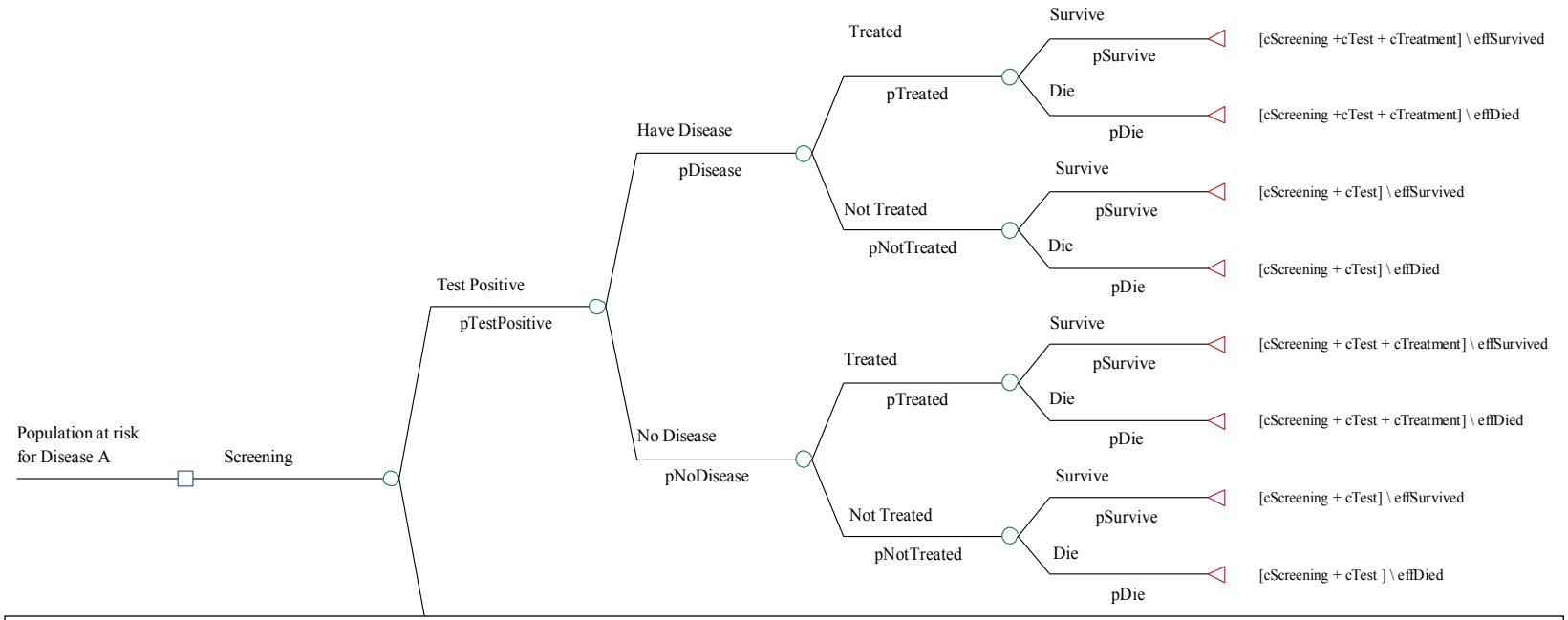


Figure 5.3 Sample of a Decision tree with input probabilities, costs and outcomes

Notes: “p” indicates probability, “c”indicates costs, “eff” indicates an effect or outcome

Analysing the decision tree

Once the probability, costs and outcomes are assigned to the decision tree, the analysis involves calculating the expected costs and expected outcomes across the various branches of the tree.[76] The calculations are straightforward and can be calculated in a Microsoft Excel spreadsheet or in a cost-effectiveness software (e.g. TreeAge). The probabilities are first multiplied across all branches. This begins at the right-hand side of the tree, the probability at each node are multiplied across a given series of events. The value of the effect (outcome) of each branch is then multiplied by its respective branch probability. This is similarly undertaken for the costs. The overall difference between the costs of the two different strategies is then divided by the difference between the total effects of the two strategies resulting in an incremental cost-effectiveness ratio (ICER).

Incremental Cost Effectiveness Ratio = Incremental Costs/ Incremental Effects

Figure 5.4: Incremental Cost-effectiveness Ratio

ICER and the Cost-effectiveness Plane

The resulting ICER is the ratio of the change in costs to the change in effects. The ICER is challenging to interpret; it is dependent on the effects (outcomes) in use, whether that is cases detected, deaths or DALYs. In the example of DALYs, an ICER would be interpreted as $ per DALY and typically this is presented as $ per DALY averted. A cost-effectiveness plane involves four quadrants and represents several possible scenarios. The figure can be used to plot incremental costs and effects of an intervention and comparator to aid in decision-making of whether or not the intervention should be adopted. If a new intervention is less costly and more effective, and is plotted in the south west corner of the plane, this would be interpreted as dominated, meaning the intervention is considered highly cost-effective. If the comparator

dominates and is less costly and more effective than the new intervention this also leads to a fairly straightforward decision-making process. More often, the new intervention is more effective but more costly, making the tradeoff of the added costs for a corresponding health benefit reliant on some level of acceptability to decision makers to pay for the added benefit (willingness-to-pay).[76]

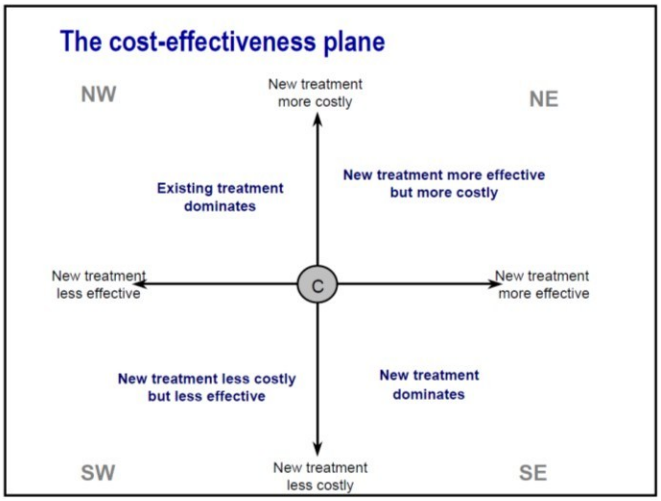


Figure 5.5 Cost-effectiveness Plane

Willingness to Pay Thresholds (WTP)

Once an ICER is produced, the assessment of whether or not this is considered cost-effective is relative to a threshold value (lambda) called the willingness-to-pay (WTP). The WTP is a measure of how much a decision-maker is "willing to pay" for an additional unit of effectiveness. WHO recommends using the gross domestic product (GDP) per capita as a threshold value to account for the local decision-maker's context. For example, an intervention estimated to have an ICER estimated at USD $20,000 per DALY averted may be considered cost-effective in the United States (WTP=USD $ 62,000) yet not cost-effective in other countries such as in Peru (WTP=USD $6,390). While the WTP is a crude measure of the true willingness-to-pay of

decision makers, it is commonly used to assess whether the ICER of an intervention to its comparator is considered cost-effective in a given context.

Uncertainty, Assumptions and Sensitivity Analysis

In every model, there are a certain amount of assumptions and uncertainty which could affect the cost-effectiveness being analyzed. An approach to examine uncertainty and its potential impact on the results is to quantitatively examine ranges of different parameters in sensitivity analysis. Sensitivity analyses in a cost-effectiveness analysis may be represented by tornado diagrams, or diagrams which individual assess a range of estimates of given parameter to assess its effect on the overall cost-effectiveness. A tornado diagram or chart is a graphical representation of one-way sensitivity analyses in which parameters are varied across a range of values one at time while all other parameters are held at baseline values. The tornado diagram displays bars from the largest to smallest. The largest bar at the top of the chart displays the parameter has the greatest impact on the results, and each successive bar has lesser impact. The WTP is also charted on the x-axis in order to examine whether given the range in uncertainty if the ICER generated would still be cost-effective given the WTP.

5.2 Manuscript: Cost-effectiveness of active case finding of household contacts of pulmonary TB patients in a low HIV, TB endemic setting, Lima, Peru.

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This manuscript is to be submitted for peer-review publication shortly

SUMMARY ABSTRACT

Objectives: We estimated the cost-effectiveness of active case finding for household contacts of smear positive TB cases enrolled in DOTS treatment compared with the passive case finding program. We also compared the integration of an Xpert/MTB RIF test for a single sputum sample in both strategies to estimate the cost-effectiveness of including this test that is more sensitive than the routinely used sputum smear microscopy.

Methods: Decision analysis was used to model the incremental costs and incremental effects of three alternate case finding strategies for household contacts in comparison to the baseline routine case finding program. The three alternate strategies included the addition of an active case finding program, the addition of an Xpert/MTB RIF diagnostic test and the addition of both of these strategies. Cost-effectiveness analysis was calculated as the incremental cost-effectiveness in terms of US dollars per disability adjusted life years (DALYs) averted. One-way sensitivity analyses were examined using ranges of apriori selected estimates and visualized using tornado diagrams.

Results: Active case finding for household contacts of sputum smear positive TB cases was found to be cost effective compared with passive case finding with an incremental cost-effectiveness of $1,941 per DALY averted. The addition of the Xpert/MTB RIF resulted in $ 3,099 per DALY averted if implemented in a passive case finding program, and $3,368 per DALY averted if implemented in addition to an active case finding program. Although these were all more costly and effective then the passive case finding, all strategies remained within the threshold of the willingness to pay of $6,390 per DALY averted.

Conclusions: The addition of active case finding would result in a cost per disability adjusted life year averted of $1,941, suggesting active case finding, including with the inclusion of a home visit and evaluation with sputum smear microscopy, is highly cost-effective in Peru. The

addition of Xpert/MTB RIF was also cost-effective, however in sensitivity analyses was not cost-effective if TB patients had severe outcomes from failures or defaults resulting or if treated TB patients did not regain full health.

BACKGROUND AND RATIONALE

In 2012, the World Health Organization (WHO) reported nearly 9 million new cases of active tuberculosis (TB) and 1.4 million TB-related deaths. It was also estimated that a third of the world's population (>2 billion persons) is infected with *M. tuberculosis*.[26,178] The World Health Organization's (WHO) recommended Directly Observed Therapy Short Course (DOTS) strategy is the current cornerstone for TB control and is followed by the majority of low and middle income countries.[46,179,180] The strategy aims to detect active pulmonary TB cases through sputum smear microscopy and by the provision of standardized and supervised first-line treatments, in order to ensure that TB cases are diagnosed and treated appropriately. Although the global TB incidence is estimated to have peaked in 2003 and appears to be slowly declining, this reduction is too gradual to meet global WHO TB elimination targets by 2050. DOTS is an essential component for TB control although alone, is insufficient to stop TB.[178] The ongoing spread of TB in the community has now become a pressing concern for TB researchers and control programs alike. In addition to new TB diagnostics and improved therapeutics, expanding case finding through contact tracing is a potential avenue to achieve reductions in the TB burden.

Recent evidence suggests that active case finding of TB cases in the community may substantially improve TB case detection rates and contribute to overall and more rapid reductions in TB prevalence and incidence in high-burden, low-resource settings. In some instances, active case finding has been attributed to TB prevalence reductions of 30% to 50% annually .[58,72,180] The active evaluation of close contacts of infectious TB cases, in order to identify secondary TB cases and latent TB infections, is considered essential for TB control in Canada and in the U.S. where TB prevalence is low.[10,181] In contrast, active evaluation for TB

cases in high TB burden settings is reserved primarily for groups including children under 5 years of age, HIV co-infected contacts, and contacts of known drug resistant TB cases, given the resource implications of active evaluation for all close contacts.[182] Despite the likelihood that 50% of household contacts of active TB cases will have latent TB and of this group, a further 5 to 10% develop active disease during contact investigations, routine evaluation of all household contacts for active TB disease remains a low priority in most high-burden TB control programs. This is due, in part, to the perceived need to solely focus on active TB case management.[7,13] Based on the potential of earlier detection of cases through active case finding, recommendations are emerging for conducting contact investigations in high–incidence settings.[13,15,19,20] In 2012, the WHO outlined new household contact tracing recommendations for low and middle income countries, including the systematic evaluation of household contacts exposed to all smear positive TB cases, the diagnosis of active TB or latent TB among household contacts and the provision of appropriate treatment to these secondary cases.

In several of the high TB burden countries, systematic active case detection of household contacts is rarely undertaken despite the WHO recommendations and national policies.[12] Amongst the challenges of active case detection of household contacts are the resource implications and limited evidence on effectiveness within programmatic conditions including cost-effectiveness. Estimates of the effectiveness and cost-effectiveness of active TB case finding among household contacts of TB cases in high-burden, low-resource regions in comparison with the current DOTS strategy of passive case detection, have not been published for low HIV incidence areas and where a strong NTP is in place.[21] Understanding the cost-effectiveness of implementing active evaluation of household contacts in high-burden, low-resource areas is an urgent priority in order to improve TB control globally.[21,22]

Our objective was to evaluate the cost-effectiveness of actively evaluating household contacts of all smear positive TB patients in the detection of active TB cases in conjunction with the routine DOTS program compared to the DOTS program in a region in Peru with low HIV rates and amongst highest TB and MDR-TB rates in the Western Hemisphere.

METHODS:

This economic evaluation was conducted from a health system perspective with a target population of household contacts of smear-positive pulmonary TB patients in Peru.

Decision analytic model

A decision analysis model was developed to determine if active TB case finding amongst household contacts was cost-effective compared with a passive case finding strategy (TreeAge Software Inc, Williamstown, MA, USA). The baseline strategy in the decision tree was a routine passive case finding program, where symptomatic persons self-report for TB diagnosis and are diagnosed using sputum smears and clinical evaluation (Algorithm 1). The first alternative strategy was the addition of an active case finding strategy for household contacts of smear positive TB case (Algorithm 2). In active case finding, all smear positive TB cases are interviewed to identify their household contacts and all household contacts are evaluated during a home visit to the case patients' residence or at the health center. Household contacts are diagnosed using sputum smear microscopy on a spot sputum sample (sample taken at the time of symptom screening by the TB program nurse).

Xpert MTB/RIF is a rapid nucleic acid amplification test (NAAT) for TB which detects TB DNA by polymerase chain reaction (PCR).[40] In 2010, the WHO endorsed the Xpert MTB/RIF for use in endemic countries given its higher sensitivity and specificity both in smear positives and smear negatives when compared to smear microscopy. In Peru, several sites including SJL have been used for research purposes, though currently Xpert MTB/RIF is not used in household contact tracing or as part of the NTP. [40,183] The second comparison was a passive case finding program with the addition of a rapid diagnostic tool with greater sensitivity (Xpert MTB/RIF) to test one spot sputum sample (Algorithm 3) compared to a passive case finding program using smear microscopy. In the third comparison, an active case finding program with an Xpert MTB/RIF test of one spot sputum sample was compared to the baseline passive case finding program (Algorithm 4). In all scenarios, patients who were detected either smear positive with microsocopy or Xpert MTB/RIF positive for TB were assumed to be treated.

Decision analysis estimated the probability and costs for each of four possible strategies: The passive case finding program for household contacts within the routine TB program (baseline) (Algorithm 1), with the addition of an active case finding program to detect household contacts (using sputum smear screening (Algorithm 2), the baseline passive program only with the addition of Xpert MTB/RIF (Algorithm 3), and the baseline program with the addition of active case finding and Xpert MTB/RIF (Algorithm 4).

Input parameters

Probabilities of transition through decision tree

The model follows household contacts of patients with active pulmonary TB. These contacts are followed through a single cross-sectional cycle of screening as would occur within the

DOTS program in Peru. Each branch probability was assigned a likelihood given the screening strategy and the input probabilities for each branch were obtained from published literature or from NTP program data (Table 5.1). Where possible, data were selected from controlled clinical trials and cohort studies, however, in order to include figures from local Peruvian studies, locally available NTP data were also included. Each input probability consisted of a base case which was included in the main analyses and a range of estimates (low value and high value) which was included sensitivity analysis. (Table 5.1)

Program direct costs

The direct costs were expenditures from the government and health system related costs, and did not include patients' out of pocket expenditures or costs related to personal disability. Operational cost estimates were estimated from published data and NTP programmatic estimates. The ingredient costing approach was used whereby all of the costs to perform tests and to deliver the active case finding program were used to arrive at an average cost-per-test per-person (Table 5.2). [76] Average program costs for active case finding home visits and time for evaluating household contacts were compiled using direct reports from local NTP health care staff and validated on a convenience sample of health centers by a supervisory study research team. Average duration of time for providing counseling, symptom screening, sputum and radiology request, clinical evaluation time for physicians, transportation to and from home visits, were included in cost estimate for active case finding within SJL health centers (Table 5.2). These data were intensively recorded on case report forms and collected for a period of four weeks and an average reported from eight health centers conducting active case finding was obtained. In addition, estimated costs of materials and training and start up of the active case finding program, including supervisory and central program management costs were

included from study logs of an active case finding implementation study underway in SJL district. For the base case, we estimated a cost of Xpert MTB/RIF of US$16.38 (assuming an existing Xpert instrument the cost of this was excluded from the model), and the cost of first line treatment was estimated at US$ 350 including treatment, DOTS supervision, cultures and smears and adverse events.[92,184] All costs are presented in 2014 US dollars.

Model outcomes

The primary outcomes of the model are the expected costs, TB cases detected among household contacts and estimated disability-adjusted life years (DALYs) for the active case finding strategy. Expected costs are based on primary data collection and NTP estimates for passive and active case detection (sputum smear diagnostics, DOTS treatment, personnel time and programmatic management). Incremental cost-effectiveness ratios (ICERs) are expressed as US dollars per DALY averted.

Uncertainty and Sensitivity Analysis

In one-way sensitivity analyses, we varied the following parameter values: the cost of the diagnostic test, the cost of the active case finding program, the proportion of secondary active TB cases detected amongst contacts through active case finding or through passive case finding, the effect value amongst those treated and cured, the effect value amongst patients treated and defaulting treatment. Each range of parameters was varied to observe its effect on the overall ICER, which are presented in tornado diagrams (Figure 5.8, 5.9,5.10). According to the World Bank, the 2014 gross national income per capita for Peru was US $6, 390.[185]

RESULTS

Incremental costs

The base case scenario passive case finding costs were estimated at US$ 89.24 per household contact. With the addition of an active case finding, including a home visit to evaluate all household contacts the costs increased by US$19.41 (incremental increase of 21.7%). The implementation of an Xpert MTB/RIF test to evaluate household contacts detected through the routine passive finding program resulted in an incremental cost of US$185.94 per household contact. The overall costs of implementing an Xpert MTB/RIF test with active case finding would result in an incremental cost over of US$ 235.76 in comparison to a passive case finding program using sputum smear microscopy alone (Table 5.3).

Incremental effects

The passive case finding strategy resulted in the highest DALYs (0.17) per household contact. While the strategy using active case finding and the addition of the Xpert MTB/RIF resulted in the fewest DALYs per household contact (0.10). The incremental DALYs averted per 10,000 household contacts compared to the passive case finding strategy alone was an additional 100 DALYs averted with the implementation of active case finding, 600 DALYs averted with the addition of Xpert MTB/RIF to the detection of household contacts in the passive case finding program and 700 DALYS averted for implementing active case finding with Xpert MTB/RIF as a diagnostic tool in addition to sputum smear microscopy.

Cost-effectiveness

Compared to the baseline passive case finding program alone, implementing active case finding was associated with an ICER of US$1,941 per DALY averted. Incorporating an Xpert

MTB/RIF to evaluate one sputum sample in the evaluation of household contacts detected in the passive case finding strategy and with the addition of an active case finding strategy was associated with an ICER of US$3,099 per DALY averted and US$3,368 per DALY averted, respectively. All were considered highly cost-effective compared to the willingness-to-pay threshold for Peru (US$ 6,390).

Sensitivity analysis

We conducted one-way sensitivity analysis with each strategy compared to the baseline passive case finding strategy (Figures 5.5, 5.6 and 5.7). The ICER for the active case finding strategy, when compared to passive case finding, was considered highly cost-effective at the WTP threshold. If the cost of active case finding was varied from the base value of around 10$ per contact to a maximum value of 4 times the cost, this would increase the ICER to $5500 per DALY averted, though this value remained within the threshold considered cost-effective. This increase in costs of the active case finding intervention would be in scenarios such as requiring multiple visits for a given home or for time required in seeking out contacts or for overtime costs related to active case finding on evening or weekends. In one-way sensitivity analyses, including Xpert MTB/RIF in passive case finding or in active case finding, the largest impact was if the overall effect in treated patients having failed or default treatment were to have severe outcomes or die.

DISCUSSION

We compared three alternative strategies to the current passive case finding of household contacts within a routine TB program in Peru. The first alternative considered the addition of active case finding of household contacts to the passive case finding program, the second alternative considered the addition of the Xpert MTB/RIF test to the passive case finding program and the third alternative considered the addition of active case finding with an Xpert MTB/RIF test. Overall, all three alternatives were considered cost-effective compared with the routine passive case finding alone when ICERs were considered against the threshold value of the WTP (Table 5.3 and Figure 5.3). There was an incremental increase in cost for each alternative and an increase in effect, such that active case finding was cost-effectiveness in comparison to the passive case finding, and the addition of the more sensitive test, Xpert MTB/RIF, led to detecting more cases and resulted in greater incremental costs and greater incremental effects (or greater DALYs averted). Adding a more sensitive diagnostic tool such as Xpert MTB/RIF was found to have ICERs which represented incremental costs almost 10 fold that of the active case finding program using smear positive microscopy and incremental effects in DALYs averted of six to seven times greater. Even at ICER of over US $3,000 per DALY averted, strategies including Xpert MTB/RIF were considered cost-effective when considered against a WTP threshold of US$6,390 (Figure 5.15).

The current model directly reflects the activity of screening household contacts at the time the index TB patient enters treatment. We attempted to include direct measures of costs of undertaking active case finding, considering the time spent by front-line staff ability to undertake these activities. This estimation included nursing time to undertake home visits and screen contacts and physician time to evaluate the contacts clinically. However, these measures may be subject to variability. The costs assume a single home visit for an average number of

four contacts, although the average household size can be smaller or much larger. In order to account for this variability we included a range of estimated costs of active case finding of up to US$ 40.00 (or 4 times that of the estimated cost per contact). This upper limit could account for either multiple home visits for the same contact, repeated attempts to capture pending contacts not captured during the home visit, increases in the time required to undertake any of the activities related to contact tracing, increases to salaries or to account for overtime costs if activities related to contacts were required on evenings or weekends. In sensitivity analysis, the active case finding strategy remained cost-effective compared with passive case finding even considering a cost of active case finding program of upto 4 times higher then what was evaluated as a baseline estimate. Though increasing the overall cost of active case finding to $40.00 per contact in sensitivity analyses had an impact on the overall ICER of active case finding, it remained within the WTP threshold.

In both the passive case finding and active case finding strategies, the addition of Xpert MTB/RIF diagnostic tests had only a marginal impact on the overall ICER, even with the consideration of price increases of the cartridges. In sensitivity analyses, the ICER of integrating Xpert MTB/RIF in a case finding strategy was no longer considered cost-effective when the effect measures for cure of patients treated for TB decreased or when the overall effect of failure and default of patients resulted in more severe outcomes such as death. This would indicate that detecting more cases is only highly cost-effective if these identified cases are treated and cured, and do not develop more severe outcomes due to treatment failures. An active case finding community survey undertaken in Capetown, South Africa found 26% of TB cases detected through active case finding did not initiate treatment within two months of detection and were considered initial defaulters.[74] Although in Peru there is no data to suggest differential treatment failure or treatment initiation, between cases detected through active case

finding and cases detected through passive case finding, it should be considered as a factor in cost-effectiveness evaluation. If cases detected through active case finding strategies have differentially low uptake or delay TB treatment, this could greatly diminish the overall cost-effectiveness observed in practice.

This analysis is subject to limitations. The current analytic models do not account for future effects over time, such as estimating the impact of an active case finding program over a period of several decades. The findings represent the short-term impact of a cross-sectional program to actively detect active TB cases amongst household contacts of TB cases. However, this analysis also provides valuable new information including the local perspective on the cost-effectiveness of an active case finding program as would be seen within a routine NTP program. Secondly, the analysis does not account for transitional states, or recurrent cases. For example, a household contact not captured by the active case finding at one time, may eventually develop symptoms and be diagnosed eventually by passive case finding. However, all alternative strategies included the costs and effects of this routine passive case finding system assuming that this system, and its costs and effects would continue even with the introduction of new strategies.

This analysis was undertaken from the program perspective and does not consider out-of-pocket expenditures for patients or the overall societal perspective. Costs such as transportation, loss of work or livelihood, patient time, caregiver costs to patients are all amongst the potential impacts to patients. These are challenging to measure and were not included as part of this study, though their inclusion may alter the cost-effectiveness of the interventions we observed. Future studies should integrate data on the overall economic burden that can be averted to households with an active case finding program.

Historically, the argument in favour of passive case finding as cost-effective in LMICs was the assumption that all symptomatic would present and be detected by the DOTS program and that active case finding would be of an added cost with limited impact on effect.[47] Our findings suggest that active case finding, including home visits to case homes to locate contacts, is highly cost-effective. The integration of an Xpert MTB/RIF did result in higher incremental costs then the passive case finding or active case finding programs with sputum smear microscopy alone, nonetheless, the ICERs of $3,000 per DALY averted remained cost-effective and within the WTP threshold.

Our findings are consistent with those recently reported in Cambodia, which found active case finding was highly cost-effective when compared with passive case finding ($US 330 per DALY averted). Though the active case finding approach used in this study involved notifying all household and symptomatic neighborhood contacts of registered TB patients from the past two years to attend screening at mobile centers.[65] Dynamic modelling studies of the cost-effectiveness of active case finding using data from India, China and South Africa also found that active case finding is highly cost effective for both discrete active case finding strategies and when integrated within ongoing TB control programs.[85]

Active case finding for household contacts represents various approaches and more studies are needed that consider systematically incorporating a prospective active case finding program within an existing routine DOTS program. There is limited existing information on the cost-effectiveness of active case finding for household contacts in LMICs, although data that are reported both from modelling studies and a few studies using data from operational studies, including the current data, suggest that active case finding may be highly cost-effective in a range of contexts.

Conclusions

We compared integrating active case finding of household contacts, by considering provider initiated screening, and compared to the routine program based primarily on self-presenting symptomatic patients. Few studies have included estimates of the time and cost to undertaking active case finding of household contacts by routine programmatic staff. These findings are specific to a TB endemic area where HIV co-infection is less than three percent of all cases and represents the use of active case finding in a large, densely populated urban environment. The addition of an active case finding intervention without and with use of the Xpert MTB/RIF diagnostic test are highly cost-effective for evaluating household contacts in Lima, Peru.

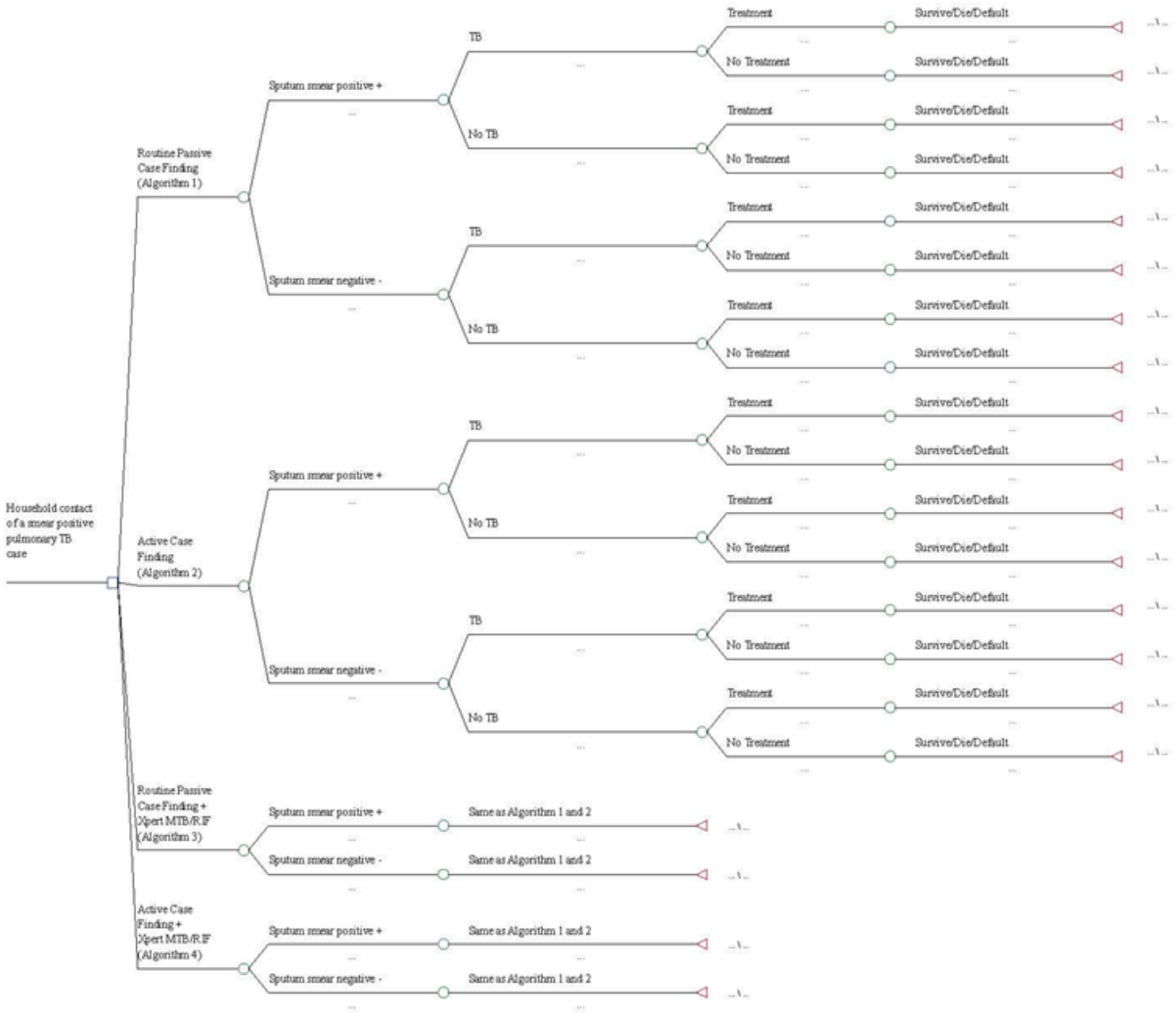


Figure 5.7 Decision analysis model. Not all branches are shown

Table 5.1 Model parameters and source

	Base Case	Low	High	Reference
Epidemiology				
Prevalence of TB in SJL District	0.2%	0.1%	0.4%	[87]
Prevalence of Active TB in household contacts at the time of diagnosis of index case	3.6%	2.5%	5.1%	[182]
Prevalence of TB detected in HC in PCF	1.0%	0.1%	1.2%	[87]
Prevalence of TB detected in HC in ACF	3.0%	2.0%	6.0%	[15,87]
Diagnostic Tests				
Sensitivity, symptom screening	92.3%	83.0%	99.0%	[39]
Sensitivity, smear microscopy (ZN)	65.0%	32.0%	94.0%	[186]
Specificity, smear microscopy (ZN)	95.0%	91.0%	100.0%	[39]
Sensitivity, Xpert MTB/Rif for smear positive TB	99.3%	70.0%	99.9%	[183]
Sensitivity, Xpert MTB/RIF for smear negative TB, HIV-negative	88.1%	75.0%	94.8%	[183]
Specificity, Xpert MTB/RIF	99.0%	95.0%	100.0%	[183]
Sensitivity Xpert MTB/RIF, Rifampin Resistance detection (MDR-TB)	95.7%	79.0%	99.2%	[183]
Specificity Xpert MTB/RIF, Rifampin Resistance detection (MDR-TB)	99.4%	96.6%	100%	[183]
Outcomes for newly diagnosed TB patients				
Treated				
Smear Positive, Cured/Completed	84.0%	65.0%	91.0%	[106]
Smear Positive, Died	2.0%	1.0%	10.0%	[106]
Smear Positive, Default Failure	28.0%	10.0%	30.0%	[106]
Smear Negative, Cured/Completed	69.0%	65.0%	91.0%	[106]
Smear Negative, Died	2.0%	1.0%	3.0%	
Smear Negative, Default Failure	#			
Smear Positive MDR-TB, Cure/Completed	54.0%	45.0%	75.0%	[106]
Smear Positive MDR-TB, Died	11.0%	5.0%	20.0%	[187,188]
Smear Positive MDR-TB Default Failure	#			
Untreated				
Smear Positive, Cured/Completed	30.0%	55.0%	70.0%	[189]
Smear Positive, Died	70.0%	65.0%	75.0%	[189]
Smear Negative, Cured/Completed	80.0%	65.0%	95.0%	[189]
Smear Negative, Died	20.0%	5.0%	25.0%	[189]
Utility				
Disability weight for TB	0.271	0.264	0.294	[176]

 # = 1- (probabilities of the Cured/Completed and Died)

Table 5.2: Program Costs for Active Case Finding of Household Contacts in SJL District (detailed breakdown)

Unit		In Soles	In USD	Duration	Totals	Total need for 10,000 household contacts (US Dollars)
Staffing Costs						
Home visit by Program Nurse	In Minutes	0.22	0.08	120 minutes per visit (Range 60 to 180 minutes)	Per household (Average 4 household members)	24,719.10
Physician Consults	In Minutes	0.39	0.15	15 minutes (10 to 25 minutes)	Per contact	21,910.11
Operational Costs						
Photocopies Household Contact Tracing Forms	Per copy	0.05	0.02		Per contact	187.27
Transportation	Round trip HC to Household	4.00	1.50		Per home visit	14,981.27
Materials						
Flip Chart on TB Infection Control	Per flip chart	30.00	11.24		Per health center	382.02
Clipboards	Per Clipboard	10.00	3.75		Per health center	131.09
Pens	Per box of 20	10.00	3.75		Per 100 home visits	374.53
Smear Microscopy Requisition Forms	Per 100	50.00	18.73		Per 100 contacts	1,872.66
X-ray Requisition Forms	Per 100	50.00	18.73		Per 100 contacts	1,872.66
Sputum Smear	Per sputum smear and reading	4.01	1.50		Per contact	15,000.00
N95 Respirators Masks	Per box of 25	82.24	30.80		Per 25 home visit	3,080.00
Training, Monitoring and Supervision						
Start-up training for household contact management	Per training session (16 hours)	500.00	187.27		Per health center	6,367.04
Overall program management	In Minutes	34.00	12.73	60 minutes per session	Per supervisory session	764.04
Field supervision of ACF	In Minutes	0.40	0.15	120 minutes per visit	Per minute of supervision	1,498.13
TOTAL COST OF ACF	PER 10,000 HOUSEHOLD CONTACT					93,139.93
COST OF ACF	PER HOUSEHOLD CONTACT					9.31

Table 5.3 Incremental Cost, DALYs and Incremental Cost-Effectiveness of Screening 10,000 Household contacts

	Total costs for 10,000 contacts	Incremental Cost*	DALYs (eff)	Incremental DALYs*	CE Ratio	ICER ($ per DALY averted)
PCF	892,400	ref	1,700	ref	525	ref
PCF + ACF	1,086,500	194,100	1,600	-100	679	1,941
PCF + Xpert	2,751,800	1,859,400	1,100	-600	2,502	3,099
PCF + ACF + Xpert	3,250,000	2,357,600	1,000	-700	3,379	3,368

***All referencing baseline PCF only strategy**

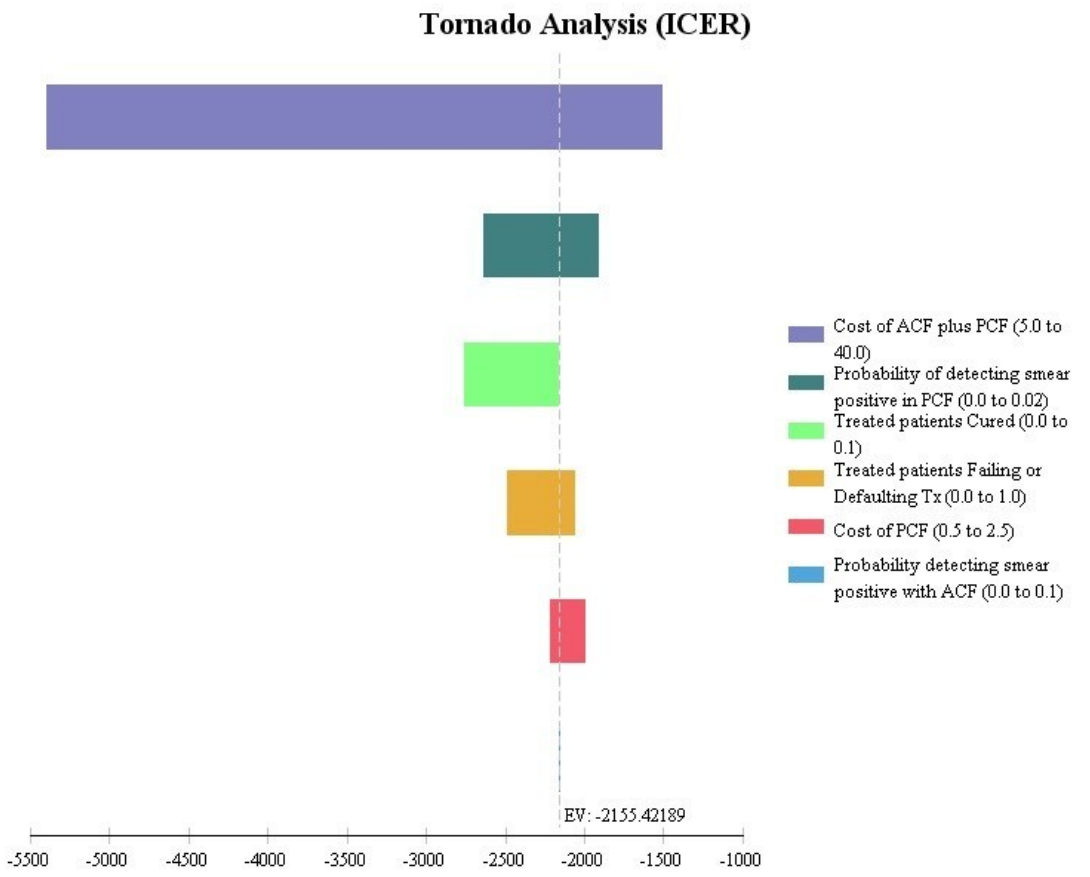


Figure 5.8 One-way sensitivity analysis of incremental cost-effectiveness ratio comparing active case finding (ACF) of household contacts to a passive case finding (PCF)

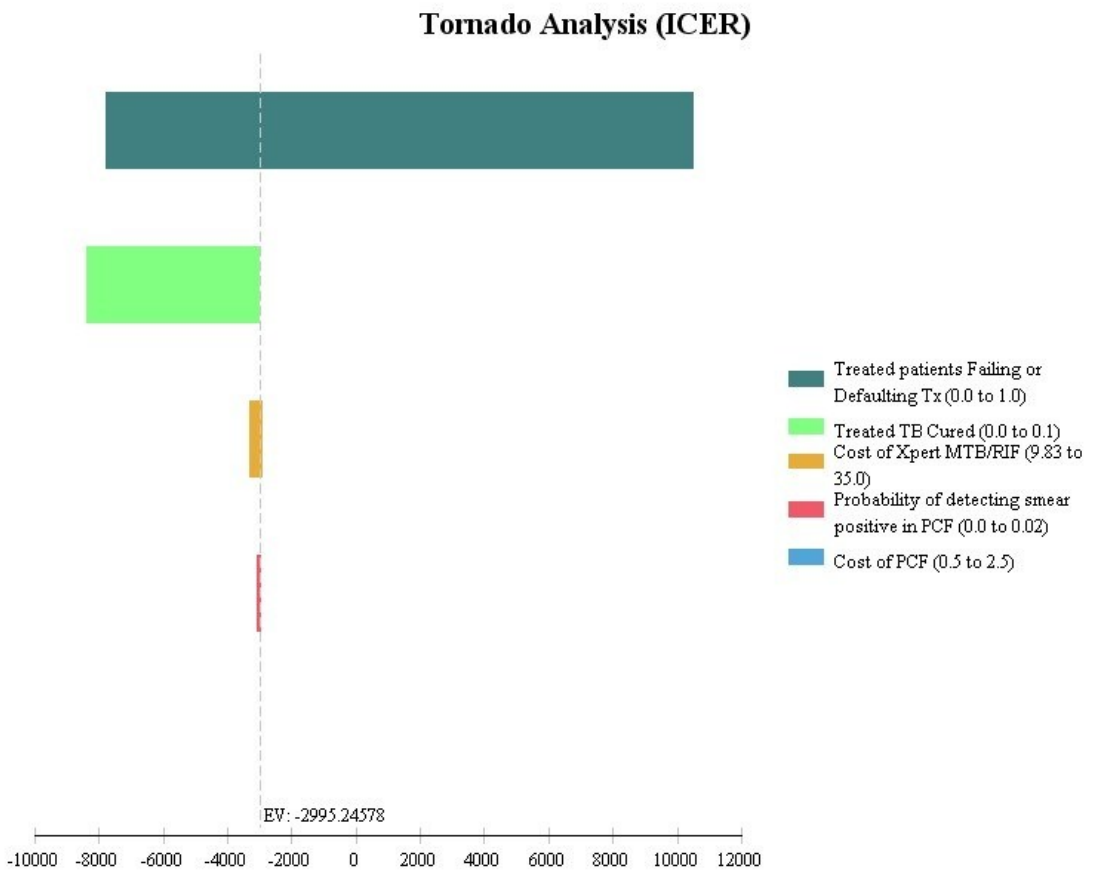


Figure 5.9 One-way sensitivity analysis of incremental cost-effectiveness ratio comparing passive case finding of household contacts with an integrated Xpert MTB/RIF (PCF+XPERT) to passive case finding strategy using sputum smear microscopy only.

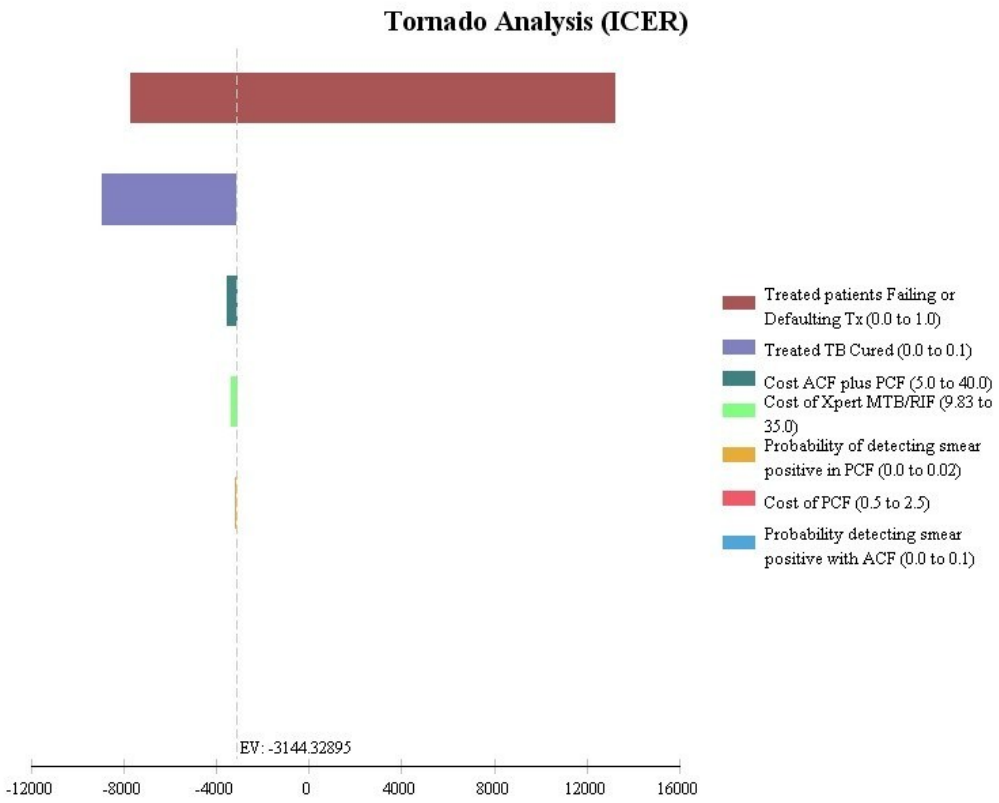


Figure 5.10 One-way sensitivity analysis of incremental cost-effectiveness ratio comparing active case finding household contacts with an integrated Xpert MTB/RIF test (ACF+XPERT) to passive case finding strategy with an integrated Xpert MTB/RIF test

CHAPTER 6 : Discussion

6.1 Summary

The goal of my thesis was to examine the role of active case finding of TB cases within a routine TB control program in the TB endemic setting of San Juan de Lurigancho (SJL) district, Lima, Peru. This was achieved through four specific objectives:

1. To examine the geographic clustering of Primary MDR-TB cases compared with DS-TB in the district of SJL to prioritize areas for targeted active case-finding prevention and prevent the continued community spread of drug resistant TB cases.
2. To design and implement an active case finding program for household contacts across all NTP health centres in the district of SJL.
3. To discuss the strengths and challenges of using the pragmatic stepped wedge cluster randomized trial design in operational research for TB programs in endemic settings.
4. To estimate the cost-effectiveness of an active case finding program of household contacts of new infectious TB cases in the district of SJL, in comparison with the standard passive case finding program.

6.2 Overall Strengths and Limitations

6.2.1 Strengths and limitations of thesis

This thesis contributes important to the expanding literature around active case finding of TB cases in SJL district. Overall, there are several strengths and limitations to the manuscripts presented.

In Manuscript 1, the geographic clustering was estimated using available data with epidemiologic and geographic information. The findings pertain to the time period in which the data were obtained and whether these are consistent with the current situation in SJL district is unclear. Based on NTP programmatic data, the 8 catchment areas detected in the SatScan cluster analysis continue to report high rates of primary MDR-TB. Additionally, MDR-TB is also reported from other catchment areas in SJL district previously not within the cluster identified. Updated analyses are needed to examine if clustering of primary MDR-TB cases is now occurring beyond the initial cluster identified.

Genotyping is routinely available in high-income settings, however in resource restricted settings these data are limited.[190] Therefore, whether or not primary MDR-TB identified in a single cluster are considered genetically related remains uncharacterized. Further studies on transmission could be valuable, however would be costly and time consuming in this population, with limited added benefit to the targeted case finding strategies. The analyses presented also did not examine space-time clustering; TB and primary MDR-TB cases are assigned to the date of treatment initiation, which in TB disease could be greatly different then disease onset and very different also from the time of exposure. Future studies could consider modelling sharp increases or decreases in cluster or case rates in certain areas of the district. Local cluster data could also help uncover localized outbreaks or changes to the epidemic, if more timely analyses were possible.

In Manuscript 2, active case finding in households of TB cases, is rarely undertaken systematically in LMICs. Stepped-wedge CRCT designs are among the study designs recommended to evaluate the implementation of household contact programs within NTPs,

however few if any have been conducted.[16] Case finding activities, including door-to-door campaigns and home visits to TB patients, do occur in settings like SJL in Peru. For example, home visits are routinely used to follow up patients who have abandoned treatment, and for verifying the jurisdiction of primary residence of the TB case for mandatory administrative procedures. A greater amount of added supervision was required to continually motivate staff to undertake the active case finding for the purpose of household contact evaluations. We used routine programmatic staff to undertake the intervention; however we did have dedicated supervision throughout the study period. A limitation of this study is that following implementation, added supervision will likely be needed to ensure sustainability of the intervention, though long term support for integrating systematic contact tracing for household contacts in terms of resource allocation is variable at the local level. During the work described in the thesis, the doctoral student was responsible for designing the study and the original grant submission (CIHR Operation Grant Funds) and has undertaken all of the groundwork to set up this project. This in part was additional support to the NTP which may not always be available. However, there are local supervision teams and managers who could take on similar roles during implementation plans or stepped-wedge designs. Training and supervision is adapted to the local context, for which local NTP programmers have in-depth knowledge and can easily take on these responsibilities.

In Manuscript 3, cost-effective analysis does provide new analyses for gaps in the overall cost of active case finding for household contacts and compares it with the inclusion of a more sensitive Xpert MTB/RIF test to detect TB disease. Like numerous modelling studies, these are subject to numerous assumptions. Firstly, many of the assumptions that lead to these case finding strategies being cost-effective is the assumption of an underlying effective passive

DOTS case finding program, with high degrees of cure and completion rates and with active efforts to minimize default and treatment failures. Implementing new diagnostic tools such as Xpert MTB/RIF, which would improve the sensitivity of detecting TB cases in both smear positive and smear negative cases, would be valuable investments assuming that the active TB cases detected using these methods all enter and complete treatment successfully and limited numbers of defaulters to treatment are generated.

Though these studies have limitations, to date, available data on active case finding implemented within routine TB programs from LMICs is very limited. Systematic reviews of active case finding strategies and household contact investigations in LMIC, in addition to the new WHO recommendations for screening all household contacts of smear positive TB, highlight that a higher quality of evidence is needed. Currently available data are primarily cohort studies, cross-sectional studies and mainly undertaken with dedicated and highly trained research staff. Despite the study limitations in this thesis, this doctoral thesis contributes new and valuable information on active case finding activities in TB endemic areas. The work presented in this dissertation will be particularly relevant to local TB programmers and decision makers in Peru and will also be pertinent to the many LMIC countries with endemic TB.

6.2.2 Generalizability of findings

The major strength and limitation of this thesis is its focus on a low HIV, TB endemic areas of Lima, Peru. Generalizability to high HIV burden settings, with different social, geographic and economic situations, for example as those in Sub-Saharan Africa, may be somewhat limited. Additionally, the findings of this thesis pertain to a large urban setting, where TB

programming, education and socioeconomic levels and the access to health services may differ from rural areas. In Peru, for example the Amazonian Jungle areas (Loreto Province) report high rates of TB, however local laboratory infrastructure, geographic isolation, limited road access and variable access to health centers are major challenges to TB control. The active case finding strategies deployed in rural areas of Peru may require different case detection strategies then those undertaken in urban Lima. The data we present are specific to SJL district, however SJL and its TB epidemic are comparable to several of the high risk TB districts in Central and North Eastern Lima. These areas have equally high rates of TB and MDR-TB and similar challenges in terms of informal housing and security in the community.

6.3 Implications

In general case finding activities locally involves both intramural and extramural (outside of the health clinics context). Passive case finding is a fundamental component of TB programs that aim to diagnosis and adequately treat symptomatic cases who present themselves to care. In contrast, the realm of active case finding includes a wide range of activities, including house to house campaigns, pointed and targeted interventions, working in high risk populations and in the community generally. In general the active case finding implicates a provider-initiated activity around identifying, seeking out and locating and evaluating persons at high risk for active TB and requires an input of public resources, both in materials, consumables, diagnostics and therapeutics as well as health personnel. In SJL district, overall a high burden TB district, typically extramural activities, including door to door campaigns and costly diagnostic tests (such as culture, DST and rapid drug susceptibility testing), including rapid diagnostics are deployed across the entire district health centers either adhoc or in response to a particular short term agenda. Incorporating a systematic program to evaluate all household contacts

using active case finding could be a cost-effective method to capture active TB cases in the community.

This thesis is the culmination of efforts made to strengthen and bridge the gap between researchers and local NTP in SJL district. For the most part in Peru, there are numerous TB researchers conducting important and groundbreaking work in the areas of new therapeutics, new diagnostics, management of MDR-TB cases. A major strength of this doctoral thesis is that it expanded and strengthened an international research network between Peruvian, Canadian and US collaborators. The doctoral thesis work was undertaken within an existing partnership between Dr. Timothy Brewer and Dr. Eduardo Gotuzzo. Numerous other relationships exist between various McGill University researchers and various Peruvian institutions and the three studies presented strengthened the interconnectivity of these relationships and built up partnerships between junior level Peruvian and Canadian researchers. This doctoral thesis also contributes and extends these efforts by working closely within the NTP at the local health center level. Previously the DISA NTP program and the SJL district NTP program were not directly involved in research activities undertaken locally in providing their sites and patients from their NTP district. In order to make the findings of this thesis useful to the local perspective, a collaborate integrated knowledge translation approach was used from the outset of this doctoral work.

6.4 Future directions for research

Several future areas of research were identified during the thesis work undertaken in SJL district. The following are select priority areas for consideration:

6.4.1 LTBI and preventive prophylactic treatment

The research presented in this thesis discusses the role of active case finding for active TB cases in SJL district. The role of preventive prophylactic treatment in reducing the overall number of exposed cases progressing to active TB should also be considered. INH prophylaxis is currently provided free of charge to children under 5 years old who are household contacts of TB cases in treatment. In SJL district, in 2011 and 2012, initiation of INH prophylaxis was low (less than 30% initiated) in all health centers of SJL; the proportion of completion of 6 months of INH prophylaxis was even lower. [87] In 2011, SJL district TB program carried out a cross-sectional Knowledge, Attitudes and Practices (KAP) survey with TB patients in treatment. Of 137 TB patients interviewed, 68.18% percent had a household member of 15 years of younger. Of those with children living in the same household, 66.1% did not know there was a preventive therapy or prophylaxis and 59.4% did not know that INH could be used as a means of preventing TB disease in children. This was a rapid survey undertaken in a convenience sample of patients in SJL health centers, however it suggests potential areas of further enquiry. Further data are required to better understand the effect of INH and the operational aspects of providing preventive prophylactic treatment to pediatric populations.

6.4.2 Social network analyses and social venues

Household contact tracing for smear positive TB cases targets persons at highest risk of acquiring TB. In developed settings, traditional contact tracing prioritizes household and close contacts and assigns less priority to casual contacts. This strategy is considered to have limited use in marginalized populations such as in the homeless, mobile or substance using populations. Transmission can occur at other social venues, including school, at work, and at pubs, bars and community centers are also important places to consider.[123,191–194] Anecdotally places such as internet cafes, and drug using hangouts have been suggested as locales where

TB cases may frequent in addition to their household. Further structured social network studies could help better characterize venues of importance for potential active case finding strategies.

6.4.3 CONSORT extension for stepped-wedge designs

Currently, a systematic review is underway by researchers at University of Birmingham (U.K), University of Warwick (U.K.) and Monash University (Australia) to inform the development of new CONSORT guidelines for stepped-wedge designs.[195] The review will identify papers in order to generate knowledge on the following topics: methodology, general design considerations, sample size and power calculations, analysis, rationale, and reporting. The protocol described in this dissertation is amongst the few undertaken in LMICs, in operational and infectious disease research and could contribute new information which will lead to future guidelines.

6.4.4 Qualitative research studies

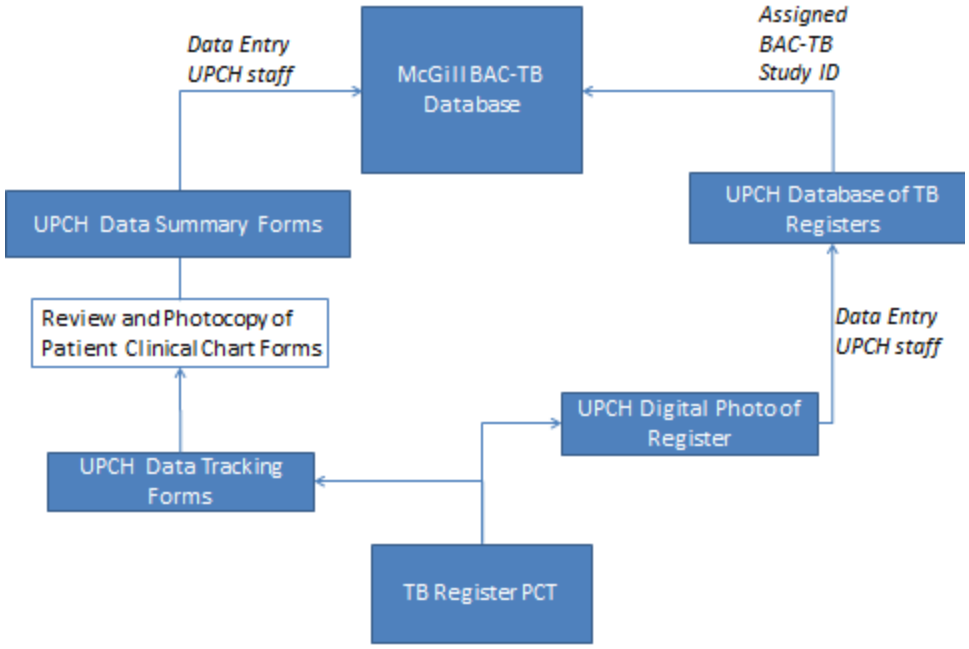
Quantitative evidence of the effectiveness of active case finding for TB cases and incorporating household contact investigations into a routine NTP program remains a fundamental need. Additionally, qualitative data on the perceptions and perspectives of those undertaking and receiving these programs could be useful and complement current knowledge on the feasibility of scaling up active case finding strategies. Currently, a qualitative research protocol is being developed in order to understand the perspectives of the nurses and physicians at the health center level in SJL who undertake active case finding with household contacts. The perspectives of TB patients who undergo household contact tracing will also be included. Our observational experience through the development and implementation of active case finding also highlighted the important role local NTP staff play

in the success of contact tracing strategies. The overall willingness of local health care staff to initiate and continue contact tracing over the long term relies on their perceived value of this activity, the burden of other responsibilities and challenges which cannot be measured easily with quantitative surveys. Anecdotal and observational data have highlighted some of the gaps and challenges faced by staff. In-depth information obtained through focus groups and key informant interviews could help local programmers and researchers understand the frontline challenges to systematically evaluate household contacts from an operational perspective.

CHAPTER 7 : Conclusions

In 2014, TB remains one of the top global infectious disease priorities and a major cause of morbidity and mortality worldwide. Countries such as Peru have made numerous strides in TB control, including in scaling up of a national DOTS programs and strengthening of laboratory infrastructure.[131] Despite these advances, improving the early and strategic detection of cases in the community remains a central concern for TB control programs in endemic areas. Increasingly, active case finding is becoming a priority for national TB control programs in TB endemic settings, including in Peru.[17,21,22,196] This thesis dissertation aimed to contribute to the growing literature and identified gaps in knowledge in the area of designing and implementing active case finding protocols, the estimated cost-effectiveness of active case finding compared to the routine programs. The findings of this thesis could be relevant to Peruvian TB control programmers and also to those working in similar settings, where TB rates are high, HIV rates are relatively low and where the basic infrastructure and operations of DOTS program are in place.

APPENDICES



The overall strategy for study teams to obtain information on cases and contacts during the intervention and control arms SJL health centers

Description of Roles and responsibilities in public health

	Decisions
Policy Maker National TB Program	'The Policy: its rationale, context communication, Guidelines, Resource recommendations'
Local TB Programmer	Organization, timing implementation, people affected, settings, monitoring, enforcement, day-to-day operations of the TB program, distribution, training, supplies, supervision, questions, ensuring high quality DOTS and Laboratory. Collating indicator and reporting performance to the National TB program'
Infectious Disease and Epidemiologic Researchers	Grant proposals with statistical methods plan, run focus groups, run scientific advisory, matching and blocking, randomization methods, blinding of analysis, statistical analyses, assess generalizability, overall interpretation, publication of findings
Joint Decisions	Duration of delay, size and location, whether to randomize, units of randomization, subset of population to randomize, baseline data availability, outcome measures, extra outcome data if needed, recruitment if needed, resources

REFERENCES

1 Global tuberculosis control - surveillance, planning, financing. World Health Organization, 2009.

2 The global plan to stop TB 2011-2015: transforming the fight towards elimination of tuberculosis. World Health Organization .

3 Glaziou P, Floyd K, Raviglione M. Global burden and epidemiology of tuberculosis. *Clin Chest Med* 2009; **30**: 621–36, vii.

4 Zumla A, Raviglione M, Hafner R, Fordham von Reyn C. Tuberculosis. *N Engl J Med* 2013; **368**: 745–755.

5 Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC *et al.* The Growing Burden of Tuberculosis. 2010; **163**: 1009–1021.

6 Espinal MA. The global situation of MDR-TB. *Tuberculosis* 2003; **9792**: 44–51.

7 Marais BJ, Raviglione MC, Donald PR, Harries AD, Kritski AL, Graham SM *et al.* Scale-up of services and research priorities for diagnosis, management, and control of tuberculosis: a call to action. *Lancet* 2010; **375**: 2179–2191.

8 Dye C, Lonnroth K, Jaramillo E, Williams BG, Raviglione M. Trends in tuberculosis incidence and their determinants in 134 countries. *Bull World Health Organ* 2009; **87**: 683–691.

9 Tuberculosis Prevention and Control, Public Health Agency of Canada, Canadian Lung Association. Canadian Tuberculosis Standards, 6th edition. Ottawa, 2007.

10 Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. *MMWR Recomm Rep* 2005; **54**: 1–47.

11 *International Standards for Tuberculosis Care (ISTC), second edition.* The Hague, 2009.

12 World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low-and middle-income countries. 2012http://apps.who.int/iris/handle/10665/77741 (accessed 16 Jul2014).

13 Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Infect Dis* 2008; **8**: 359–68.

14 Corbett EL, Bandason T, Duong T, Dauya E, Makamure B, Churchyard GJ *et al.* Comparison of two active case-finding strategies for community-based diagnosis of

symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. *Lancet* 2010; **376**: 1244–53.

15 Becerra MC, Pachao-Torreblanca IF, Bayona J, Celi R, Shin SS, Kim JY *et al.* Expanding tuberculosis case detection by screening household contacts. *Public Health Rep* 2005; **120**: 271–277.

16 Cavalcante SC, Durovni B, Barnes GL, Souza FB, Silva RF, Barroso PF *et al.* Community-randomized trial of enhanced DOTS for tuberculosis control in Rio de Janeiro, Brazil. *Int J Tuberc Lung Dis* 2010; **14**: 203–209.

17 Murray CJ, Salomon JA. Modeling the impact of global tuberculosis control strategies. *Proc Natl Acad Sci U S A* 1998; **95**: 13881–13886.

18 Currie CS, Williams BG, Cheng RC, Dye C. Tuberculosis epidemics driven by HIV: is prevention better than cure? *AIDS* 2003; **17**: 2501–2508.

19 Bayona J, Chavez-Pachas AM, Palacios E, Llaro K, Sapag R, Becerra MC. Contact investigations as a means of detection and timely treatment of persons with infectious multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2003; **7**: S501–9.

20 Becerra MC, Appleton SC, Franke MF, Chalco K, Arteaga F, Bayona J *et al.* Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: A retrospective cohort study. *Lancet* 2011; **377**: 147–152.

21 Fox GJ, Dobler CC, Marks GB. Active case finding in contacts of people with tuberculosis. *Cochrane Database Syst Rev* 2011; **9**: CD008477.

22 Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. *Int J Tuberc Lung Dis* 2005; **9**: 1183–1203.

23 Lienhardt C, Cobelens FG. Operational research for improved tuberculosis control: the scope, the needs and the way forward. *Int J Tuberc Lung Dis* 2011; **15**: 6–13.

24 Sculier D, Getahun H, Lienhardt C. Improving the prevention, diagnosis and treatment of TB among people living with HIV: the role of operational research. *J Int AIDS Soc* 2011; **14 Suppl 1**: S5.

25 Nunn P, Harries A, Godfrey-Faussett P, Gupta R, Maher D, Raviglione M. The research agenda for improving health policy, systems performance, and service delivery for tuberculosis control: a WHO perspective. *Bull World Health Organ* 2002; **80**: 471–476.

26 World Health Organization. Global tuberculosis report 2012. 2012.

27 Dye C, Ottmani S, Laasri L, Bencheikh N. The decline of tuberculosis epidemics under chemotherapy: a case study in Morocco. *Int J Tuberc Lung Dis* 2007; **11**: 1225–1231.

28 Grzybowski S, Allen EA. The Challenge of Tuberculosis in Decline. A Study Based on the Epidemiology of Tuberculosis in Ontario, Canada. *Am Rev Respir Dis* 1964; **90**: 707–720.

29 Laurenti P, Bruno S, Quaranta G, La Torre G, Cairo AG, Nardella P *et al.* Tuberculosis in sheltered homeless population of Rome: an integrated model of recruitment for risk management. *ScientificWorldJournal* 2012; **2012**: 396302.

30 Nardell E, McInnis B, Thomas B, Weidhaas S. Exogenous reinfection with tuberculosis in a shelter for the homeless. *N Engl J Med* 1986; **315**: 1570–1575.

31 Bleed D, Dye C, Raviglione MC. Dynamics and control of the global tuberculosis epidemic. *Curr Opin Pulm Med* 2000; **6**: 174–179.

32 Global tuberculosis control: WHO report 2011. World Health Organization: Geneva, 2011.

33 Lawn SD, Zumla AI. Tuberculosis. *Lancet* 2011; **378**: 57–72.

34 Coberly G.W. JS. C. Epidemiology of Tuberculosis. In: Raviglione MC (ed). *Tuberculosis. A Comprehensive International Approach, 3rd edition, Part A*. 2006.

35 Schluger NW. The pathogenesis of tuberculosis: the first one hundred (and twenty-three) years. *Am J Respir Cell Mol Biol* 2005; **32**: 251–6.

36 Lonnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. *Soc Sci Med* 2009; **68**: 2240–2246.

37 Ministerio de Salud. Norma Tecnica de Salud para el Control de la Tuberculosis. Lima, Peru, 2006.

38 Harries AD, Dye C. Tuberculosis. *Ann Trop Med Parasitol* 2006; **100**: 415–431.

39 Vassall A, van Kampen S, Sohn H, Michael JS, John KR, den Boon S *et al.* Rapid Diagnosis of Tuberculosis with the Xpert MTB / RIF Assay in High Burden Countries: A Cost-Effectiveness Analysis. *PLoS Med* 2011; **8**: e1001120.

40 Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F *et al.* Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med* 2010; **363**: 1005–1015.

41 Chew R, Calderon C, Schumacher SG, Sherman JM, Caviedes L, Fuentes P *et al.* Evaluation of bleach-sedimentation for sterilising and concentrating Mycobacterium tuberculosis in sputum specimens. *BMC Infect Dis* 2011; **11**: 269.

42 Harries AD, Dye C. Tuberculosis. Ann. Trop. Med. Parasitol. 2006; **100**: 415–431.

43 Tostmann A, Kik S V, Kalisvaart NA, Sebek MM, Verver S, Boeree MJ *et al.* Tuberculosis transmission by patients with smear-negative pulmonary tuberculosis in a large cohort in the Netherlands. *Clin Infect Dis* 2008; **47**: 1135–1142.

44 Kenyon TA, Creek T, Laserson K, Makhoa M, Chimidza N, Mwasekaga M *et al.* Risk factors for transmission of Mycobacterium tuberculosis from HIV-infected tuberculosis patients, Botswana. *Int J Tuberc Lung Dis* 2002; **6**: 843–850.

45 Elzinga G, Raviglione MC, Maher D. Scale up: meeting targets in global tuberculosis control. *Lancet* 2004; ***363***: 814–819.

46 Veron LJ, Blanc LJ, Suchi M, Raviglione MC. DOTS expansion: will we reach the 2005 targets? *Int J Tuberc Lung Dis* 2004; **8**: 139–146.

47 Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. *Lancet* 1998; ***352***: 1886–1891.

48 Dye C, Hosseini M, Watt C. Did we reach the 2005 targets for tuberculosis control? *Bull World Health Organ* 2007; **85**: 364–369.

49 Dye C, Maher D, Weil D, Espinal M, Raviglione M. Targets for global tuberculosis control. *Int J Tuberc Lung Dis* 2006; **10**: 460–462.

50 Onozaki I, Raviglione M. Stopping tuberculosis in the 21st century: goals and strategies. *Respirology* 2010; **15**: 32–43.

51 Dowdy DW, Chaisson RE. The persistence of tuberculosis in the age of DOTS: reassessing the effect of case detection. *Bull World Heal Organ* 2009; : 296–304.

52 Farmer P, Bayona J, Becerra M, Furin J, Henry C, Hiatt H *et al.* The dilemma of MDR-TB in the global era. *Int J Tuberc Lung Dis* 1998; **2**: 869–876.

53 Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Mishustin S *et al.* Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. *Int J Tuberc Lung Dis* 2007; **11**: 1314–1320.

54 Victor TC, Streicher EM, Kewley C, Jordaan AM, van der Spuy GD, Bosman M *et al.* Spread of an emerging Mycobacterium tuberculosis drug-resistant strain in the western Cape of South Africa. *Int J Tuberc Lung Dis* 2007; **11**: 195–201.

55 Dye C, Williams BG. Criteria for the control of drug-resistant tuberculosis. *Proc Natl Acad Sci U S A* 2000; **97**: 8180–8185.

56 Otero L, Krapp F, Tomatis C, Zamudio C, Matthys F, Gotuzzo E *et al.* High prevalence of primary multidrug resistant tuberculosis in persons with no known risk factors. *PLoS One* 2011; **6**: e26276.

57 Nachega JB, Chaisson RE. Tuberculosis drug resistance: a global threat. *Clin Infect Dis* 2003; **36**: S24–30.

58 Corbett EL, Bandason T, Duong T, Dauya E, Makamure B, Churchyard GJ *et al.* Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. *Lancet* 2010; **376**: 1244–1253.

59 Lorent N, Choun K, Thai S, Kim T, Huy S, Pe R *et al.* Community-based active tuberculosis case finding in poor urban settlements of Phnom Penh, Cambodia: a feasible and effective strategy. *PLoS One* 2014; **9**: e92754.

60 Monney M, Zellweger JP. Active and passive screening for tuberculosis in Vaud Canton, Switzerland. *Swiss Med Wkly* 2005; **135**: 469–474.

61 Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis : historical perspective and future prospects. *Int J Tuberc Lung Dis* 2005; **9**: 1183–1203.

62 Murray CJ, Salomon JA. Expanding the WHO tuberculosis control strategy: rethinking the role of active case-finding. *Int J Tuberc Lung Dis* 1998; **2**: S9–15.

63 Moulton LH, Golub JE, Durovni B, Cavalcante SC, Pacheco AG, Saraceni V *et al.* Statistical design of THRio: a phased implementation clinic-randomized study of a tuberculosis preventive therapy intervention. *Clin trials* 2007; **4**: 190–199.

64 Miller AC, Golub JE, Cavalcante SC, Durovni B, Moulton LH, Fonseca Z *et al.* Controlled trial of active tuberculosis case finding in a Brazilian favela. *Int J Tuberc Lung Dis* 2010; **14**: 720–726.

65 Yadav RP, Nishikiori N, Satha P, Eang MT, Lubell Y. Cost-effectiveness of a tuberculosis active case finding program targeting household and neighborhood contacts in Cambodia. *Am J Trop Med Hyg* 2014; **90**: 866–72.

66 Fox GJ, Nhung NV, Sy DN, Britton WJ, Marks GB. Household contact investigation for tuberculosis in Vietnam: study protocol for a cluster randomized controlled trial. *Trials* 2013; **14**: 342.

67 Borgdorff MW, Floyd K, Broekmans JF. Policy and Practice Interventions to reduce tuberculosis mortality and transmission in low- and middle-income countries *. 2010; **80**.

68 Veen J. Microepidemics of tuberculosis: the stone-in-the-pond principle. *Tuber Lung Dis* 1992; **73**: 73–76.

69 Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. *Bull Int Union Tuberc* 1975; **50**: 90–106.

70 Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. *Bull Int Union Tuberc Lung Dis* 1975; **50**: 90–106.

71 Fok A, Numata Y, Schulzer M, FitzGerald MJ. Risk factors for clustering of tuberculosis cases: a systematic review of population-based molecular epidemiology studies. *Int J Tuberc Lung Dis* 2008; **12**: 480–492.

72 Cavalcante SC, Soares EC, Pacheco AG, Chaisson RE, Durovni B. Community DOT for tuberculosis in a Brazilian favela: comparison with a clinic model. *Int J Tuberc Lung Dis* 2007; **11**: 544–549.

73 Liu E, Cheng S, Wang X, Hu D, Zhang T, Chu C. A systematic review of the investigation and management of close contacts of tuberculosis in China. *J Public Health (Oxf)* 2010; **32**: 461–6.

74 Den Boon S, Verver S, Lombard CJ, Bateman ED, Irusen EM, Enarson DA *et al.* Comparison of symptoms and treatment outcomes between actively and passively detected tuberculosis cases: the additional value of active case finding. *Epidemiol Infect* 2008; **136**: 1342–1349.

75 Getahun H, Raviglione M. Active case-finding for TB in the community: time to act. *Lancet* 2010; **376**: 1205–1206.

76 Gray AM, Clarke PM, Wolstenholme J, Wordsworth S. *Applied Methods of Cost-effectiveness Analysis in Health Care.* Oxford University Press: New York, 2011.

77 Sekandi JN, Neuhauser D, Smyth K, Whalen CC. Active case finding of undetected tuberculosis among chronic coughers in a slum setting in Kampala, Uganda. *Int J Tuberc Lung Dis* 2009; **13**: 508–513.

78 Dasgupta K, Schwartzman K, Marchand R, Tennenbaum TN, Brassard P, Menzies D. Comparison of cost-effectiveness of tuberculosis screening of close contacts and foreign-born populations. *Am J Respir Crit Care Med* 2000; **162**: 2079–2086.

79 Etkind J. SC. V. The Role of Contact Tracing in Low- and High-Prevalence Countries. In: Raviglione MC (ed). *Tuberculosis. A Comprehensive International Approach, 3rd edition. Part A.* 2006.

80 Verver S, van Loenhout-Rooyackers JH, Bwire R, Annee-van Bavel JA, de Lange HJ, van Gerven PJ *et al.* Tuberculosis infection in children who are contacts of immigrant tuberculosis patients. *Eur Respir J Off J Eur Soc Clin Respir Physiol* 2005; **26**: 126–132.

81 Zellweger JP. Tuberculosis in households of index patients: is there another way to control tuberculosis? *Int J Tuberc Lung Dis* 2002; **6**: 181–182.

82 Pooran A, Booth H, Miller RF, Scott G, Badri M, Huggett JF *et al.* Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost effectiveness analysis. *BMC Pulm Med* 2010; **10**: 7.

83 Kranzer K, Houben RM, Glynn JR, Bekker L-G, Wood R, Lawn SD. Yield of HIV-associated tuberculosis during intensified case finding in resource-limited settings: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10**: 93–102.

84 Kranzer K, Houben RM, Glynn JR, Bekker LG, Wood R, Lawn SD. Yield of HIV-associated tuberculosis during intensified case finding in resource-limited settings: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10**: 93–102.

85 Azman AS, Golub JE, Dowdy DW. How much is tuberculosis screening worth? Estimating the value of active case finding for tuberculosis in South Africa, China, and India. *BMC Med* 2014; **12**: 216.

86 Suarez PG, Watt CJ, Alarcon E, Portocarrero J, Zavala D, Canales R *et al.* The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru. *J Infect Dis* 2001; **184**: 473–478.

87 Pena MR. NTP Programmatic Operation Data, DISA, Red de San Juan de Lurigancho. 2012.http://www.redsasjl.gob.pe/index.php?cont=estadistica.

88 Chavez Pachas AM, Blank R, Smith Fawzi MC, Bayona J, Becerra MC, Mitnick CD. Identifying early treatment failure on category I therapy for pulmonary tuberculosis in Lima Ciudad, Peru. *Int J Tuberc Lung Dis* 2004; **8**: 52–58.

89 Ministerio de Salud. Información Estadística Dirección de Salud IV Lima Este. 2012.http://www.limaeste.gob.pe/Virtual/Estadistica/IframeEstadistica.asp.

90 Petitti DB. *Meta-Analysis, Decision Analysis, and Cost-Effectivness Analysis. Methods for Quantitative Synthesis in Medicine, 2nd edition.* Oxford Press: New York, 2000.

91 De Jonghe E, Murray CJ, Chum HJ, Nyangulu DS, Salomao A, Styblo K. Cost-effectiveness of chemotherapy for sputum smear-positive pulmonary tuberculosis in Malawi, Mozambique and Tanzania. *Int J Heal Plann Manag* 1994; **9**: 151–181.

92 Resch SC, Salomon JA, Murray M, Weinstein MC. Cost-effectiveness of treating multidrug-resistant tuberculosis. *PLoS Med* 2006; **3**: e241.

93 Suarez PG, Floyd K, Portocarrero J, Alarcon E, Rapiti E, Ramos G *et al.* Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. *Lancet* 2002; **359**: 1980–1989.

94 Otero L, Ugaz R, Dieltiens G, Gonzalez E, Verdonck K, Seas C *et al.* Duration of cough, TB suspects' characteristics and service factors determine the yield of smear microscopy. *Trop Med Int Heal* 2010; **15**: 1475–1480.

95 Instituto Nacional de Estadistica e Informatica (INEI). Peruvian National Census, 2007. 2007.http://www.inei.gob.pe/.

96 Kiefer EM, Shao T, Carrasquillo O, Nabeta P, Seas C. Knowledge and attitudes of tuberculosis management in San Juan de Lurigancho district of Lima, Peru. *J Infect Dev Ctries* 2009; **3**: 783–788.

97 Gardy JL, Johnston JC, Ho Sui SJ, Cook VJ, Shah L, Brodkin E *et al.* Whole-genome sequencing and social-network analysis of a tuberculosis outbreak. *N Engl J Med* 2011; **364**: 730–739.

98 Dye C, Watt CJ, Bleed DM, Williams BG. What is the limit to case detection under the DOTS strategy for tuberculosis control? *Tuberculosis* 2003; **83**: 35–43.

99 Enarson DA, Wang JS, Grzybowski S. Case-finding in the elimination phase of tuberculosis: tuberculosis in displaced people. *Bull Int Union Tuberc Lung Dis* 1990; **65**: 71–72.

100 Dye C, Watt CJ, Bleed DM, Hosseini SM, Raviglione MC. Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally. *JAMA* 2005; **293**: 2767–2775.

101 Lonnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. *Soc Sci Med* 2009; **68**: 2240–2246.

102 Brewer TF, Choi HW, Seas C, Krapp F, Zamudio C, Shah L *et al.* Self-reported risks for multiple-drug resistance among new tuberculosis cases: implications for drug susceptibility screening and treatment. *PLoS One* 2011; **6**: e25861.

103 Shah L, Choi HW, Berrang-Ford L, Henostroza G, Krapp F, Zamudio C *et al.* Geographic predictors of primary multidrug-resistant tuberculosis cases in an endemic area of Lima, Peru. *Int J Tuberc Lung Dis* 2014; **18**: 1307–14.

104 Mukherjee JS, Rich ML, Socci AR, Joseph JK, Viru FA, Shin SS *et al.* Programmes and principles in treatment of multidrug-resistant tuberculosis. *Lancet* 2004; **363**: 474–481.

105 Raviglione MC. The TB epidemic from 1992 to 2002. *Tuberculosis* 2003; **83**: 4–14.

106 World Health Organization. Global tuberculosis report. 2012.

107 Nachega JB, Chaisson RE. Tuberculosis drug resistance: a global threat. *Clin Infect Dis* 2003; **36**: S24–30.

108 Lin HH, Shin SS, Contreras C, Asencios L, Paciorek CJ, Cohen T. Use of spatial information to predict multidrug resistance in tuberculosis patients, Peru. *Emerg Infect Dis* 2012; **18**: 811–813.

109 Bonilla C. Situacion de la Tuberculosis en el Peru. *Acta Med Per* 2008; **25**: 163–170.

110 Ministerio de Salud. Estadísticas Población. 2013; **2013**.http://www.minsa.gob.pe/estadisticas/estadisticas/Poblacion/PoblacionMarcos.asp?15.

111 Acuna-villaorduna C, Vassall A, Henostroza G, Seas C, Guerra H, Vasquez L *et al.* Cost-effectiveness analysis of introduction of rapid, alternative methods to identify multidrug-resistant tuberculosis in middle-income countries. *Clin Infect Dis* 2008; **47**: 487–495.

112 Hernandez Tejada FN. Determinantes de fracaso al esquema uno de tratamiento anti tuberculosis en Lima Norte, Perú: estudio de cohorte retrospectivo. Universidad Peruana Cayetano Heredia: Lima, Peru, 2007.

113 Kulldorff M, Huang L, Pickle L, Duczmal L. An elliptic spatial scan statistic. *Stat Med* 2006; **25**: 3929–3943.

114 Kulldorff M. and Information Management Services I. SaTScanTM v8.0: Software for the spatial and space-time scan statistics. http://www.satscan.org/. 2009.http://www.satscan.org/.

115 Team RC. R: A Language and Environment for Statistical Computing. 2013.http://www.r-project.org.

116 Escombe AR, Oeser CC, Gilman RH, Navincopa M, Ticona E, Pan W *et al.* Natural ventilation for the prevention of airborne contagion. *PLoS Med* 2007; **4**: e68.

117 Munch Z, Van Lill SW, Booysen CN, Zietsman HL, Enarson DA, Beyers N. Tuberculosis transmission patterns in a high-incidence area: a spatial analysis. *Int J Tuberc Lung Dis* 2003; **7**: 271–277.

118 Vieira AA, Ribeiro SA, Siqueira AM, Galesi VM, Santos LA, Golub JE. Prevalence of patients with respiratory symptoms through active case finding and diagnosis of pulmonary tuberculosis among prisoners and related predictors in a jail in the city of Carapicuiba, Brazil. *Rev Bras Epidemiol* 2010; **13**: 641–650.

119 Wanyeki I, Olson S, Brassard P, Menzies D, Ross N, Behr M *et al.* Dwellings, crowding, and tuberculosis in Montreal. *Soc Sci Med* 2006; **63**: 501–511.

120 Verver S, Warren RM, Munch Z, Vynnycky E, van Helden PD, Richardson M *et al.* Transmission of tuberculosis in a high incidence urban community in South Africa. *Int J Epidemiol* 2004; **33**: 351–357.

121 Schaaf HS, Michaelis IA, Richardson M, Booysen CN, Gie RP, Warren R *et al.* Adult-to-child transmission of tuberculosis: household or community contact? *Int J Tuberc Lung Dis* 2003; **7**: 426–431.

122 Klovdahl AS, Graviss EA, Yaganehdoost A, Ross MW, Wanger A, Adams GJ *et al.* Networks and tuberculosis: an undetected community outbreak involving public places. *Soc Sci Med* 2001; **52**: 681–694.

123 Murray EJ, Marais BJ, Mans G, Beyers N, Ayles H, Godfrey-Faussett P *et al.* A multidisciplinary method to map potential tuberculosis transmission "hot spots" in high-burden communities. *Int J Tuberc Lung Dis* 2009; **13**: 767–774.

124 Dye C, Espinal MA. Will tuberculosis become resistant to all antibiotics? *Proc Biol Sci* 2001; **268**: 45–52.

125 Cohen T, Murray M. Modeling epidemics of multidrug-resistant M. tuberculosis of heterogeneous fitness. *Nat Med* 2004; **10**: 1117–1121.

126 Gagneux S, Burgos M V., DeRiemer K, Enciso A, Muñoz S, Hopewell PC *et al.* Impact of bacterial genetics on the transmission of isoniazid-resistant Mycobacterium tuberculosis. *PLoS Pathog* 2006; **2**: 0603–0610.

127 Verdonck K, Gonzalez E, Henostroza G, Nabeta P, Llanos F, Cornejo H *et al.* HTLV-1 infection is frequent among out-patients with pulmonary tuberculosis in northern Lima, Peru. *Int J Tuberc Lung Dis* 2007; **11**: 1066–1072.

128 Verdonck K, Gonzalez E, Schrooten W, Vanham G, Gotuzzo E. HTLV-1 infection is associated with a history of active tuberculosis among family members of HTLV-1-infected patients in Peru. *Epidemiol Infect* 2008; **136**: 1076–1083.

129 Nardell EA. Catching droplet nuclei: toward a better understanding of tuberculosis transmission. *Am J Respir Crit Care Med* 2004; **169**: 553–554.

130 Horna-Campos OJ, Bedoya-Lama A, Romero-Sandoval NC, Martin-Mateo M. Risk of tuberculosis in public transport sector workers, Lima, Peru. *Int J Tuberc Lung Dis* 2010; **14**: 714–719.

131 Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990; **1**: 43–46.

132 Haase I, Olson S, Behr MA, Wanyeki I, Thibert L, Scott A *et al.* Use of geographic and genotyping tools to characterise tuberculosis transmission in Montreal. *Int J Tuberc Lung Dis* 2007; **11**: 632–638.

133 Falzon D, Jaramillo E, Schunemann HJ, Arentz M, Bauer M, Bayona J *et al.* WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur Respir J Off J Eur Soc Clin Respir Physiol* 2011; **38**: 516–528.

134 Guyatt G, Oxman AD, Akl E a, Kunz R, Vist G, Brozek J *et al.* GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; **64**: 383–94.

135 Maclure M. Explaining pragmatic trials to pragmatic policy-makers. *CMAJ* 2009; **180**: 1001–1003.

136 Allotey P, Reidpath DD, Ghalib H, Pagnoni F, Skelly WC. Efficacious, effective, and embedded interventions: implementation research in infectious disease control. *BMC Public Health* 2008; **8**: 343.

137 Volmink J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane database Syst Rev* 2007; **4**: 1–32.

138 Sanson-Fisher RW, D´Este CA, Carey ML, Noble N, Paul CL. Evaluation of Systems-Oriented Public Health Interventions: Alternative Research Designs. *Annu Rev Public Health* 2014; **35**: 9–27.

139 Rychetnik L, Frommer M, Hawe P, Shiell A. Criteria for evaluating evidence on public health interventions. *J Epidemiol Community Health* 2002; **56**: 119–127.

140 Hussey M a, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials* 2007; **28**: 182–191.

141 Mdege ND, Man MS, Taylor Nee Brown CA, Torgerson DJ. Systematic review of stepped wedge cluster randomized trials shows that design is particularly used to evaluate interventions during routine implementation. *J Clin Epidemiol* 2011; **64**: 936–948.

142 Handley MA, Schillinger D, Shiboski S. Quasi-Experimental Designs in Practice-based Research Settings: Design and Implementation Considerations. *J Am Board Fam Med* 2011; : 589–596.

143 Rhoda DA, Murray DM, Andridge RR, Pennell ML, Hade EM. Studies With Staggered Starts: Multiple Baseline Designs and Group-Randomized Trials. *Am J Public Health* 2011; **101**: 2164–2169.

144 Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. *BMC Med Res Methodol* 2006; **6**: 54.

145 Mdege ND, Man M-S, Taylor Nee Brown C a, Torgerson DJ. Systematic review of stepped wedge cluster randomized trials shows that design is particularly used to evaluate interventions during routine implementation. *J Clin Epidemiol* 2011; **64**: 936–48.

146 Mdege ND, Man MS, Taylor Nee Brown CA, Torgerson DJ. Systematic review of stepped wedge cluster randomized trials shows that design is particularly used to evaluate interventions during routine implementation. *J Clin Epidemiol* 2011; **64**: 936–948.

147 Kitson AL, Schultz TJ, Long L, Shanks A, Wiechula R, Chapman I. The prevention and reduction of weight loss in an acute tertiary care setting: protocol for a pragmatic

stepped wedge randomised cluster trial (the PRoWL project). *BMC Health Serv Res* 2013; **13**: 1.

148 Palmay L, Elligsen M, Walker SSAN, Pinto R, Einarson T, Simor A *et al.* Hospital-wide Roll-out of Antimicrobial Stewardship: A Stepped-Wedge Randomized Trial. *Clin Infect Dis* 2014; **59**: 867–74.

149 Zhan Z, Heuvel ER Van Den, Doornbos PM, Burger H, Verberne CJ, Wiggers T *et al.* Strengths and weaknesses of a stepped wedge cluster randomized design: its application in a colorectal cancer follow-up study. *J Clin Epidemiol* 2014; **67**: 454–461.

150 Haddow J, Adwan H, Clark S, Tayeh S, Antonowicz S, Jayia P *et al.* Use of the surgical Apgar score to guide postoperative care. *Ann R Coll Surg Engl* 2014; **96**: 352–8.

151 Brown BB, Young J, Smith DP, Kneebone AB, Brooks AJ, Xhilaga M *et al.* Clinician-led improvement in cancer care (CLICC) - testing a multifaceted implementation strategy to increase evidence-based prostate cancer care: phased randomised controlled trial - study protocol. *Implement Sci* 2014; **9**: 64.

152 Van de Steeg L, IJkema R, Langelaan M, Wagner C. Can an e-learning course improve nursing care for older people at risk of delirium: a stepped wedge cluster randomised trial. *BMC Geriatr* 2014; **14**: 69–76.

153 Bouwsma EV, Anema JR, Vonk Noordegraaf A, Knol DL, Bosmans JE, Schraffordt Koops SE *et al.* The cost effectiveness of a tailored, web-based care program to enhance postoperative recovery in gynecologic patients in comparison with usual care: protocol of a stepped wedge cluster randomized controlled trial. *JMIR Res Protoc* 2014; **3**: e30.

154 Badenbroek IF, Stol DM, Nielen MMJ, Hollander M, Kraaijenhagen RA, de Wit GA *et al.* Design of the INTEGRATE study: effectiveness and cost-effectiveness of a cardiometabolic risk assessment and treatment program integrated in primary care. *BMC Fam Pract* 2014; **15**: 90.

155 Chavane L, Merialdi M, Betrán AP, Requejo-Harris J, Bergel E, Aleman A *et al.* Implementation of evidence-based antenatal care in Mozambique: a cluster randomized controlled trial: study protocol. *BMC Health Serv Res* 2014; **14**: 228.

156 Kenyon S, Dann S, Clarke P, Hogan A, Jenkinson D, Hemming K. PD.01 Stepped wedge cluster trial to evaluate training to community midwives to improve membrane sweeping to reduce induction of labour. *Arch Dis Child Fetal Neonatal Ed* 2014; **99 Suppl 1**: A80–2.

157 Franklin BD, Reynolds M, Sadler S, Hibberd R, Avery AJ, Armstrong SJ *et al.* The effect of the electronic transmission of prescriptions on dispensing errors and prescription enhancements made in English community pharmacies: a naturalistic stepped wedge study. *BMJ Qual Saf* 2014; **23**: 629–38.

158 Maclure M, Carleton B, Schneeweiss S. Designed Delays Versus Rigorous Pragmatic Trials. *Med Care* 2009; **45**: 44–49.

159 Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC *et al.* The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; **163**: 1009–1021.

160 Construyendo alianzas estragecias para detener la tuberculosis: la experencia peruana/ Ministerio de Salud. Lima, Peru: Direccion General de Salad de las Personas-Programa de Control de la Tuberculosis; 2006. Peru.

161 Hill PC, Ota MOC. Tuberculosis case-contact research in endemic tropical settings: design, conduct, and relevance to other infectious diseases. *Lancet Infect Dis* 2010; **10**: 723–32.

162 Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B *et al.* Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008; **337**: a2390.

163 Durovni B, Cavalcante SC, Saraceni V, Vellozo V, Israel G, King BS *et al.* The implementation of isoniazid preventive therapy in HIV clinics: the experience from the TB/HIV in Rio (THRio) study. *AIDS* 2010; **24 Suppl 5**: S49–56.

164 Maclure M, Carleton B, Schneeweiss S. Designed Delays Versus Rigorous Pragmatic Trials. *Med Care* 2009; **45**: 44–49.

165 Frieden TR. Six Components Necessary for Effective Public Health Program Implementation. *Am J Public Health* 2013; **104**: 17–22.

166 Marais BJ, Gie RP, Hesseling AC, Schaaf HS, Lombard C, Enarson DA *et al.* A refined symptom-based approach to diagnose pulmonary tuberculosis in children. *Pediatrics* 2006; **118**: e1350–9.

167 Jackson-Sillah D, Hill PC, Fox A, Brookes RH, Donkor S a, Lugos MD *et al.* Screening for tuberculosis among 2381 household contacts of sputum-smear-positive cases in The Gambia. *Trans R Soc Trop Med Hyg* 2007; **101**: 594–601.

168 Dowdy DW, Lourenco MC, Cavalcante SC, Saraceni V, King B, Golub JE *et al.* Impact and cost-effectiveness of culture for diagnosis of tuberculosis in HIV-infected Brazilian adults. *PLoS One* 2008; **3**: e4057.

169 Floyd K, Arora VK, Murthy KJ, Lonnroth K, Singla N, Akbar Y *et al.* Cost and cost-effectiveness of PPM-DOTS for tuberculosis control: evidence from India. *Bull World Heal Organ* 2006; **84**: 437–445.

170 Diel R, Nienhaus A, Loddenkemper R. Cost-effectiveness of interferon-gamma release assay screening for latent tuberculosis infection treatment in Germany. *Chest* 2007; **131**: 1424–34.

171 Okello D, Floyd K, Adatu F, Odeke R, Gargioni G. Cost and cost-effectiveness of community-based care for tuberculosis patients in rural Uganda. *Int J Tuberc Lung Dis* 2003; **7**: S72–9.

172 Resch SC, Salomon J a, Murray M, Weinstein MC. Cost-effectiveness of treating multidrug-resistant tuberculosis. *PLoS Med* 2006; **3**: e241.

173 Brewer TF, Heymann SJ, Ettling M. An effectiveness and cost analysis of presumptive treatment for Mycobacterium tuberculosis. *Am J Infect Control* 1998; **26**: 232–238.

174 Voigt K, King NB. Disability weights in the global burden of disease 2010 study: two steps forward , one step back ? *Bull World Heal Organ* 2014; **92**: 226–228.

175 Murray CJL, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C *et al.* GBD 2010: Design, definitions, and metrics. 2012.

176 World Health Organization. Global Burden of Disease 2004 Update : Disability weights for diseases and conditions. 2004.

177 Tan-Torres Edejer T, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans DB *et al.* *WHO guide to cost-effectiveness analysis*. 2003.

178 Lonnroth K, Raviglione M. Global epidemiology of tuberculosis: prospects for control. *Semin Respir Crit Care Med* 2008; **29**: 481–491.

179 Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C. Tuberculosis. *Lancet* 2003; **362**: 887–899.

180 Dye C, Floyd K. Tuberculosis. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB *et al.* (eds). *Disease Control Priorities in Developing Countries*. Washington (DC), 2006http://www.ncbi.nlm.nih.gov/pubmed/21250305.

181 Canadian Thoracic Society/Public Health Agency of Canada. Canadian Tuberculosis Standards, 6th Edition (2007). 2007.http://www.phac-aspc.gc.ca/tbpc-latb/pubs/tbstand07-eng.php.

182 Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2013; **41**: 140–56.

183 Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R *et al.* Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet* 2011; **377**: 1495–1505.

184 Suárez PG, Floyd K, Portocarrero J, Alarcón E, Rapiti E, Ramos G *et al.* Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. *Lancet* 2002; **359**: 1980–1989.

185 World Bank, GNI per capita data. http://data.worldbank.org/indicator/NY.GNP.PCAP.PP.CD.

186 Steingart KR, Henry M, Ng V, Hopewell PC, Ramsay A, Cunningham J *et al.* Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis* 2006; **6**: 570–581.

187 Dalton T, Cegielski P, Akksilp S, Asencios L, Campos Caoili J, Cho SN *et al.* Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries: a prospective cohort study. *Lancet* 2012; **380**: 1406–1417.

188 Kurbatova E V., Taylor A, Gammino VM, Bayona J, Becerra M, Danilovitz M *et al.* Predictors of poor outcomes among patients treated for multidrug-resistant tuberculosis at DOTS-plus projects. *Tuberculosis* 2012; **92**: 397–403.

189 Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJD. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PLoS One* 2011; **6**: e17601.

190 Gardy JL, Johnston JC, Ho Sui SJ, Cook VJ, Shah L, Brodkin E *et al.* Whole-genome sequencing and social-network analysis of a tuberculosis outbreak. *N Engl J Med* 2011; **364**: 730–739.

191 Classen CN, Warren R, Richardson M, Hauman JH, Gie RP, Ellis JH *et al.* Impact of social interactions in the community on the transmission of tuberculosis in a high incidence area. *Thorax* 1999; **54**: 136–140.

192 Jackson a D, Seagar a-L, Reid ME, Doig C, Forbes KJ, Laurenson IF *et al.* Characterising transmission of a tuberculosis genotype in Scotland: a qualitative approach to social network enquiry. *Int J Tuberc Lung Dis* 2009; **13**: 486–93.

193 McElroy PD, Rothenberg RB, Varghese R, Woodruff R, Minns GO, Muth SQ *et al.* A network-informed approach to investigating a tuberculosis outbreak: implications for enhancing contact investigations. *Int J Tuberc Lung Dis* 2003; **7**: S486–93.

194 Cook VJ, Sun SJ, Tapia J, Muth SQ, Arguello DF, Lewis BL *et al.* Transmission network analysis in tuberculosis contact investigations. *J Infect Dis* 2007; **196**: 1517–27.

195 Hemming K, Girling A, Haines T, Lilford R, Sciences P. Protocol: Consort extension to stepped wedge cluster randomised controlled trial. *http://www.equator-network.org/wp-content/uploads/2009/02/Consort-SW-Protocol-V1.pdf* 2014; : 1–11.

196 Getahun H, Raviglione M. Active case-finding for TB in the community: time to act. *Lancet* 2010; 376: 1205-1206.