EFFECTIVENESS OF COMMUNITY ACTIVE CASE FINDING OF UNDETECTED TUBERCULOSIS DISEASE AMONG URBAN RESIDENTS IN UGANDA

by

JULIET NABBUYE SEKANDI

(Under the Direction of Christopher Whalen)

ABSTRACT

Statement of the Problem: Tuberculosis case detection remains a major challenge for TB control especially in Africa. Nearly 30% of infectious TB cases remain undetected leading to continuing transmission, individual suffering and death. In addition, TB disrupts the socio-economic welfare of society because it affects the most productive age-group of 15 to 54 years. The standard passive case finding (PCF) strategy for detecting TB cases has met with limited success in Africa. The major reasons include patients' delays, a lack of awareness of TB symptoms and lack of access to health care. **Goal:** To improve TB control by increasing case detection. **Purpose:** To examine the role of community active case finding (ACF) as an alternative approach for TB case detection. **Methods:** We conducted two studies; first, a primary epidemiologic study to determine the yield of active TB and TB-HIV cases when using ACF. Door-to-door cough surveys were conducted among 5,102 adult urban residents in Uganda over a period of 18 months by trained health care workers. Sputum specimens were collected for *Mycobacterium tuberculosis* examination in the laboratory. Second, an economic evaluation study was conducted using a decision analytic modeling framework to evaluate the effectiveness, costs and cost-effectiveness of ACF and household contact investigation (HCI) in the context of an existing PCF program. Data were drawn from the primary study, TB program data, published literature. **Results:** The primary study found that 24.4% of people reporting chronic cough had

infectious TB disease that was previously undetected and 8% were TB-HIV co-infected. The number-needed-to-screen to detect one TB case was 131 in the general population. The economic analysis showed that adding HCI to an existing PCF program was cost-effective at US$ 443.62 per additional case detected. **Conclusions:** Community active case finding obtained a high yield of previously undetected active TB and TB/HIV cases among people reporting cough lasting 2 weeks or more. However, it is more cost-effective to detect additional TB cases using HCI in combination with existing PCF programs than community ACF in the urban African context.

INDEX WORDS: Case detection, Undetected Tuberculosis; Passive case finding, Active case finding, Household contact investigation, Chronic cough, Number-needed-to-screen, TB/HIV co-infected, Cost, Cost-effectiveness

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DEDICATION

This dissertation work is dedicated to the Almighty God, the creator of heaven and earth who has blessed me beyond measure and divinely enabled me to do what I couldn't do in my own strength. Ebenezer, "Thus far the LORD has helped us" **1 Samuel 7:12**

May this work be used to bring the most glory to His name, Amen!

To my mother, Mrs. Mary Luyombya whose continuous encouragement to pursue doctoral education over the years saw me through to the fulfillment of this goal; I will always treasure your parental support and honor your grand walk in life for the remainder of my years.

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CHAPTER 1

INTRODUCTION

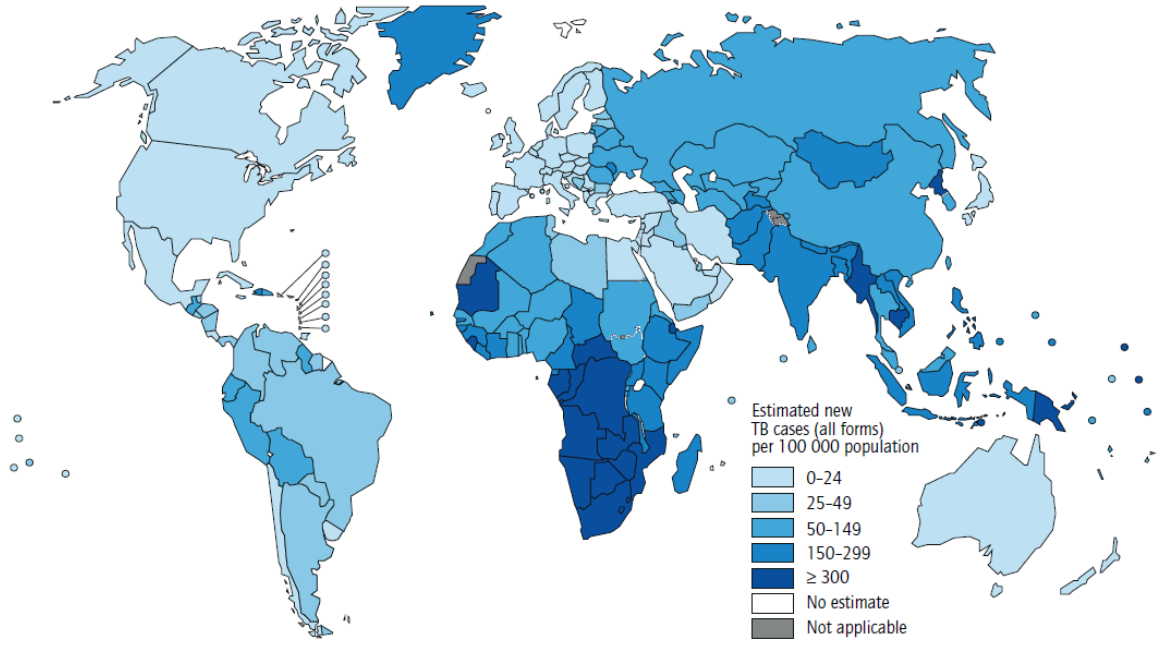
Public Health Significance

Despite more than 50 years of effective treatment, tuberculosis (TB) remains a threat to public health especially in the developing world. In 2011, the World Health Organization estimated that there were 8.7 million incident cases of TB globally, translating to 125 cases per 100,000 populations (Figure 1.1). The burden of TB is disproportionately distributed globally; 85% of the estimated new cases occur in Africa and Asia with incidence rates of more than 300 cases per 100,000 (World Health Organization, 2012).

Dual infection with the human immunodeficiency virus (HIV) compounds the TB problem; nearly 1.2 million of 8.7 million new cases of TB were infected with HIV. Of the TB-HIV coinfected cases, 79% were 44in the African region (World Health Organization, 2012). In 2011, death due to TB was estimated to have claimed 1.4 million lives, of which about 0.4 million were HIV-infected persons and nearly 89% of deaths occurred in Sub-Saharan Africa (Lienhardt et al., 2012; K. Lonnroth et al., 2010; World Health Organization, 2012). Furthermore, the risk of death from TB disease increases at least 2-fold for individuals who are TB-HIV coinfected if they are not on anti-retroviral therapy (ART) (Komati et al., 2010; Whalen et al., 2000).

Although the global trends in TB incidence, prevalence and mortality have shown a general decline over the last 20 years, the incidence rate is declining at a much slower rate than expected (Dye,

Lonnroth, Jaramillo, Williams, & Raviglione, 2009; World Health Organization, 2012). Part of the explanation could be the fact that incidence of TB cannot be measured directly but is mostly based on modeling thus there is potential for overestimation (Dye, Glaziou, Floyd, & Raviglione, 2013; World Health Organization, 2012). Nonetheless, the fact that new disease cases continue to surface points to on-going transmission of TB.



Source: WHO, Global Tuberculosis Report 2012

Figure 1.1. Estimated TB incidence rates in 2011.

The Problem of Undetected TB Cases

Undetected cases of TB disease pose a major problem for TB control because they perpetuate transmission while increasing morbidity and mortality (Boehme et al., 2011). It is estimated that nearly one third of TB cases remain undetected globally (Zarocostas, 2010). Recent population-based TB

prevalence surveys conducted in Kenya, Vietnam, Cambodia, India and Bangladesh consistently showed that 13-64% of sputum smear positive cases, the most infectious form of TB, were previously undetected (Hoa et al., 2010; Rao et al., 2012; van't Hoog et al., 2011; Zaman et al., 2012). In Uganda, two community-based prevalence surveys done in peri-urban Kampala found that 53-76% of the detected TB cases were previously undiagnosed (Guwatudde, Zalwango, et al., 2003; J. N. Sekandi, Neuhauser, Smyth, & Whalen, 2009). This mounting evidence strongly suggests that a substantial pool of prevalent TB cases remains undiagnosed and hence serves as a source of on-going TB transmission in the community. It is estimated that one undetected infectious case can result in 8-15 new infections in a year depending on the annual risk of infection and the prevalence (Blower & Daley, 2002).

The Economic Burden of TB and Undetected Cases

In developing countries, TB disrupts the socio-economic welfare of individuals and society. The economic impact of TB mainly due to the fact 75% of people affected are in the most productive age group of 15-54 years and accounts for about 20% of deaths (Murray & Chen, 1993; Murray & Lopez, 1996). It is estimated that 50-70% of people with TB will die of disease within 10 years if untreated with effective therapy (Murray & Lopez, 1997; Tiemersma, van der Werf, Borgdorff, Williams, & Nagelkerke, 2011). A World Bank study projected that the cost of TB-related deaths (including HIV co-infection) would be US$ 519 billion in Sub-Saharan Africa from 2006 to 2015 if effective TB treatment is not instituted (Laxminarayan, 2007).

The TB Problem in Uganda

Uganda is ranked 16th among the 22 high-burden countries that contribute about 80% of the total caseload of notified TB cases annually. In 2011, the TB incidence rate was estimated to be 234 cases per 100,000 populations, of which 143 per 100,000 were sputum smear positive which is the highly infectious form of TB, the rest were smear negative or extra-pulmonary TB cases. The estimated prevalence was 193/100,000 cases and the death rate was approximately.15/100,000 (World Health Organization, 2012).

Over 30% of estimated TB cases in Uganda remain undetected; approximately 57% of smear positive cases are detected annually. However, the total number of reported TB cases has increased more than two-fold from 19,016 cases in 1991 to 45, 004 in 2010 (World Health Organization, 2010). This may reflect a true overall increase in TB cases or it could be secondary to population growth and/or improvement in case finding efforts.

In Uganda, the dual TB and HIV epidemics pose a serious challenge to the health care system; 35 to 53% of the TB patients are HIV co-infected (World Health Organization, 2012). Kampala city, our study area is a unique setting in that it is the capital district of Uganda and is known to bear the highest burden of TB and HIV infection compared to the rest of the country. In 2011, approximately 8,000 cases were reported from Kampala alone accounting for nearly 25% of the national total TB caseload (Ministry of Health, 2008).

The Global Tuberculosis Control Strategy

A core element of any effective tuberculosis control program is to diagnose cases with active disease and initiate effective therapy promptly. The overarching goal is to reduce individual morbidity, mortality and transmissions before and after diagnosis as well as prevent the development of drug resistance (Acuna-Villaorduna et al., 2008; Boehme et al., 2011; World Health Organization, 2012). The World Health Organization (WHO) recommends the Directly Observed Treatment Short course (DOTS) as the standard TB control strategy targeting to detect at least 70% of new smear positive TB cases (Raviglione & Pio, 2002). The strategy has been widely adopted by national TB control programs to perform passive case finding with bacteriological diagnosis and administration of effective TB chemotherapy.

The standard passive case finding (PCF) approach detects active TB or TB/HIV cases by medically evaluating symptomatic persons who voluntarily present to the health system. Despite the effective and relatively cheap chemotherapy, passive case finding has not been very successful in creating

major changes in the course of the TB epidemic in low-income countries (Dye, Scheele, Dolin, Pathania, & Raviglione, 1999). In Sub-Saharan Africa the main reasons for failure are patients' delay in seeking care due to lack of awareness of symptoms and/or barriers to health care access (Bailey et al., 2011; den Boon et al., 2008; Golub, Bur, et al., 2005; Kiwuwa, Charles, & Harriet, 2005; Sendagire, Schim Van der Loeff, Mubiru, Konde-Lule, & Cobelens, 2010). The PCF approach therefore leaves large pools of undetected prevalent TB cases (Hoa et al., 2010; Tadesse, Demissie, Berhane, Kebede, & Abebe, 2011; van't Hoog et al., 2011). Epidemiologic analyses and mathematical modeling demonstrate that the DOTS strategy alone is not sufficient to control TB in countries with high TB-HIV prevalence (Blower & Daley, 2002; Corbett, Marston, Churchyard, & De Cock, 2006; K. Lonnroth et al., 2010).

Tuberculosis Control in Uganda

The Ugandan Ministry of Health established the National Tuberculosis and Leprosy Control Program (NTLP) in 1990 to manage TB and leprosy. In 1995, the NTLP adopted the WHO recommended Directly Observed Treatment Short course (DOTS) strategy, using passive case finding as the primary method of detection of TB smear positive cases. Under DOTS, the estimated case detection rate of smear positive TB cases was 57% in 2010, far below the WHO target of 70% (World Health Organization, 2011a). Although the official DOTS coverage in Uganda is 100%, measured as living in an area with health clinics that are implementing the DOTS strategy, only about 50% of the population had access to general health services in 2002 (Adatu et al., 2003).

Purpose of the Study and Underlying Theory

The overarching goal is to improve TB control by increasing case detection at an early point in the natural history of disease. This study seeks to examine the efficiency and cost-effectiveness of community-based active case finding as a strategy for detecting cases of active TB disease and HIV co-

infections. This study is based on the theoretical underpinning of infectious disease control; early removal of the source of infection interrupts transmission (Tiemersma et al., 2011). In keeping with the basic concepts of epidemic control, the number of secondary cases that arise from a point source of infection should be less than one. This situation can be achieved by substantially reducing one or all of the following parameters: the duration of infectiousness, the contact rate between the infectious source and susceptible hosts and, the probability of infection given contact (K. Lonnroth, Corbett, E., Golub, J., Godfrey-Faussett, P., Uplekar, M., Weil, D., Raviglione, M.,, 2013). Our study implicitly targets the reduction of duration of infectiousness through early detection.

Rationale of Active Case Finding

Active Case Finding (ACF) is an alternative approach to TB case detection. Active case finding can take on several forms, depending on the nature of the TB problem and the available resources. The forms that have been studied are household contact investigation and community case finding (Golub, Mohan, Comstock, & Chaisson, 2005; Morrison, Pai, & Hopewell, 2008). A household contact investigation (HCI) is a targeted form of ACF where a health professional evaluates contacts of index TB cases. Community active case finding is a provider-initiated effort to identify TB cases in the community through door-to-door surveys using cough symptom or chest x-ray screening (Golub, Mohan, et al., 2005; K. Lonnroth, Corbett, E., Golub, J., Godfrey-Faussett, P., Uplekar, M., Weil, D., Raviglione, M.,, 2013). If properly implemented, ACF holds promise for enhancing early detection of TB cases, timely initiation of effective treatment, reducing the duration of infectiousness, and thus interrupting the transmission chain at the community level (Golub, Mohan, et al., 2005; Kranzer et al., 2013). Additionally, ACF has the potential benefit to individuals such as increasing access to TB services, reducing duration of morbidity and risk of mortality particularly in TB-HIV co-infected individuals while alleviating the

economic consequences (Eang et al., 2012; Kranzer et al., 2013). It is important to note that ACF is currently not a component of the TB control strategy.

Gaps in the Literature

Currently few studies have focused on identifying undetected TB and TB/HIV coinfected cases using the ACF approach in Africa (Ayles et al., 2009; Corbett et al., 2010). Moreover, there is limited evidence from cost-effectiveness studies comparing ACF strategies with passive case finding in high TB burden settings (Datiko & Lindtjorn, 2010; Eang et al., 2012; Mupere et al., 2013; Nishikiori & Van Weezenbeek, 2013). To our knowledge, no published study has so far compared community ACF and HCI in the context of an existing passive case finding program.

Specific Aims

To address the overall goal of the study, two interrelated studies were performed, each with its own specific aims (Figure 1.2).

Part I: Epidemiologic Study

The first study was an epidemiologic study with the following specific aims:

Specific Aim 1: Determine the effectiveness of active case finding by using chronic cough as a screening tool to detect TB and HIV cases in an urban community in Kampala, Uganda

Aim1a: Estimate the prevalence of chronic cough, undetected active TB disease and TB-HIV co-infection

Aim1b: Estimate the number-needed- to-screen to detect a case of active TB disease and TB-HIV co-infection

Part II: Economic Evaluation Study

The second study was a cost-effectiveness analysis of TB case detection strategies conducted from the societal and health provider perspectives within an African context.

Specific Aim 2: Evaluate the cost-effectiveness of community active case finding strategies for detecting active TB disease

Aim 2a: Estimate the cost of detecting a TB case by community active case finding and household contact investigation

Aim 2b: Evaluate the incremental cost-effectiveness of community active case finding and household contact investigations under an existing passive case finding program

Study Designs

In order to address the specific aims of the study, we utilized epidemiologic and decision analysis model designs to evaluate the yield, efficiency (number-needed-to-screen), cost, and cost-effectiveness of community-based active case finding (study design flow diagram, Figure 1.2). The studies were implemented among urban residents in Kampala city, the capital of Uganda (see map of Uganda in figure 1.3). The city has an estimated population of two million people occupying an area of 189 square kilometers; about 47% of the people live in crowded settings (UBOS, 2011) which makes it a favorable environment for transmission of tuberculosis. The prevalence of TB in Kampala is not well documented, but one study estimated it to be between 416 and 920/100,000 (Guwatudde, Zalwango, et al., 2003). Kampala contributes nearly 25% of the total TB cases registered by the national TB program annually (Uganda Ministry of Health, 2010). The prevalence of HIV in Kampala is estimated to be 8.0%, and nearly one in every 3-4 people with TB disease is co-infected with HIV infection.

Part I is a primary cross-sectional study which was conducted in a large urban community in Kampala, Uganda in order to answer the following questions: (a) what is the prevalence of undetected active TB disease? (b) What is the prevalence of undetected TB-HIV co-infection (c) How many people need to be screened in order to find one TB or TB-HIV coinfected case? (d) Is chronic cough an efficient screening tool for detecting TB cases at the community level?

Part II is an economic evaluation study, where community active case finding and household contact investigation are compared to the standard passive case finding strategies in terms of their costs and effectiveness. The study utilized decision analytic modeling as a quantitative framework to synthesize the available data on costs and effectiveness to evaluate the cost-effectiveness of three case finding strategies in order to choose the optimal strategy for case detection. The main data sources included the primary data from the cross-sectional study in part I, national TB program records, and published literature. Expert opinions of TB clinicians were used occasionally to fill gaps in the available data. The analysis was guided by the following questions: (a) what is the cost of detecting one case of TB when using PCF, ACF and HCI case finding strategies? (b) Which of the three alternative strategies is most cost-effective for detecting TB cases?

Deliverables

In summary, this dissertation has two main deliverables. First, the research findings provide insights into efficient ways to improve TB control. In Africa, decision makers in National TB programs are constantly faced with critical choices in allocating scarce resources to competing health interventions. The cost-effectiveness analysis study provides key information on the optimal case detection strategy in an African context. Second, this dissertation work will culminate into two published scientific papers which will be a contribution to the existing evidence base in the field of TB control. The first manuscript

reports on the yield of TB and TB-HIV co-infection from active case finding, and number-needed-to screen to detect a case. The second manuscript reports on the cost and cost-effectiveness of community active case finding and household contact investigation in addition to the standard passive case finding. This dissertation emphasizes the importance of secondary prevention through screening for disease and evidence-based policy decision making for TB control in Africa.

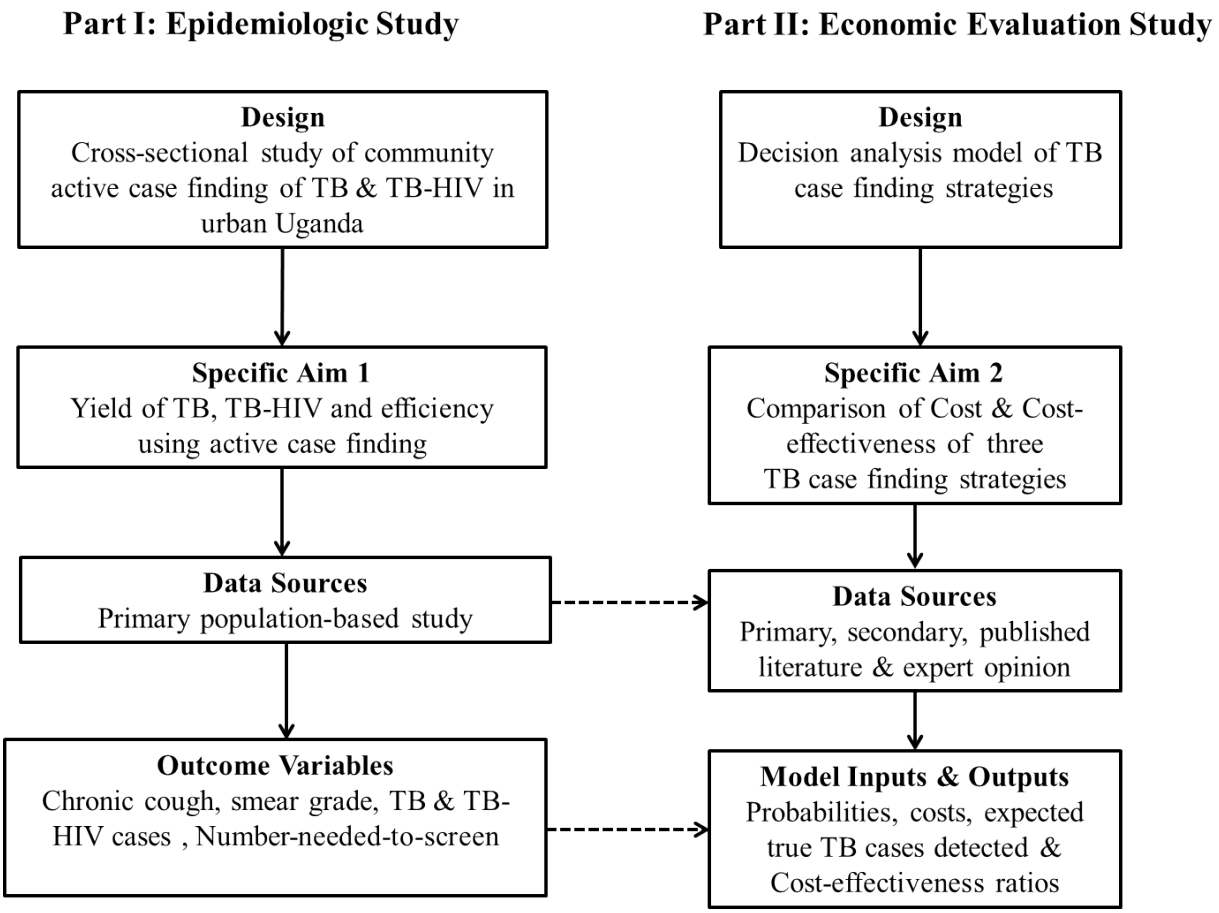


Figure 1.2 Flow Diagram of Study Designs

The Map of Uganda showing Kampala

Source: Uganda Bureau of Statistics, 2010

Figure 1.3. Map of Uganda showing Kampala Study Area

CHAPTER 2

LITERATURE REVIEW

This chapter provides a critical review of the state of the existing literature on tuberculosis case finding especially in Sub-Saharan Africa and highlights some existing gaps in knowledge that will be filled by this dissertation research. First, a brief background of TB control using the standard DOTS strategy and its limitations are explained. Second, a brief historic perspective of work on active case finding is provided. Third, a critical summary of the recently published literature (2005-to present) on active case finding studies done in developing country settings where the burden of TB and HIV is particularly high is provided.

The review of the studies mainly focuses on four interrelated themes including; 1) the study designs and approaches that have been used in community active case finding strategies 2) household contact investigation as a form of active case finding strategy 3) measuring the effectiveness of active case finding strategies and its variation in different settings 4) the evaluation of cost and cost-effectiveness of case finding strategies.

Methods for Literature Search

A search was performed in the Medline, Embase, Global Health and Web of Science databases for potentially relevant articles. Journal articles published in English between 2005 and 2013 were mostly included. The following phrases in conjunction with 'tuberculosis': 'case detection', 'case finding', 'active case finding', 'community case finding', 'enhanced case finding', 'intensified case finding', 'household contact tracing', 'household contact investigation', 'screening', 'cost', 'effectiveness', 'cost-effectiveness', 'cost-utility analysis', 'economic evaluation' ,'health state utilities' and ' mathematical

modeling' and markov modeling' were used in the search. A decision was made to focus on more recent articles published from 2001 to present since these are the ones that contained newer information.

The Natural History of Tuberculosis

Tuberculosis is caused by a group of five closely related species of bacilli, which form the *Mycobacterium tuberculosis* complex: *Mycobacterium tuberculosis* (MTB) is responsible for nearly 80% of TB cases in the world (Wirth et al., 2008). The organism is spread by human to human contact through airborne droplets expelled when a person with active TB disease sneezes, coughs, laughs or talks. Exposure results from inhalation of the infected droplet after which, infection may occur in 10-30% of individuals while the rest remain uninfected (Dye, 2000). Of those who acquire TB infection, about 5-10% may immediately progress to active TB disease (primary progressive disease); this occurs more often in children aged 5 years or younger (Horsburgh, 2004). If treated with effective chemotherapy, a person with disease will be cured after 8-12 months. If left untreated, 70% of smear positive and 20% of smear negative TB patients will self-cure or die within a period of 2-3 years (Tiemersma et al., 2011). In the remaining 90% of those infected but do not progress to TB disease, the body's immune system is able to kill the mycobacteria or suppress the bacilli into a state of dormancy known as latent TB infection (LTBI).

The LTBI stage is an asymptomatic, bacteriologically and radiologically undetected process in humans. Most commonly, a positive tuberculin test (TST) or positive blood-based interferon gamma results remain the only indicator of LTBI, and therefore does not signify active disease. After a long period of latency, active TB disease may develop due to disruption of the immune system; this is known as reactivation TB. Immunocompetent persons are believed to have an estimated cumulative 10% lifetime risk of developing active disease due to reactivation (Oxlade et al., 2011). With HIV infection, the

lifetime risk of reactivation disease is increased to perhaps 10% per year (Horsburgh, 2004). Preventive therapy and highly active anti-retroviral therapy (HAART) are highly beneficial in reducing the incidence of TB disease in HIV infected TST positive individuals (Akolo, Adetifa, Shepperd, & Volmink, 2010).

Global TB Control Strategies

Case Detection

Early case detection and prompt initiation of effective treatment is a principle means of controlling transmission and reducing tuberculosis (TB) incidence (De Cock & Chaisson, 1999). Globally, the overall estimated case detection rate is 60% but is as high as 89% in developed countries and as low as 55% in developing countries. For any given year, the case detection rate is calculated as the total number of new and relapse cases diagnosed and reported divided by the estimated number of incident cases (World Health Organization, 2011b). Case detection has stagnated in recent years, while the rate of decline in estimated TB incidence has been slower than expected (K. Lonnroth, Jaramillo, Williams, Dye, & Raviglione, 2009; World Health Organization, 2012). This trend is indicative of a potential detection gap.

Following a sharp rise in tuberculosis incidence in the early 1990s, TB was declared a global emergency. In response, the World Health Organization (WHO) launched the standard DOTS TB control strategy (Dye, Garnett, Sleeman, & Williams, 1998). The primary focus of DOTS strategy is to detect and effectively treat the most infectious cases. A passive case detection approach, where symptomatic individuals present to the health care system for evaluation and diagnosis on their own initiative is used (Raviglione & Pio, 2002). Under this strategy, global target was to detect at least 70% of the estimated new smear positive cases and successfully treat 85% of them by the year 2005. In 2012, the global

treatment success has improved remarkably from 43% in 1994 to 85% (World Health Organization, 2012). However, case detection has remained relatively low in developing countries.

Limitations of Passive Case Finding Under the DOTS TB Control Strategy

The standard passive case finding (PCF) approach relies on patients who present voluntarily to the health system. However, the reliance on self-presentation of patients has several limitations. First, patients often present late to the health system after transmitting TB for weeks and months before diagnosis and initiation of effective therapy (Bailey et al., 2011; den Boon et al., 2008; Golub, Bur, et al., 2005; Kiwuwa et al., 2005; Millen, Uys, Hargrove, van Helden, & Williams, 2008). In Uganda, the average patients' delay is 3-4 months, from onset of symptoms to time of diagnosis (Kiwuwa et al., 2005). This could be due to a lack awareness of symptoms and signs of TB. This also means that patients are likely to be sicker when they present themselves to the health system (den Boon et al., 2008). Second, even when people are aware of the symptoms, access barriers exist that may prevent them from ever seeking care (Dye, Watt, & Bleed, 2002; K. Lonnroth et al., 2009). In Africa for example, some patients cannot afford the high costs of travel to the conventional public health clinics where TB services are typically offered free of charge (Mauch et al., 2013). In this way, ACF caters to the poor and eliminates inequities (K. Lonnroth et al., 2009). Third, missed opportunities for diagnosis occur even when potential TB patients interface with the health system, this is sometimes due to a low index of suspicion for TB among the health workers (Bailey et al., 2011; Millen et al., 2008; Sendagire et al., 2010). Alternative intervention strategies should therefore aim at early case detection and uncovering patients who may fail to seek care on their own.

Case Detection and Barriers to Accessing TB Care

Although majority of countries report DOTS coverage of 100%, access to health care is below 60% in most developing countries (K. Lonnroth, Corbett, E., Golub, J., Godfrey-Faussett, P., Uplekar, M., Weil,

D., Raviglione, M.,, 2013). Access to TB services is a barrier to case detection of TB especially among poor communities (Mauch et al., 2011). The access barriers are many; these may include socio-economic barriers which are encountered along the entire pathway of TB care. Lack of money for transportation, meals, accommodation or payment for specific service fees has been cited as a major reason for either delaying or not seeking care (Laokri et al., 2013). Geographic barriers as they relate to the distance from the TB diagnostic and treatment services may further worsen the economic barriers. Social-cultural barriers especially stigma and discrimination related to the link between TB and HIV have been documented as a hindrance to detection of TB (Li et al., 2013). A common misperception that TB care is very expensive prevented people from seeking help among poor communities in Kenya (Mauch et al., 2011). Health system barriers can arise from a lack of well trained personnel that are capable of identifying TB cases at an early stage. A nationwide survey in China showed that 40% of the TB patients they studied had sought health care but had not been diagnosed with TB (Li et al., 2013; World Health Organization, 2008). Increasing access to health care for people who do not seek care and improving awareness TB symptoms and signs is critical to case detection.

Other TB Control Strategies

Bacillus Calmette–Guérin **(**BCG) vaccination is a primary prevention strategy. The vaccine is given at birth to provide protection against the most severe forms of childhood TB (miliary and meningeal tuberculosis), but these forms of disease are not associated with transmission (Rodrigues, Diwan, & Wheeler, 1993). A meta-analysis of published efficacy studies of BCG vaccine against TB reported a summary protective effect of 51% (Colditz et al., 1994). However, BCG does not prevent reactivation of latent pulmonary infection to active disease, which is the principal source of bacillary spread in the

community. The impact of BCG vaccination on transmission of *Mycobacterium tuberculosis* is therefore limited (Blower & Daley, 2002).

Treatment of latent TB infection is a secondary level control strategy. A person who is infected with *Mycobacterium tuberculosis* is treated using one or more anti-tuberculosis drugs to prevent the development of active TB. The WHO recommends tuberculosis preventive therapy for all HIV-infected populations because they are at greatest risk for developing active disease (World Health Organization, 2012). Efficacy trials done among HIV infected people in Haiti and Uganda suggested that Isoniazid given for at least six months offers a short-term protective effect against active tuberculosis (Halsey et al., 1998; Whalen et al., 1997). A recent systematic review suggested that treating only those that are tuberculin skin test positive among people living with HIV/AIDS is likely to offer the greatest benefit (Kerkhoff et al., 2012).

Infection control through work practice and administrative measures has the greatest impact on preventing TB transmission in healthcare settings (World Health Organization, 1999). The goal is to prevent TB exposure to health workers and patients, reduce the spread of infection by ensuring rapid diagnostic investigation and treatment for those suspected or known to have TB. Environmental control measures including the use of N95 personal respirators, negative pressure ventilation, ultraviolet lights in TB wards and clinics, constitute a second line of defense in health settings. They all have been shown to have some benefit in preventing the spread of TB to health workers and among patients in hospital settings (Fennelly, 1998; Fennelly & Nardell, 1998). But, these measures are impractical in most resource-limited settings due to prohibitive costs.

Alternative TB Case Detection Strategies

Effective alternative strategies to improve TB case detection should be geared towards reducing delays in diagnosis and the potential risk of transmission at the community level. Several alternative strategies mainly requiring extra efforts by the health care workers have been tried in the past. These include various forms of active case finding (ACF): *community active case finding* as summarized in a systematic review (Golub, Mohan, et al., 2005), *household contacts investigations* (Guwatudde, Nakakeeto, et al., 2003; A. E. Shapiro et al., 2012; Whalen et al., 2011) *enhanced case finding* (ECF) by raising symptom aware and active referral to health facilities (Ayles et al., 2013) or *intensified case finding* applied to high-risk populations such as the HIV-infected or prisoners (Mugisha et al., 2006; Vinkeles Melchers, van Elsland, Lange, Borgdorff, & van den Hombergh, 2013). However, it is unclear which of the available approaches work best to improve case finding (Borgdorff, Yew, & Marks, 2013). Cost-effectiveness studies of these approaches are largely lacking yet, they provide valuable evidence to inform decisions on the most efficient strategies in the face of constrained budgets.

A Historical Perspective of Approaches to Active Case Finding

It is important to recognize that the practice of active case finding has a long standing history dating back nearly 80 years. Active case finding of TB was first documented in the early 1930s and has since evolved to-date in several ways. Golub et al, (2005) conducted a systematic review of 88 active case finding (ACF) studies published over a period 7 decades. The review clearly demonstrated that there has been an overall paradigm shift in the methods of active case finding majorly from focusing on all persons to focusing on symptomatic individuals.

In the pre-chemotherapy era (1930s to 1960s), the primary ACF strategy in industrialized countries was large scale mass miniature radiography (MMR) campaigns. Chest x-rays were performed on all community residents regardless of presence of TB symptoms to identify those with radiological abnormalities. This mass screening was followed by referrals of TB suspects to public health centers for further evaluation by physicians (Golub, Mohan, et al., 2005). Mass radiography was shown to be successful in early detection of previously unknown active TB thereby reducing the morbidity and mortality due to TB. The isolation of the patients from society reduced the transmission of TB to others in the community.

A series of mass radiography surveys of over 150,000 residents in New York city done in the early 1930s concluded that targeting the most-at-risk population for TB including the poor, prisoners and transient groups would the most effective method of case detection (Douglas, Birkelo, Harmon, & Vaughan, 1940; Plunkett, 1939). In the developing world, the first studies of mass radiography case finding were conducted in rural village in South India reported a high yield of 800-424/100, 1000 active TB cases (Aspin, 1947; Frimodt-Moller, 1960). However, it later became evident that use of the MMR approach was less practical in developing countries due to the prohibitive costs, logistical challenges and less developed public health infrastructure (Raviglione & Pio, 2002). This observation led to a policy decision to abandon the approach and seek for more cost-efficient ways to detect active TB disease.

After the 1960s, there was a shift in the trend by researchers to seeking more effective methods of ACF that focus on identifying only the symptomatic patients. In 1963, a seminal study conducted in sixty-two villages in South India found that at least 70% of the patients found to have active TB were aware of their symptoms; more than 50% had sought care. The study concluded that a well-established health system infrastructure could detect most of the symptomatic cases (Andersen & Banerji, 1963), leading to the endorsement of passive case finding (PCF) is a the standard strategy for TB case finding (Raviglione & Pio, 2002). However, this conclusion overlooked the main shortcoming of passive case finding; even

when the symptomatic patients are motivated to seek care voluntarily; most of them may arrive to the health system far too late after transmitting TB to several close contacts in the community. An epidemiologic underpinning of infectious disease control rests in the reduction in the duration of infectiousness of a case, in order to limit the number of secondary cases that may arise from each case (Whalen et al., 2011). This is theoretical basis that justifies active case finding of TB among symptomatic patients before they seek care on their own.

Cross Sectional Studies of Active Case Finding

Despite the current recommendations for passive case finding, several ACF studies have since been performed using various designs in Sub-Saharan African countries and elsewhere (Golub, Mohan, et al., 2005). The majority of the studies are door-to-door surveys that used symptom inquiry that were conducted in untargeted populations. They involved trained field workers who visit people's homes and administered a variety of symptom screening tools in order to identify symptomatic patients who had not sought health care (Ayles et al., 2009; J. N. Sekandi et al., 2009; Wood et al., 2007). In general the studies have demonstrated that ACF identifies previously undetected TB or TB-HIV co-infected cases.

High proportions of undetected TB/HIV cases are found in settings where the two epidemics are highly prevalent. Individuals who have TB and are coinfected with HIV are at a significantly high risk of death before they receive effective TB or anti-retroviral therapy (Whalen et al., 2000). In a cross-sectional study done in South Africa used home visits and referrals to the public clinics in order to assess the burden of undiagnosed TB and TB-HIV co-infection among 762 adults in an urban community (Wood et al., 2007). The study found that nearly 75% of the TB-HIV patients were undetected. This finding suggests that ACF was beneficial for detecting those at greatest risk of dying from the two diseases.

Urban settings are likely to harbor a high caseload of undetected TB and HIV coinfected cases because the dynamic nature of the population with a greater potential for risky behavior. In a cross-sectional study done in rural and urban Zambia, 8,044 adults residents were surveyed using house-to-house symptom inquiry to estimate the prevalence of undiagnosed TB and TB-HIV in the study communities (Ayles et al., 2009). The authors found a higher proportion of undetected TB in the urban areas and a higher prevalence of TB in HIV infected individuals suggesting that ACF might be more useful in urban settings particularly in HIV infected subpopulation.

Lack of access to health care and/or poor health seeking behavior may affect the detection of prevalent TB cases. In 2011, a door-to-door survey in 40 rural villages in Kenya used symptom inquiry to assess the point prevalence of undetected TB, TB-HIV and health care seeking behavior in 20,566 adults. This study found 2.5/1000 smear positive TB cases were undetected, with 52% of them HIV infected and 64% had not sought care (van't Hoog et al., 2011). This is in contrast to previous studies that showed that majority of the undetected cases had sought care (Andersen & Banerji, 1963). The authors also pointed out that the study was conducted in a setting where access to TB services was limited. The lesson from this study is that in the absence of adequate access to the health system, ACF has a supplemental role in TB control especially among the rural poor populations.

Screening for TB among persons reporting chronic cough can result in a high yield of undetected disease. In Uganda, only one published study of community active case finding was found. The study was a cross-sectional door-to-door survey of 930 adults in a slum setting that used cough inquiry as a screening tool to identify TB suspects for diagnostic evaluation (J. N. Sekandi et al., 2009). The study found 35/1000 previously undetected smears positive TB, far greater than the reported notification of 4.5/1000 case in Kampala. Moreover, 20% of persons reporting chronic cough had active TB disease. These finding underscores potential efficiency of targeting screening to persons with chronic cough in order to identify undetected TB disease. However, this result is not conclusive because the study was

done in a high risk population; more ACF studies are needed in the urban context to build on the existing knowledge of how to design the most efficient strategies.

All these studies consistently showed that regardless of the specific approach, ACF was useful for identifying previously unknown TB cases. These studies employed a variety of innovative ACF methods singularly or in several combinations including door-to-door/ house-to-house surveys, outreach clinics, TB education leaflet distribution and sensitization campaigns and referrals trained extension workers. The major limitation of these cross-sectional studies was the lack of comparison groups rendering it hard to conclude that ACF strategies offered greater benefits than the standard passive case finding approach.

Randomized Community Trials of Active Case Finding

Between 2006 to date at least six randomized controlled trials (RCT) of ACF have been published in the literature, reflecting an upward shift in the hierarch of epidemiologic designs (Ayles et al., 2013; Churchyard et al., 2011; Corbett et al., 2010; Datiko & Lindtjorn, 2009; Miller et al., 2010; Shargie, Morkve, & Lindtjorn, 2006). Five of these studies were conducted in Sub-Saharan Africa, while one was done in Brazil.

Active case finding may result in reduction of the duration of symptoms at the time diagnosis in patients. This indicates that patients are likely to be less sick and the duration of infectiousness is also shortened. The earliest published RCT of active case finding by Shargie et al (2006) was done in Ethiopian rural communities. The study compared ACF through a village outreach program which included distribution of TB education leaflets and a monthly clinic run by healthcare workers to the standard passive case finding. The results showed that there was a 55-60% greater reduction in pre-treatment duration symptoms in the intervention arm but no significant difference in TB cases detected and treatment success rates between the two arms (Shargie et al., 2006). The strength of this study was the

comparison of the effects of active and passive case finding on case detection. However, one of the methodological limitations of this study was the failure to minimize the potential for mixing (contamination) between the two intervention study communities. The contamination could have diluted the effect of the intervention on case detection hence biasing the results towards the null. The design could have been improved by creating a buffer zone of non-randomized villages to separate study arms.

Active case finding using trained community health care workers enhances detection of additional cases of TB. Another RCT conducted in Ethiopia assessed whether ACF by re-trained Health Extension Workers (HEWs) improved TB case detection compared to non-retrained HEW using passive case finding in village health TB programs. The HEW intervention resulted in a 53% higher mean detection rate of sputum positive cases (Datiko & Lindtjorn, 2009). These findings suggest that specific training of the health providers to increase their suspicion index to evaluate symptomatic individuals could bolster routine case finding by the health system. The strength of this study was the inclusion of the standard passive case finding strategy as a comparison arm.

The RCT conducted in Zimbabwe by Corbett et al (2010) compared two ACF strategies in an urban population. Communities were randomized to door-to-door symptom surveys by lay field workers and to community awareness campaigns through the distribution of TB-specific educational leaflets, use of loudspeaker to publicize TB services and a mobile health van to provide access to services to all study communities. The results showed that both strategies detected previously undetected case but the mobile van approach was more effective in identifying additional TB cases, perhaps supporting the observation that symptomatic patients are motivated to seek care as long as they have access to diagnostic services (Corbett et al., 2010). The study was limited because the ACF strategies were not compared with the standard PCF approach. The authors also attempted to examine the impact of ACF on TB prevalence over a 2- year using a pre-post intervention design. They concluded that ACF strategies led to a 40% reduction in TB prevalence. However, it can be argued that the decline in prevalence may not be simply attributable

only to the ACF interventions but could have been partly influenced by other secular events such as on-going health programs or emigration during the study period.

Active case finding using the door-to-door approach has been shown to more effective than providing educational materials suggesting that human interaction positively influences case detection. The RCT conducted in a large urban impoverished *favela in* Rio de Janeiro, Brazil compared PCF with ACF strategies using door-to-door symptom screening in one arm and TB educational pamphlets in the other arm. The study also improved access by providing free TB services at a designated location within the community (Miller et al., 2010). The door to door approach was more effective at detecting prevalent infectious cases. The unique study finding was that the observed effect of higher case detection disappeared in the door-to-door arm when ACF was extended 60-days beyond the initial 283-day active intervention period. This suggests that there might be a saturation point beyond which ACF can no longer detect any more TB cases in the community. This supports the argument that conducting short but periodic ACF surveys may be a better to way maximize the yield (Dodd, White, & Corbett, 2011).

Active case finding is beneficial for early detection of infectious cases hence minimizing the duration of morbidity and the chances of spreading infection to other persons. Churchyard et al conducted a randomized trial in South African that targeted urban largely asymptomatic gold miners, comparing 6-monthly and 12-monthly chest X-rays to screen for active TB then followed by sputum bacteriologic examinations (Churchyard et al., 2011). Both interventions equally identified smear positive TB cases. However, the 6-monthly chest X-rays detected significantly more TB suspects but this did not translate to TB cases. This scenario has cost implications as well as benefits and therefore would best be evaluated further in a cost-benefit or cost-effectiveness analysis. Additionally, 6 monthly chest x-rays detected cases with less radiologically severe disease compared to the 12-monthly screening. Two important insights are reinforced from this study; first, that chest X-rays can have valuable utility in TB case detection when used in a targeted relatively high risk population such as gold miners. Second, chest X-rays can help

detect infectious TB cases that have very minimal or no symptoms. The limitation of this study is that it did not evaluate the influence of HIV status on the performance of the chest X-ray interventions. Recent experiences in HIV populations suggest a possible role for routine radiographic screening of this high-risk group (Corbett et al., 2004; Lewis et al., 2009).

The role of active case finding in reducing the burden of tuberculosis has been long questioned. A large community trial conducted in 24 communities Zambia and South Africa to test two public health interventions: community-level enhanced case finding and household investigations for active TB, HIV and latent TB infection. The authors compared reduction in prevalence and incidence of infection the community; they found that both the interventions had some effect on burden of disease in the community compared to the control although the effect was not statistically significant. This may have been due to a loss of statistical power due to high attrition rates. The study was also able to uncover previously undetected infectious TB and HIV cases in the community. Given the relative short duration of study follow up, one can argue that the impact of ACF on the prevalence could not have been detected since there is still on-going progression from latent infection to active disease from a portion of already latently infected persons in the population.

In summary, all the six published RCT in ACF taken together show that previously undetected active TB diseases cases were identified using a mix of case finding methods and screening tools in untargeted populations. However, the results on effectiveness of ACF in achieving higher case detection and better treatment completion compared to PCF are still mixed. Two of the studies compared different ACF strategies without including PCF as a control strategy (Churchyard et al., 2011; Corbett et al., 2010). Nonetheless, we learn and reinforce some lessons about active case finding of TB disease. First, ACF enhances early case detection as shown by reduced duration of pre-treatment symptoms and the radiologically less severe disease among detected cases. Second, that when ACF strategies were coupled with improve access to TB services and health educational campaigns, this boosted health care seeking

for TB symptoms in communities. Third, that those ACF strategies that trained health personnel and provided access to TB services in the local communities contributed to health system strengthening that augmented case finding. Fourth, that effectiveness of the ACF can be high in the short-term but wanes over time. Therefore, there is need to understand the role of that periodic ACF cycles and the optimal frequency that may result in a sustained effectiveness.

The major limitation to all these studies were the short durations of follow up, ranging from 8 month to 3 years, this period would be insufficient for measuring important outcomes such as TB relapse and the impact of ACF on disease incidence. To fill this gap in knowledge, it will be valuable to conduct well designed prospective cohort studies with longer follow up time and comparing TB outcomes in exposed contacts of index cases identified by passive and active case finding.

Household Contact Investigation

Household contact investigation (HCI) is a special type of active case finding strategy which involves targeted evaluation of household members of a known infectious index TB case; the health providers rely on the index case to provide information about their contacts for follow up. The rationale for this strategy is that people who are in close contact with individuals who have the infectious form of TB are at increased risk of acquiring infection and progressing to TB disease (Morrison et al., 2008). Consequently, the identification and evaluation of TB contacts, hereafter referred to as contact investigation is a recommended component of TB control programs in most developed countries and has contributed to the successful control of TB (Taylor, Nolan, & Blumberg, 2005). However, in developing countries where the burden of TB is high contact investigations is not commonly done.

Contact investigation has been well documented as means of TB case finding in the Sub-Saharan Africa region, including South Africa, Uganda and Malawi (Claessens et al., 2002; Guwatudde,

Nakakeeto, et al., 2003; A. E. Shapiro et al., 2012) and other developing country settings such as Peru, India, Brazil, Pakistan (Becerra et al., 2005; Wares, Akhtar, Singh, & Luitel, 2000). In 2008, Morrison et al published a systematic review and meta-analysis of all the on conducted in low and middle income. The authors determined the cumulative yield of 4.5% (95% CI 4.3-48) bacteriologically and clinically diagnosed TB among household contacts (Morrison et al., 2008). This suggests that contact investigation has utility detecting additional TB cases.

Contact investigation may be more effective in detecting TB and HIV co-infection among contact than passive case finding. A study that was conducted in rural Malawi compared the yield of TB disease from passive and active case finding in household contacts. The results showed that the yield of TB cases was nine times more when using active case finding in contacts who were HIV coinfected (Zachariah et al., 2003). In principle, the household contact investigation approach should be more efficient than untargeted door-to-door surveys. A study done in South Africa compared household contact investigation and house-to-house active case finding. The TB yield from contacts investigation was 19% compared to 1% from the ACF done in the general community (A. E. Shapiro et al., 2012). On the other hand, contact investigation may turn out to be less effective in the absence of a well-developed public health infrastructure through which to index case are followed to their homes. Regardless of the systemic limitations, contact investigation is a key strategy for TB detection and its cost-effectiveness warrants evaluation to inform policy decision making.

Effectiveness and Efficiency of Active Case Finding

Although the majority of ACF strategies were successful in the context in which they were assessed, their effectiveness has not been measured in a standard way. Studies have expressed effectiveness of ACF in a variety of ways including short-term outcomes: cumulative yield of TB cases,

prevalence of undiagnosed TB cases detected, case notification rates; clinical outcomes, percent reduction in duration of pre-treatment symptoms, severity of disease based on smear grade or radiological changes or intermediate, percent reduction in TB prevalence, treatment completion and the cure rates (Golub, Mohan, et al., 2005). The effectiveness can vary depending on the disease burden in the population screened and the sensitivity of the screening and/or the diagnostic tools (World Health Organization, 2013b).

Measuring efficiency of ACF using the number-needed-to-screen (NNS) is a useful generic metric that could reflects the amount of resources that might be consumed to implement an ACF strategy. The NNS has been widely used to show efficiency of breast and prostate cancer screening programs (Gulati, Mariotto, Chen, Gore, & Etzioni, 2011; Mandelblatt et al., 2009). Therefore, using the number-need-to screen provides a broader context for comparison of the efficiency of TB screening programs with other screening programs that utilize the same measure. There is no single optimal cut-off for NNS; however, it has to be applied to the specific context with considerations of the background prevalence and incidence in the screened population (Auvinen, 2011). Our study aimed to determine the yield and the NNS to detect a case of undetected TB and TB/HIV in Kampala. The study expands on the existing evidence-base that supports ACF as a supplemental strategy for improved TB case detection in Africa.

Cost-effectiveness of Active Case Finding

Although expensive, active case finding may prove to be cost-effective in the long run because of new cases prevented. The second manuscript provides new evidence on the cost and cost-effectiveness of ACF in an attempt to address the long-standing policy claim that active case finding is very costly and labor-intensive (Murray & Salomon, 1998a; World Health Organization, 2013b). This claim has been made based on very sparse supporting evidence. For example, only a few active case finding studies have

evaluated the cost-effectiveness of ACF compared to passive case finding (Datiko & Lindtjorn, 2010; Eang et al., 2012; Mupere et al., 2013; Nishikiori & Van Weezenbeek, 2013). Moreover, the studies neither considered costs to the society nor a broad enough range of strategies that include household contact investigation.

Mathematical modeling studies have also shown that ACF would be cost-effective due to the great potential long-term benefits from preventing new cases, shortening duration of morbidity and minimizing the risk of death (Dodd et al., 2011; Murray & Salomon, 1998a).The strength of these mathematical models is the ability to account for the dynamic nature of TB by capturing transmission events, progression from latent to active disease and future cases averted. In the present study we utilize primary data, TB program data and information from published literature in a decision analytic model to compare ACF with the standard PCF approach and household contact investigations as competing alternatives for case detection.

Tuberculosis has significant a negative impact on the health care system and individual patients with their households particularly in low-resource settings. The estimated global burden of TB amounts to approximately US$12 billion annually, the bulk of which stems from the estimated 2 million annual deaths associated with an average loss of 15 years' income (World Health Organization, 2011b). Moreover, the vast majority of people affected by TB are in the productive age-group of 15-65 years.

Costs to the health systems are mainly associated with inpatient care for an average length of stay of 84 days for individuals with advanced disease secondary to late presentation as may often be the case in passive case detection and treatment of multi-drug resistant TB (World Health Organization, 2011b). According to WHO policy standard, TB treatment and care is offered ‘free of charge’ in government-owned public facilities in most developing countries but several studies show that most patients incur huge costs throughout the process of receiving this care (Moalosi et al., 2003; Nganda, Wang'ombe, Floyd, & Kangangi, 2003; Okello, Floyd, Adatu, Odeke, & Gargioni, 2003).

A multi-country study done across countries in different continents including Africa, Asia and South America observed that TB-related costs with an average total patient cost of US$538-1268, approximately equivalent to one year of individual income (Mauch et al., 2013).The authors concluded that 'free' tuberculosis diagnosis and treatment are simply not enough for patients suggesting that alternative approaches that address the cost issue are necessary.

Most studies on economic burden of TB have demonstrated that patients costs largely arise from direct out-of-pocket expenses on transportation, hospitalization and meals (Laokri et al., 2013; Mauch et al., 2013) and to a varying extent from indirect costs from patients' time lost from work and/or death (Elamin, Ibrahim, Sulaiman, & Muttalif, 2008; Wyss, Kilima, & Lorenz, 2001). Moreover, passive case finding results in high losses in income before diagnosis and treatment because of health system delays (Aspler et al., 2008; Croft & Croft, 1998).

A recent systematic review of studies on economic burden of tuberculosis for patients and households in Africa revealed that the mean patient pre-diagnostic costs ranged between US$36 and US$196, corresponding to 10.4% and 35% of annual household income (Ukwaja, Modebe, Igwenyi, & Alobu, 2012). The analyses of economic burden of TB done to-date are based on the current standard practice of passive case finding approach and may be partly a reflection of lack of equitable access to health services especially for the poor. Evidently, strategies that are highly efficient with the potential to relieve the economic burden to the patients and the health system are urgently needed.

Mathematical modeling has shown that its benefits could far outweigh the costs and even increase efficiency in the long term (Murray & Salomon, 1998a, 1998b; Nishikiori & Van Weezenbeek, 2013). For example, ACF has been shown to detect TB cases earlier than they would present through the PCF system thereby minimizing the likelihood of complications and the need for hospitalization (Eang et al., 2012). Additionally, when cases are detected earlier it is plausible to assume that transmission is interrupted and future cases are prevented (Currie, Williams, Cheng, & Dye, 2003). Furthermore, when

health care workers reach out to search for potential TB patients in the community, the pre-treatment transportation costs which indeed constitutes a large portion of patient costs is removed while access to health services is increased (Borgdorff et al., 2013). In light of these potential economic advantages, an earlier call to rethink the role of ACF in TB control (Murray & Salomon, 1998a) was recently reiterated by Getahun and others (Getahun & Raviglione, 2010). These calls have currently stimulated active policy discussions of what, when and how ACF programs could be implemented as an alternative to the passive strategy alone. However, for the policy debate to be meaningful, the cost and cost-effectiveness of these strategies must be evaluated.

Studies that specifically focus on the cost-effectiveness of tuberculosis active case finding strategies are very limited (Dasgupta et al., 2000; Mupere et al., 2013; Murray & Salomon, 1998a). A systematic review conducted on economic evaluation studies relevant to TB control that were published between 1982 and 2003 identified only three of 94 studies focused on TB case finding strategies (Floyd, 2003). Majority of these economic evaluation studies published in this 20-year period were undertaken in developed countries indicating the relatively low priority in the high TB burden countries. An evaluation of the impact that the studies had on policy and practice in TB control revealed that one study on cost-effectiveness of community-based care in Uganda (Okello et al., 2003) impacted policy on delivery of TB care in Africa. This suggests that the findings from this economic evaluation have potential to influence policy and practice in the local setting and the African region.

Murray & Salomon (1998) conducted one of the earliest published studies that used mathematical modeling to demonstrate that ACF strategies are cost-effective at a global level. The authors estimated the maximum cost at which ACF strategies would still be cost-effective compared the PCF strategy from a TB program decision maker's perspective considering the period 1998 to 2050. The strength was that the analyses undertaken were very comprehensive taking into account separate case detection rates for each clinical form of disease, the average delay from onset of symptoms to diagnosis and the interaction

between TB and HIV. These considerations are important because they lend clinical and epidemiologic validity to the interpretation of results. The authors used disability life years (DALYs) averted as the outcome measure and the society's maximum willingness-to-pay instead of the incremental cost per additional case of TB detected in the ACF program. This makes it possible to compare ACF with other health sector interventions. They conclude that the expected benefits from a single cycle or continuous ACF programs particularly in Sub-Saharan Africa are likely to be so large that society should be willing to invest considerable resources to achieve these gains.

Contact investigation has been shown to be a cost-effective strategy for detecting TB disease and latent infection in specific high risk populations. A study conducted from the Canadian government perspective evaluated the cost-effectiveness of active screening for TB disease and latent infection among the immigrants and close contacts of index TB foreign born persons (Dasgupta et al., 2000). The study is unique because of its focused on two high-risk populations and compared two well-known strategies for active TB case detection, passive surveillance and close contact investigation. The study utilized a simple Markov model with three health states to estimate the costs per active cases detected, completing treatment and cases prevented over a period of 20 years. The authors concluded that investigations of close contacts for active TB had a high case detection rate, produced high program efficiency and resulted in net cost savings. The strength of the study was the ability to capture the future risk of active TB in persons with latent infection, an important outcome that reflects long-term benefits of the strategy. The limitation of this study was the lack of explicit discounting of health effects of the program to reflect their net present value; this could have led to underestimation of the cost-effectiveness of the strategies under comparison. Secondly, the study did not use generic outcome measures such as QALYs or DALYs which limits the comparison and generalizability of study findings to other settings.

A recently published study that was conducted from the Ugandan government's perspective examined the cost-effectiveness of passive case finding compared to active plus passive case finding

(Mupere et al., 2013). The study utilized a 5-state Markov model to examine the cost per case TB detected, life years saved, deaths prevented and QALYs saved over a 5-year time horizon. The authors concluded that the ACF plus PCF combined strategy was cost-effective at $109 per additional QALY. The strength of this study was that they showed that ACF was least cost effective in the younger age group of 10-14 years. The limitation of this study was that contact investigation was not included as one of the alternative strategies for case finding. Therefore, our study fills this gap by adding contact investigation to the range of alternative case detection strategies being compared to the standard passive case finding.

Partial economic evaluation studies that assess the costs and effects of ACF as a single strategy without comparing it to alternatives have been done (Eang et al., 2012; Hinderaker et al., 2011; Kranzer et al., 2012; Nishikiori & Van Weezenbeek, 2013), but their results cannot be used when making a choice from among competing alternatives. For example, Hinderaker et al (2011) published results from 51 operations research studies of innovative case detection projects across 18 countries (Hinderaker et al., 2011). The cost analysis involved pooling the total number additional cases detected and the costs incurred to find TB cases in each project using a mix of ACF strategies. The authors reported the mean and median cost per additional case detected beyond what PCF had detected without explicit comparison among strategies used by each project. The results can be utilized within local context of the project settings for budget planning but they are not very informative for decision making on the most efficient case finding strategy. In summary, there is dearth of published cost-effectiveness studies comparing passive case finding and active case finding and household contact investigation as TB detection strategies. None of the published studies identified so far have compared the cost-effectiveness of the three most commonly practiced TB case detection strategies. Therefore, our study is novel in that it seeks to fill this important knowledge gap in the literature.

Summary of Gaps in the Literature

In summary, the results from the majority of published and observational studies consistently show that ACF with components of health education on awareness of symptoms, increasing access and re-training health personnel enhances identification of previously undetected active TB cases in the community but it is still unclear what components work the best. There is no established threshold of what makes an optimal yield and the number needed to screen to detect one case from ACF. There is likely to be a wide variation because of differences in risk of disease in different populations. A critical gap is the lack of cost- effectiveness studies that evaluate ACF with other existing case finding strategies.

Current Thinking and Future Directions in TB Case Finding

The body of knowledge from the earlier and more recent studies of ACF can be utilized to refine our current thinking in two ways; first, that extensive questioning is no longer necessary when screening general communities, but rather brief symptom inquiry that focuses on identifying persons who are suspected to have TB disease could be more efficient. Second, that targeting ACF to high-risk groups such as household contacts or people living with HIV/AIDs is likely to be more efficient than untargeted approaches. Third, the effectiveness of ACF can be augmented by a mix of several component parts such as increasing awareness of symptoms through education, improving access to diagnostic services and ensuring that there are well trained health care workers with the capacity to identify TB suspect.

In future, approaches to ACF strategies should be tailored to specific settings based on a clear understanding of whether the weaknesses in the health system are a more serious problem than the awareness of symptoms among patients. Future research should also focus on conducting more cohorts, quasi-experimental and experimental studies that can measure the long-term impact of ACF on incidence of TB disease. Lastly, research on the cost-effectiveness of ACF strategies is needed to generate evidence that will be used to inform policy decision making for TB case detection and control.

CHAPTER 3

THE YIELD OF UNDETECTED TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS COINFECTION FROM ACTIVE CASE FINDING IN URBAN UGANDA[1]

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Abstract

Setting: An urban community located in Kampala, Uganda

Objectives: To determine the yield of undetected active TB and TB/HIV and the number-needed-to-screen to detect a case using active case finding (ACF) in an urban community

Methods: A door-to-door survey was conducted in Rubaga community from January 2008 to June 2009. Residents aged ≥ 15 years were screened for chronic cough (≥ 2 weeks) and then tested for tuberculosis disease using smears and/or cultures. Rapid testing was used to screen for HIV infection. The number-needed-to-screen to detect one case was calculated based on population screened and the undetected cases found.

Results: Of the 5,102 participants, 3,868 (75.8%) were females and the median age (IQR) was 24 (20-30). There were 199 (4%) with chronic cough, 160 (80.4%) submitted sputum of which 39 (24.4%; 95% CI: 17.4%, 31.5%) had undetected active TB and 13 (8.1%; 95% CI: 6.7, 22.9) were TB/HIV co-infected. The number-needed-to-screen to detect one TB case was 131 in the whole study population but was only five among the subgroup of persons with chronic cough.

Conclusions: Active case finding obtained a high yield of previously undetected active TB and TB/HIV cases. The number-needed-to-screen in the general population was 131 but the number-needed-to-test to detect a TB case was five persons with chronic cough. These findings suggest that boosting the identification of persons with chronic cough may increase the overall efficiency of TB case detection at a community level.

Key words: Case detection, Tuberculosis; chronic cough, number-needed-to-screen, TB/HIV co-infected

Introduction

Case detection is a principle means of controlling transmission and reducing tuberculosis (TB) incidence (De Cock & Chaisson, 1999). Globally, case detection has stagnated in recent years, while the rate of decline in estimated TB incidence has been slower than expected (K. Lonnroth et al., 2009; World Health Organization, 2012). Passive case finding (PCF); the detection of active TB or TB/HIV among symptomatic persons voluntarily presenting to the health system is the standard approach adopted by most national TB programs (Golub, Mohan, et al., 2005). Using PCF alone leaves large pools of undetected prevalent TB cases that may fail to seek care (Hoa et al., 2010; Tadesse et al., 2011; van't Hoog et al., 2011). In Sub-Saharan Africa, health system delays occur in TB diagnosis or initiation of treatment even with functional TB programs. Patients also delay due to lack of awareness of symptoms or lack of access to health services especially in Sub-Saharan Africa (Bailey et al., 2011; den Boon et al., 2008; Golub, Bur, et al., 2005; Kiwuwa et al., 2005; Sendagire et al., 2010). In essence, many TB patients infect others before they are diagnosed and placed on effective treatment. Alternative strategies to overcome the detection gap should be geared towards shortening these delays and reducing the potential risk of transmission at the community level.

Active Case Finding (ACF) is a known alternative strategy for case detection (Golub, Mohan, et al., 2005; K. Lonnroth, Corbett, E., Golub, J., Godfrey-Faussett, P., Uplekar, M., Weil, D., Raviglione, M.,, 2013). It refers to provider-initiated efforts to find, evaluate, and diagnose active TB among asymptomatic and symptomatic individuals who have not sought care (K. Lonnroth, Corbett, E., Golub, J., Godfrey-Faussett, P., Uplekar, M., Weil, D., Raviglione, M.,, 2013). Ideally, ACF can interrupt transmission of TB through early detection and prompt initiating effective treatment (Corbett et al., 2010; den Boon et al., 2008; Golub, Mohan, et al., 2005). Additionally, ACF can reduce the risk of death due to TB, especially among HIV co-infected individuals (Wood et al., 2007). Mathematical models suggest that

ACF is one of the most effective ways to reduce TB incidence and mortality (Currie et al., 2003; De Cock & Chaisson, 1999). Recent randomized community trials (Corbett et al., 2010; Datiko & Lindtjorn, 2009; Miller et al., 2010) and observational studies (Ayles et al., 2009; J. N. Sekandi et al., 2009; Wood et al., 2007) done in developing countries have shown that ACF identifies previously undetected TB cases.

Uganda has an estimated annual incidence of 234/100,000 of TB cases but only 57% of smear positive cases were detected in 2011 (World Health Organization, 2012). The capital district, Kampala accounts for nearly 25% of Uganda's notified TB caseload (Ministry of Health, 2008). The purpose of this study was to determine the yield and the number-needed-to-screen (NNS) to detect a case of undetected TB and TB/HIV in Kampala. This expands on the existing evidence-base that supports ACF as a supplemental strategy for TB case detection in Africa.

Methods

Ethical Considerations

The study received approval from institutional review committees at University Hospitals of Cleveland, University of Georgia and Makerere University School of Public Health, and the Uganda National Council for Science and Technology. Written informed consent was obtained from all participants.

Study Design, Setting and Population

We conducted a door-to-door, cross-sectional survey of chronic cough in Rubaga community located in Kampala city, Uganda from January 2008 to June 2009. The division is subdivided into 13 parishes and 128 villages with approximately 75,485 households and 400,000 people. About 50% of the population are adults aged 15 years or older.(UBOS, 2009/10) Individuals can access TB and HIV

diagnostic services from two public health centres free-of-charge or two tertiary private hospitals for a fee. Treatment is offered free in both private and public facilities. Eligible residents were aged ≥15 years and lived in Rubaga division during the survey period. Participants were excluded if there was a language barrier, declined to consent, or were not at home on three separate attempts, or did not plan to stay in the study area for two subsequent weeks from the survey date.

A minimum sample size of 5,000 participants was calculated to estimate the prevalence of TB with a 95% confidence level, based on a previous ACF study of undiagnosed TB cases in Kampala (J. N. Sekandi et al., 2009). Participants were selected using a multi-stage sampling approach. A simple random sample was used to select five of the 13 parishes using a computer-based random number generator and sampling frame from the Uganda Bureau of Statistics (UBOS, 2011). Weighted proportions-to-village population sizes were calculated to estimate the number of participants to be recruited from each village. This was done to account for the variability in crowding. We identified the first house from a defined central point such as road or drainage junctions in each village and enrolled a convenience sample of persons at home.

A two-step approach was used to screen for active TB and TB/HIV; a cough interview administered to identify chronic coughers and diagnostic testing for TB and HIV infection. Trained interviewers administered a cough questionnaire that assessed the presence, duration and frequency of cough. Chronic cough was defined as self-reported cough for 2 weeks or longer at the time of the survey. Information was collected on socio-demographics, TB history, TB-related symptoms (weight loss, evening fever, hemoptysis, excessive night sweating), health care seeking assessed as “evaluation by a health provider since the start of your cough”, previous HIV testing, and current treatment for TB or HIV/AIDS. The main study outcomes were undetected active TB and TB/HIV. The secondary outcome was the number-needed-to-screen to identify a single case in the sub-group of interest.

Spot and early morning sputum samples were collected from the chronic coughers at their homes and transported in a cool box to the certified national reference TB laboratory in Kampala. Samples were processed using standard methods (Asiimwe et al., 2008), two technicians independently examined the sputum smear for acid-fast bacilli (AFB) and used Löwenstein-Jensen slants for cultures. Smears were quantified and reported as negative, scanty, 1+, 2+, 3+ using IUATLD standards.(Rieder H, 2007) Smear test results were reported within 48-72 hours.

Rapid HIV testing was performed using the serial algorithm as recommended by the Uganda Ministry of Health.(Ministry of Health, 2010) Determine HIV-1/2 assay (Abbott Laboratories, Illinois, and U.S.A) for screening and HIV-1/2 STAT-PAK Dipstick assay (Chembio Diagnostic System Inc, New York, U.S.A) for confirmation were used. Uni-Gold test (Trinity Biotech, Wicklow, Ireland) was used for confirmation in case of discordance. HIV Western Blot test was performed on a 10% random sample of blood specimens for quality control purposes.

A TB case was defined as a positive sputum smear or culture from one or more collected samples.(Mabaera et al., 2007; World Health Organization, 2011b). An HIV case was defined as a positive rapid HIV test according to the Uganda Ministry of Health algorithm (Ministry of Health, 2010) A positive TB/HIV co-infected case was defined as confirmed TB case with a concurrent positive HIV test. New cases identified during the survey were appropriately referred to public health centers for further care.

Statistical Methods

The yield of active TB and TB/HIV cases was calculated as proportions with 95% confidence intervals from undetected cases in chronic coughers. The number-needed- to-screen to identify one case of chronic cough, active TB, TB/HIV and HIV infected cases was also calculated accordingly. Appropriate statistical tests were used to test for differences in groups at $\alpha=0.05$. Data were analyzed using Stata version 11.0 (Statacorp, College Station, Texas).

Results

Description of Study Participants

The study enrolled 5,102 participants from a total 4,494 households visited (Figure 3.1) and 18 villages. The study excluded 2,289 people including 2,257 who were not at home (82.3% male) and 32 declined to consent. Of those enrolled, 3,868 (75.8%) were female with median age of 24 years (IQR, 20-30) (Table 3.1). The prevalence of self-reported cough of any duration was nearly 516 10.1%, 95% CI: 9%-11%). More than half (50.8%) of the participants were 15-24 years old. Half the sample had attained at least 8-13 years of education and 44.2% were employed with 54.4% having an average weekly income of not more than two U.S. dollars. More than one third (38.2%) of the participants reported that they had never had an HIV test.

Yield of Chronic Cough and Other TB-related Symptoms

Of the 5,102 participants, 199 (4%, 95% CI: 3.5%-4.5%) had ≥ 2weeks of cough (Table 2). Of the five most common TB-related symptoms, self-reported unintentional weight loss was the most prevalent (35.2%), followed by excessive night sweats (32.7%). Hemoptysis was the least common symptom (6.5%).

Yield of Undetected Active TB, TB/ HIV Co-infection and HIV among Chronic Coughers

Of 199 chronic coughers, 160 (80.4%) submitted sputum for examination and of those, 39 met the criterion for active TB (24.4%; 95% CI: 17.8%-31.1%) (Table 3.2); 26 were HIV seronegative or unknown (16.3%; 95% CI: 2.1%, 30.5%) and 13 (8.1%; 95% CI: 6.7, 22.9) were found to be HIV-infected. Chronic coughers with and without active TB were similar in socio-demographic, clinical characteristics and health seeking behavior. There were 57 (28.6%; 95% CI: 22.6%, 35.5%) HIV+ cases among chronic coughers. Of the 57 individuals, 25 (44%) of them were newly diagnosed (Figure 3.1).

Sputum Smear Grade of TB Cases Detected by ACF

Of the 39 active TB cases, majority (66.7%) had negative or low AFB sputum smear grade (scanty or +1). No statistically significant differences existed in levels of smear grades and other characteristics between TB cases with or without HIV infection (Table 3.3).

The Number-Needed-to-Screen Using ACF to Detect TB, TB/HIV and HIV Cases

When using chronic cough to screen the general population for TB suspects, 26 people were needed to identify one chronic cougher. In order to identify one active TB case using cough screening with smear and/or culture testing, 131 people needed to be screened in the population. However, when considering only smear results, 170 people needed to be screen to find a case of TB. Subsequently, the number- needed- to-test to find one case of TB among chronic cough was five (Table 3.4). When stratifying the subgroup of suspects by HIV sero-status, the number-needed-to-test was eight for TB/HIV sero-negative and 15 for TB/HIV co-infected persons.

Discussion

In this door-to-door cough survey of adults living in an African city, we determined the yield of undetected infectious TB using a two-step approach; screening for chronic cough with a questionnaire followed by smear microscopy and culture for diagnosis. Chronic cough was uncommon in the community at large, with a yield of 4%. Subsequently, the number-needed-to-screen to find a single case of active TB was 131 people but operationally, it could be as high as 170 if only smear microscopy is done. Once it was known that the person had a chronic cough, the number-needed-to-test was only five. This finding suggests that gaining access to residents with chronic cough is a critical step toward an efficient community active TB case finding program. Previous studies have used educational leaflets, flyers, mobile vans with loud speakers, community awareness campaigns by trained lay workers and

cellphone text messaging to enhance case finding among persons with chronic cough (Corbett et al., 2010; A. J. Khan et al., 2012; Miller et al., 2010; Shargie et al., 2006).

The number-needed-to-screen is a useful metric for comparing efficiency across screening programs in the context of resource allocation. In this study the number-needed-to-screen to find a TB case of was 131 people in the general community. This number is similar to the median number-needed-to-screen of 148 (range 29–5000) reported in a systematic review from population-based surveys of TB case finding in Africa (Kranzer et al., 2010). The number-needed-to-screen can vary depending on prevalence of TB and HIV in the target population, the screening strategy, the sensitivity of the diagnostic tests used, and functionality of TB control programs (Kranzer et al., 2012). A recent review demonstrated that the number-needed-to-screen to detect a TB case was relatively lower when high-risk populations such as prisoners or the homeless in high prevalence settings were screened (A. E. Shapiro, Golub, J. E., 2012). The number-needed-to-test of five in persons with chronic cough in our study is consistent with the average of seven suspects (range 3.3- 20) needed to test to detect one smear-positive case in TB program clinics (Rieder H, 2007).

A high prevalence of 24.4% undetected infectious TB cases among chronic coughers in Kampala is consonant with another published study in the same setting in 2009 (J. N. Sekandi et al., 2009). But importantly, low diagnostic accuracy of the tests used may have led to missed TB cases or over-diagnosis; specifically, the finding that 16 of 30 cases positive on sputum smear microscopy were culture negative. This may have been due to either specimen contamination or other quality problems with culture therefore corrective measures should be taken. We do not know the true prevalence of undetected TB in this community subgroup of chronic cough. None-the-less, the value of ACF in identifying ‘pools’ of undetected infectious TB cases in high TB prevalence settings is well highlighted.

Although the primary goal of ACF is to detect undiagnosed active TB, our study shows that also HIV-associated TB was detected. A higher proportion of smear positive cases detected were HIV

seronegative persons than seropositives. This difference could be possibly explained by the diagnostic inaccuracy especially when using smear microscopy in HIV-associated TB (Lalloo & Pillay, 2008). In Kampala where the HIV prevalence is high and the infection remains undiagnosed (J. N. Sekandi et al., 2011; UBOS, 2011), it makes sense to couple HIV testing with TB screening. As already recommended in the WHO's '3Is' policy, intensified TB case finding in HIV-infected persons should continue to occur in specialized HIV clinics as an effective way to find TB cases (Kranzer et al., 2010; A. E. Shapiro, Golub, J. E., 2012). But, ACF for TB/HIV in the general population should not be ignored because it particularly uncovers additional cases of previously unknown HIV status (Ayles et al., 2009; Kranzer et al., 2010).

Our findings support the idea that ACF detects cases much earlier based on smear grade; most detected cases had low smear grades. A similar study in Zambia found a majority of detected cases had scanty to low smear grade at diagnosis (Ayles et al., 2009). In contrast, high smear grades of 3+ suggesting more severe disease were found in 82% of TB patients at the time of diagnosis in a PCF clinic setting in Uganda (Guwatudde, Nakakeeto, et al., 2003). Higher smear positivity has been associated with a greater level of TB transmission among close contacts (Lohmann et al., 2012; Whalen et al., 2011). Theoretically, earlier detection implies shorter duration of infectiousness and a reduced likelihood of transmission. But, what remains unclear is the timing of ACF that translates into a meaningful reduction in duration of infectivity to other persons and thus incidence. A standard epidemiologic measure that captures the impact of ACF on TB epidemiology is therefore urgently needed.

This urban population-based study provides findings that are consistent with existing evidence supporting the application of ACF strategies for case detection in high TB and HIV burden areas. However, the cross-sectional design limits the interpretation of the prevalence of undetected TB and TB/HIV beyond the study period. Possible underestimation of the prevalence may be because 19.6% chronic coughers didn't produce sputum for evaluated. Ideally, further diagnostic evaluation should be

done. Selection bias could arise from the heavily female-skewed sample and non-participation of people who were not found at home during the day. Previous door-to-door studies have shown similar recruitment patterns because men mostly work outside of the home (Datiko & Lindtjorn, 2009; J. N. Sekandi et al., 2009). A study showed that men tended to seek care for TB-related symptoms earlier than females (Ahsan et al., 2004) but ACF may identify disease earlier among females.

Ideally, high quality TB diagnosis, treatment, management and support for patients should be in place before ACF is initiated. Under programmatic settings, barriers to case finding such as the low sensitivity of smear microscopy, quality assurance problems that render culture testing less sensitive as well as diagnostic delays could be overcome by deployment of rapid, highly sensitive point-of-care diagnostics, such as the Xpert MTB/RIF (Ntinginya et al., 2012; Rachow et al., 2011). Finally, ACF is more resource-intensive than passive case finding irrespective of target population, therefore more studies of cost-effectiveness comparing active and passive case finding strategies (Datiko & Lindtjorn, 2010; Mupere et al., 2013) are needed to inform policy decisions for TB control programs in Africa.

Conclusions

Active case finding obtained a high yield of previously undetected active TB and TB/HIV cases. The number-needed-to-screen in the general population was 131 but the number-needed-to-test to detect a TB case was five persons with chronic cough. These findings suggest that boosting the identification of persons with chronic cough may increase the overall efficiency of TB case detection at a community level.

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Conflict of Interest: None Declared

Table 3.1. Baseline Characteristics of Study Participants in Kampala, Uganda, 2008-2009

Characteristics	Total population N=5102	Percent
Age, yrs (Median, IQR)	24 (20-30)	
15-24	2,592	50.8
25-34	1,614	31.7
35-44	533	10.8
45-54	191	3.7
≥55	152	3.0
Sex		
Female	3,868	75.8
Male	1,234	24.2
Marital status		
Never married	1,737	34.1
Currently married	2,583	50.6
Previously married	782	15.6
Religion		
Catholic	1,683	33.0
Protestant	1,387	27.2
Muslim	1,255	24.6
Others**	777	15.2
Education attained (yrs)		
None	214	4.2
1-7	1,872	36.7
8-13	2,563	50.2
>13	453	8.9
Employed		
Yes	2,325	45.6
No	2,777	54.4
Reported weekly income† (Ugshs)*	4,000 (1,000-10,000)	
None	862	16.9
1- <1000	164	3.2
1000- 5000	2,253	44.2
5,001- 10,000	797	15.6
>10,000	1,026	20.1
Ever tested for HIV		
Yes	3,151	61.8
No	1,951	38.2
Presence of cough		
Yes	516	10.1
No	4,586	89.9
Current TB treatment		
Yes	14	0.3
No	5088	99.7

†Median income (IQR) * Ugshs 2,500~ 1.00 USD **Others-Pentecostal, Adventist or religion not specified

Table 3.2. Characteristics of Undetected TB Cases Among Persons with Chronic Cough in Kampala, Uganda

Characteristics	Total N=199 (%)†	No TB n=121(%)	Undetected TB n=39 (%)	P -value
Produced sputum	160 (80.4)	121 (75.6)	39 (24.4)	
Unable to produce sputum¥	39 (19.6)			
Sex				
Female	125 (62.8)	80 (66.1)	22 (56.4)	0.273
Male	74 (37.2)	41 (33.1)	17 (43.6)	
Age, yrs				
15-24	64 (32.2)	43 (35.5)	9 (23.1)	0.263 [a]
25-34	80 (40.2)	45 (37.2)	17 (43.6)	
35-44	28 (14.1)	17 (14.1	8 (20.0)	
45-55	13 (6.5)	6 (5.0	4 (10.3)	
>55	14 (7)	10 (8.2)	1 (3.0)	
Marital status				
Never	40 (20.1)	24 (19.8)	8 (20.5)	
Married	99 (49.8)	66 (54.5)	18 (46.2)	0.596
Currently	60 (30.2)	31 (25.6)	13 (33.3)	
Previously				
Education level (yrs of school)				
None	22 (11.1)	15 (12.4)	2 (5.1)	
1-7	106 (53.2)	62 (51.2)	19 (48.7)	0.524[a]
8-13	61 (30.7)	37 (30.6)	16 (41.0)	
>13	10 (5)	7 (5.8)	2 (5.1)	
Cough duration (wks) [c]	71 (35.7)	41(34.8)	13 (33.3)	
2-3	52 (26.1)	36 (30.5)	6 (15.4)	0.204[b]
>3-8	19 (9.6)	11(9.3)	6 (15.4)	
>8-12	57(28.6)	30 (25.4)	14 (35.9)	
>12				
TB-related symptoms				
None	90 (45.2)	59 (48.8)	15 (38.5)	
1-2	58 (29.2)	38 (31.4)	11 (28.2)	0.106[b]
3-5	51 (25.6)	24 (19.8)	13 (33.3)	
Ever had HIV test				
No	83 (41.7)	51 (42.2)	16 (41.0)	0.902
Yes	116 (58.3)	70 (57.9)	23 (59.0)	
HIV Sero-status				
Negative	138 (69.4)	86 (72.9)	25 (65.8)	
Positive	57 (28.6)	32 (27.1)	13 (34.2)	0.154
Not done	4(2)	3	1	
Healthcare seeking				
No	51 (28.7)	31 (28.7)	8 (23.5)	0.556
Yes	127 (71.3)	77 (71.3)	26 (76.5)	

[a] Fisher's exact test [b] trend test , [c] Mean & median difference in cough duration not significant,
†other totals may not add up to 199 due to 39 missing AFB smear tests, of 160 only 4 did not produce 2 samples
¥Evaluated further by chest X-ray if HIV positive

Table 3.3 Characteristics of 39 Previously Undetected TB Cases by HIV Sero-status

Characteristics	Total N=39 (%)	HIV negative n=25 (%)	HIV Positive n =13 (%)	P-value
Age, yrs				
Mean (SD)	33 (11)	33.5 (15.6)	31.0 (8.9)	0.560[a]
Median (IQR)	29 (25,42)	27 (22,39)	29 (26,33)	0.77[b]
Sex†	Not 100%			
Female	22 (56)	15 (60)	7 (53.9)	
Male	17 (44)	10 (40)	6 (46.1)	0.482
AFB smear grade†				
Negative	9 (23.1)	5 (20)	3 (23.1)	0.690
Scanty	13 (33.3)	8 (32)	5 (38.5)	
1+	4 (10.3)	2 (8)	2 (15.4)	
2+	5 (12.8)	3 (12)	2 (15.4)	
3+	8 (20.5)	7 (28)	1 (7.6)	
Smear and culture				
AFB+ & Culture +	14 (36)	4 (31)	10 (38)	0.713
AFB+ & Culture -	16 (41)	6 (46)	10 (38)	
AFB - & Culture+	9 (23)	3 (23)	6 (24)	
Cough duration (wks)				
Mean (SD)	15.7 (26.9)	11.0 (14.5)	14.7 (25.3)	0.80[a]
Median (IQR)	8.7 (3,17.4)	4.3 (2.9,8.7)	4.3 (3,13)	0.60[b]

[a]t-test [b]Mann-Whitney test, †stratified totals do not add up to 39 due to 1 HIV result missing

Table 3.4. Number-Needed-to-Screen and Number-Needed-to-Test to Detect a TB Suspect, TB or TB/HIV Case Using Active Case Finding

Study population	Total (N or n)	Number-Needed-to-Screen† (95% CI)	Number-Needed-to-Test ¥ (95%CI)
All participants enrolled	5,102		
Chronic cough (≥ 2 weeks)	199	26 (23, 30)	N/A
Previously undetected Active TB (smear and/ or culture positive)	39	131 (96, 179)	5 (5.3, 4.7)
Previously undetected Active TB (smear only)	30	170 (123, 256)	7 (7.1, 6.3)
TB+/ HIV negative	26	196 (145, 323)	8 (7.2, 8.3)
TB+/ HIV co-infected	13	393 (222, 667)	15 (14, 17)
Undetected HIV positive in chronic cough	25	N/A	8 (7.4, 8.6)

† Numerator for Number-Needed-to-Screen N=5,102 and the rest of the numbers in the column with totals constitute the denominators

¥ Numerator for number-needed-to-test n=199, the rest of the numbers in the column with totals below chronic cough constitute the denominators

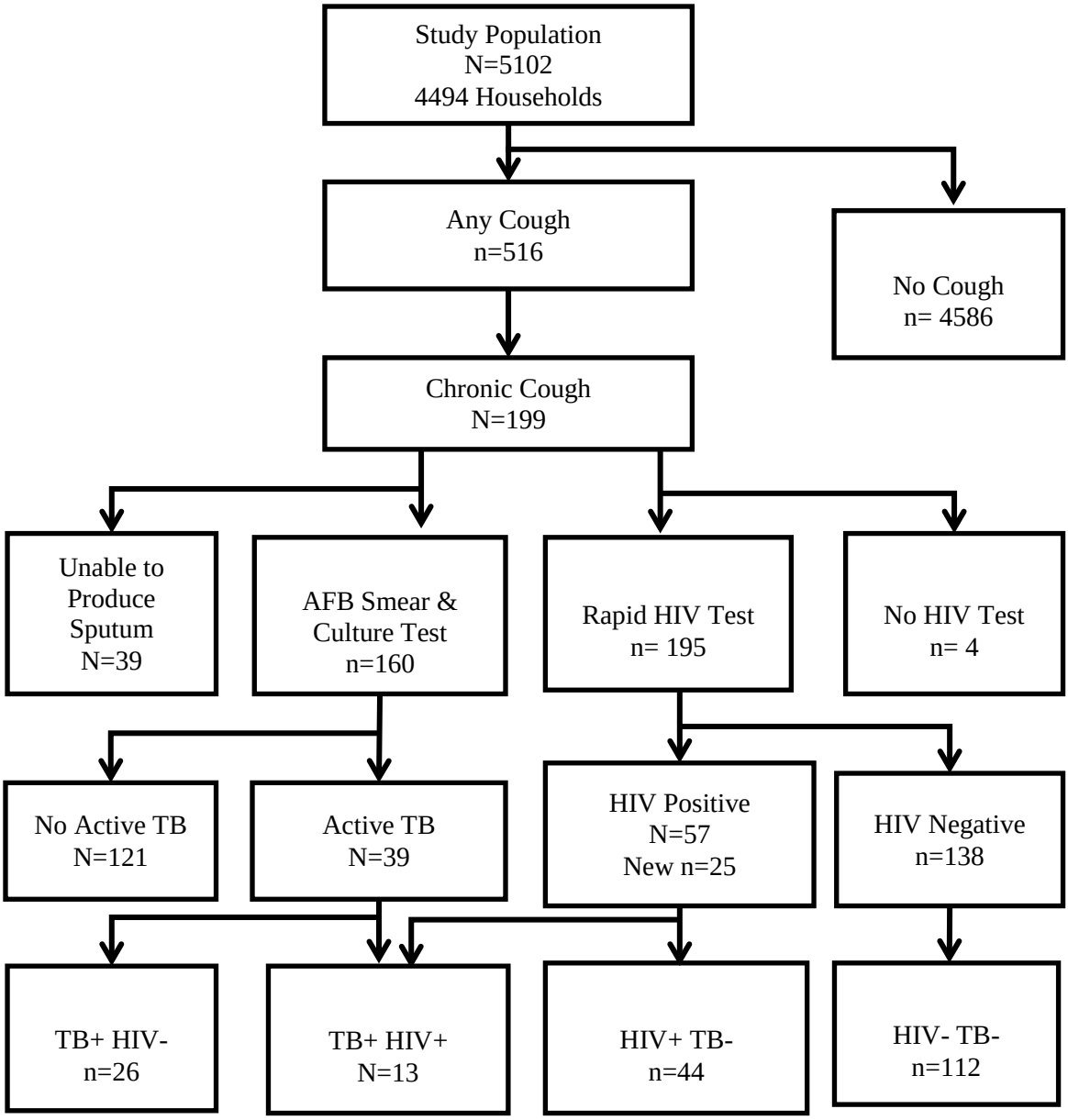


Figure 3.1. Flow Diagram of Study Participants in Kampala, Uganda

CHAPTER 4

THE COST AND COST-EFFECTIVENESS OF COMMUNITY ACTIVE CASE FINDING FOR TB DISEASE IN URBAN UGANDA[2]

[2] Juliet N.Sekandi, Kevin Dobbin, James Oloya, Christopher C. Whalen, Phaedra S. Corso. To be submitted to *International Journal of Tuberculosis and Lung Disease*

Abstract

Introduction: The standard passive case finding (PCF) strategy is inadequate in detecting all TB cases in Africa. Community active case finding (ACF) and household contact investigations (HCI) are effective alternatives but empirical evidence of their cost-effectiveness is sparse. This study evaluated the cost and cost effectiveness of community active case finding and household contact investigations compared to passive case finding in an urban African setting.

Methods: A static decision model was constructed as a framework to examine the costs and effectiveness of three TB case detection strategies, PCF alone, PCF +ACF, and PCF+HCI. Model probabilities and costs estimates were mainly obtained from the primary study conducted in Kampala and secondary sources. The analyses were performed from the societal and provider perspectives over a 1.5 year timeframe. The main effectiveness measure was the number of true TB cases detected and the outcome was incremental cost-effectiveness ratios (ICERs) expressed as cost in 2013 US$ per true case detected.

Results: Our base analysis showed that the PCF+HCI strategy was cost-effective at US$443.62 per additional case detected while PCF+ACF was not cost effective at US$1492.95. However, the PCF+ACF strategy became cost-effective when the prevalence of chronic cough in ACF increased to 40%, or when chronic cough and TB disease prevalence simultaneously increased to reach 24% and 30% respectively. Also, ACF+PCF became cost-effective with a 50% reduction in program costs for ACF.

Conclusions: Under our baseline assumptions, the addition of HCI to an existing PCF program was more cost effective than adding ACF to detect TB cases in the context of an African city. However, PCF+ACF has the potential to be cost-effective under certain conditions.

Keywords: Cost, Cost-effectiveness, Incremental cost-effectiveness ratio, Active case finding, Household contact investigation, Passive case finding

Introduction

Despite decades of sustained efforts to control tuberculosis (TB), the World Health Organization estimates that nearly 9 million new cases occur while 2 million die annually (World Health Organization, 2011b). Nearly 80% of the TB cases reside in the 22 high burden countries including Uganda. In 2011, Uganda ranked 18th among the highly burden countries with an estimated annual incidence rate of 330/ 100,000 and a death rate of 5.3% (Ministry of Health, 2010). According to a world bank study on the economic benefit of TB control, the projected cost of TB–related deaths (including HIV co-infection) in Sub-Saharan Africa from 2006 to 2015 is US$ 519 billion when there is no effective TB treatment and control as prescribed by WHO's Stop TB Strategy (Laxminarayan, 2007).

Case detection is a cornerstone to TB control but under the standard strategy of passive case finding (PCF) universal success in detecting all cases has not been achieved. It is estimated that nearly 30% of the new TB cases remain undetected (Zarocostas, 2010). For those are detected by PCF, the cases experience long delays prior to diagnosis thus transmit disease while they are still in the community. Alternative strategies of case detection such as community active case finding (ACF) and household contact investigations (HCI) have been tested in studies and are known to work (Ayles et al., 2013; Corbett et al., 2010). However, very few studies have evaluated their cost-effectiveness compared to the standard strategy (Dasgupta et al., 2000; Mupere et al., 2013).

Over the past two decades, economic evaluation studies of broad tuberculosis (TB) control interventions have become increasingly common. These studies have focused on areas such as screening for latent TB infection (Kowada et al., 2008; Nienhaus, Schablon, Costa, & Diel, 2011; Shrestha et al., 2006), screening for active TB among contacts (Dasgupta et al., 2000; Pooran et al., 2010), length and type of drug regimens (Manabe et al., 2012), diagnostic strategies (Andrews et al., 2012; Kowada, Deshpande, Takahashi, Shimbo, & Fukui, 2010; Menzies, Cohen, Lin, Murray, & Salomon, 2012; van

Cleeff, Kivihya-Ndugga, Meme, Odhiambo, & Klatser, 2005; Vassall et al., 2011), treatment of multidrug resistant TB (C. Fitzpatrick & Floyd, 2012; Floyd et al., 2012; Resch, Salomon, Murray, & Weinstein, 2006) and delivery of TB care (Floyd, Skeva, Nyirenda, Gausi, & Salaniponi, 2003; M. A. Khan, Walley, Witter, Imran, & Safdar, 2002; Moalosi et al., 2003; Okello et al., 2003; Sinanovic et al., 2003). But, far fewer studies have been published on case detection strategies of active TB even though it is a core component of TB control (Dasgupta et al., 2000; Datiko & Lindtjorn, 2010; Mupere et al., 2013; Murray & Salomon, 1998a; Nishikiori & Van Weezenbeek, 2013). Moreover, none of the studies have compared the available strategies for case detection in a full economic evaluation. The lack of specific evidence on cost-effectiveness of ACF and HCI forms a strong justification for our study.

Methods

This study utilized a static decision analytic model to evaluate the cost and cost-effectiveness of passive case finding and a combination of passive case finding and active case finding, or household contact investigations compared to passive case finding alone. Data were obtained from a primary cross-section study that was conducted in Kampala, Uganda (details in chapter 3), the national TB program registries, the published literature and elicitation of expert opinion to fill gaps in the literature. Using incremental cost effectiveness analysis, we compared the additional cost in 2013 US dollars per true TB case detected.

Study Setting and Target Population

Kampala City, Uganda's capital has a population of approximately 25 million residents. It has a government funded health system that offers free diagnostic evaluation and TB treatment for all patients who receive health care at the public clinics. Patients are responsible for costs related to the clinic visits including transportation, lodging and meals during the pre-diagnosis. The incidence of TB in Kampala

City is estimated to be 920/100,000 and of the cases reported to the national TB program nearly 20% are from the city (Guwatudde, Zalwango, et al., 2003; Uganda Ministry of Health, 2010). This evaluation focuses on a population of urban residents of all ages in Uganda. The rationale for including all ages is that each strategy is likely to reach more of one age group than another with some overlaps. For example, in Uganda, the HCI strategy would mainly finds children less than 15 years because they are likely to be at home with their parents. Community ACF targets adults 15 year or older because this group is capable of report symptoms and produce sputum samples for examination. Moreover, community case finding studies done in Kampala have shown that there is a high prevalence of undetected adult TB cases (Guwatudde, Zalwango, et al., 2003; J. N. Sekandi et al., 2009) therefore, this setting is likely to benefit from additional case finding interventions.

Study Perspective

This study was conducted primarily from the societal perspective. This includes all costs borne by the providers, patients, caregivers and the government of Uganda. The societal perspective has been recommended by the Panel on Cost-Effectiveness in Health and Medicine (Gold, 1996) because it the most pragmatic and ethical approach that provides the most useful information for resource allocation. In a secondary analysis, the health providers' perspective was considered separately because it is relevant to the TB health providers who are directly involved in detecting TB cases. Costs borne by the health providers are included in the analysis while patients' and caregivers' costs are excluded.

Study Audience

The primary target audience is the TB policy decision makers in the WHO, Uganda and Africa who make decision for resource allocation for case detection in TB control. The local context audience includes the Uganda Ministry of Health (MoH), the national TB program manager, TB zonal supervisors and the health providers at local clinics. The patients and care givers are part of the broader society audience. In line with the Uganda health sector strategic plan, the MoH must make evidence-based

decisions on how to allocate scarce resources among communicable disease health programs (Government of Uganda: Minisrty of Health, 2010) but there is a lack of evidence on the costs and health effects of TB case finding strategies.

Timeframe and Analytic Horizon

The timeframe reflects the start, maintenance and phase out periods of the intervention. The study timeframe spans 1.5 years, from January 2008 to June 2009 based on the duration of the primary ACF study that was conducted in Kampala. The analytic horizon, reflecting how far into the future the costs and effects of interventions accrue after the intervention ends (Haddix, 2003), is the same as the timeframe in this case.

Description of Alternative Strategies

Three alternative strategies for TB case detection were evaluated; the choice for PCF and HCI was based on the WHO recommended standard policy for case detection (World Health Organization, 2011b). Although HCI is current recommended it not widely practiced in Africa. Community ACF is well-known case finding approach that was practiced in early 1950s and is currently used in research settings (A. E. Shapiro, Golub, J. E., 2012; A. E. Shapiro et al., 2012). Since PCF is already an established standard, this study evaluated add-on strategies in order to improve effectiveness. The strategies to be compared are listed below.

1) Passive Case Finding (PCF)

2) Passive *plus* Active Case Finding (PCF+ ACF)

3) Passive *plus* Household Contact Investigation (PCF+ HCI)

Passive Case Finding

Passive case-finding (PCF) is the standard facility-based approach for detecting pulmonary TB cases and is practiced by the Uganda national TB control program. Persons with TB symptoms initiate the visit to the health facility for diagnostic evaluation and treatment services delivered through outpatient

care by healthcare workers (HCWs). Patients commonly present with chronic cough; defined as self-reported cough lasting 2 or more weeks at the time of first contact with the health system.

When patients first arrive at the clinic they are screened for symptoms by a nurse; those with chronic cough are then referred to a clinician for physical examination, followed by collection of one spot sputum sample for acid- fast bacilli (AFB) smear microscopy examination and culture tests. The tests are performed free of charge in public health facilities. On the second or subsequent days, the patients return to the clinic with the second 'early morning' sputum sample for drop-off to the laboratory for testing. Depending on the patient load at the clinic, patients may wait at the clinic to receive final test results or may be required to return, on average it takes 2-3 days to complete the diagnostic process (Mauch et al., 2013). According to the standard diagnostic protocol, TB disease is confirmed if one or both tests are positive on smear and/or culture test. If a patient is unable to produce sputum, then a diagnosis is made based on chest X-rays and clinical findings. Chest X-rays results are usually obtained on the same day of the procedure.

The AFB test is simple, cheap but the culture test may require more expertise and is more expensive; both tests are available in public health system in Uganda. The sensitivity of the AFB smear test ranges between 45-63% and specificity of 79- 98% in the patient population (Albert, 2004). In this study we used results from parallel testing with smear and culture, therefore the combined sensitivity of 77.6% for the two tests is considered ((Levy et al., 1989). The sensitivity of a chest X-rays ranges from 69- 92% while the specificity ranges from 52-99% (Dasgupta & Menzies, 2005). The costs associated with PCF mainly arise from the transportation, meals, caregiver costs, waiting and travel time during the multiple visits during diagnostic evaluation.

Passive plus Active Case Finding

In this strategy, ACF would be added to an existing PCF program described above in order to identify additional TB cases. ACF is a non-conventional, provider-initiated strategy to identify

symptomatic individuals within the general community or high-risk groups who are suspected to have active TB disease but have not sought care (Golub, Mohan, et al., 2005). In Uganda, ACF has been performed in research settings using door-to-door cough screening to identify TB suspects (J. N. Sekandi et al., 2009).

The health care workers (HCWs) or trained volunteers in ACF make at least 3 visits and perform a series of activities including 1) travel to the communities and visit participants in their homes 2) conduct brief cough interviews lasting 5 minutes on average, to identify persons with chronic cough 3) collect two sputum specimens for AFB smear and culture testing in the laboratory in two visits 4) return test results to the patients and refer for care if found to have TB disease. The same standard diagnostic protocol is followed as described in the PCF strategy. The provider costs associated with ACF strategy arise from the personnel time spent in travel, the community outreach activities and transportation during the home visits. Patients' costs are very minimal in ACF; those who are unable to produce sputum have to travel to the clinic to receive chest x-rays.

Passive Case Finding plus Household Contact Investigation

Household contact investigation (HCI) is a targeted form of active case finding strategy that aims to identify additional TB cases among household contacts of a confirmed index active TB cases. The strategy evaluated is a combination of HCI and the existing PCF standard strategy from which index TB cases are generated. Therefore the success of this strategy is driven by how well index cases are followed up by the health system after diagnosis. HCI is not standard practice but it is performed in some research settings in Kampala, Uganda. In the ideal HCI situation, the health care workers screen all household members defined as, persons sharing meals and residing under same roof with the index TB case (Guwatudde, Nakakeeto, et al., 2003). The standard diagnostic protocol includes screening those with and without symptoms. For purposes of this economic evaluation we assume that those without symptoms and children who cannot produce sputum will be evaluated using chest x-rays. Although we recognize that

more complex diagnostic algorithm exist including gastric aspiration for diagnosis of TB in children, we took the most pragmatic approach for this analysis.

On average a household in Kampala has four persons that would be evaluated in a given home (UBOS, 2011). We assumed that all true and false TB index cases from PCF would lead to household contact investigation. Some cases in the households could be missed by HCI but it is safe to assume that they will eventually be detected by the PCF strategy. Assuming that contacts are evaluated in their homes, the costs incurred in HCI would be very similar to those of ACF except for personnel time of travel from house to house. The travel time should be slightly less in HCI because more people would be evaluated in one place at a time.

Cost Measurements

Study costs are assessed from the societal and health provider perspectives for the period of 2008-2009 and were adjusted to 2013 U.S. dollars using the consumer price index and the general inflation rates in the reference year as recommended by the panel on cost-effectiveness (Gold, 1996). No discount rate was applied because the analytic horizon was very short (~one year). Only costs incurred during the process of diagnostic evaluation for detection of a TB case were considered. In the combined strategies the costs from PCF are added to those incurred in ACF or HCI.

The costs are broken down into three main categories: program costs, medical costs and, patient and caregiver costs. Program costs refer to costs incurred at the administrative levels outside the point of delivery and personnel costs (Johns, Baltussen, & Hutubessy, 2003). Medical costs refer to all costs at the point where health care is delivered such as tests, drugs and outpatient visits. Patient and caregiver costs are individual out-of-pocket expenses on meals, travel, accommodation and indirect costs due wages lost during the time of receiving services (Drummond, 2005; Gold, 1996).

Program Cost Data Collection

For this analysis, we considered all costs related to delivery of all three case finding interventions during a period of 18 months. Most cost information was abstracted from the national TB program budgets and actual cost records, research budgets and expense records. Efforts were made to adhere to guidelines as stipulated in the literature (Haddix, 2003). Program costs included in this analysis are personnel time and administrative activities (training, community mobilization, lay workers, transportation, and communication). Overhead costs such as utilities, custodial services, buildings, office space, computers, and maintenance of medical equipment were excluded when valuing resources. The justification for exclusion is that overhead costs are considered 'fixed' and not itemized or directly allocated to a specific service in the TB program clinics (Gold, 1996).

Personnel costs: We considered the personnel time spent by nurses, clinicians and laboratory technicians involved in patient care, from screening counseling, registration through diagnosis of TB. Time was valued based on the hourly pay rate calculated from monthly salaries as paid by the government of Uganda in 2008. The hourly rates are US $1.13 for nurses; $0.76 for laboratory technicians and $2.75 for a clinician. A full week of work is equivalent to 40 hours in the formal employment sector in Uganda. The total personnel costs were obtained from multiplying the hourly rate by estimated patient contact time with each personnel and summing up the costs. Based on our cost survey data, patients identified by PCF require 2.3 outpatient visits to complete the diagnosis process. For ACF and HCI, we estimated that on average, one hour is spent to complete each patient evaluation in the field based on time motion surveys done in a random sample of study participants in the primary ACF study.

Transportation costs: Transportation costs were incurred when HCWs travelled to the communities to perform case finding activities in ACF or HCI. Minimal costs on transportation arose from program-related activities in PCF. The cost of transportation were obtained from the annual program budget for PCF and research budget for ACF and scaled to 18 months then divided by the total number of

people screened in each program to obtain a per person cost. The cost of HCI was estimated as two thirds of the ACF program since HCI would involve slightly less travel given that more people would be evaluated within a household.

Training costs: Training costs arose from time spent on extra training of HCWs to enable them to perform the various activities in ACF and HCI. For example, during the primary ACF study, ten HCWs were trained for a total period of one month spread over the 18-month study period. We assume that similar training would be necessary for HCI. No additional training would be needed for PCF since the existing program personnel have the necessary skills to perform the routine case finding activities at the clinics. The total training costs were obtained from research project expense records and were divided by the number of persons screened to obtain the per person training cost.

Community mobilization and lay health volunteer costs: In order to perform ACF successfully, we conducted health education campaigns involving community members and their local leaders prior to the door-to-door surveys. Costs were incurred in transportation refunds for the leaders, provision of refreshments at meetings and hiring public address systems. Two lay volunteers were identified for each village to travel with the study team each day to ensure that all eligible homes were visited. There were 18 villages therefore 36 volunteers were involved in the study; each volunteer received a reimbursement fee for his/her time at a flat rate of US$2.00/ day. Costs were obtained from the project budget and verified by multiplying the daily pay rate, number of volunteers and number of days that each worked. This cost was only incurred in ACF.

Communication costs: During the ACF and HCI projects, phone communication among study teams, the laboratory, study participants, and the community volunteers were vital for the smooth running of the field activities. The total communication cost for ACF is obtained from the records as expenditure on phone services as an average of US$120.00 per month over the 18 months period. Due to lack of specific records for PCF and HCI, the cost was estimated as fraction of ACF costs: 50% for HCI and 30%

for PCF. The justification is that these programs would have a lower scale of activities requiring phone communication.

Medical Costs

Medical costs included in the analysis are costs of smear test, culture test, sputum cups, gloves, and chest x-rays as of 2008. Costs are market-based and are the same regardless of the case finding strategy. The costs were $3.00 for two smear tests, $15.00 for culture test and $8.00 for chest x-rays per person during the study period in 2008 and 2009. These costs were adjusted to 2013 US dollars.

Patient and Caregiver Costs

Patient and caregiver direct costs: We estimated total direct patient and caregiver costs including out-of pocket costs from transportation and meals while attending TB clinic visits for diagnostic evaluation using a patient survey. Patients detected through the PCF strategy incurred an average total cost of $17.26 because of the need to travel at least two times to the clinic before a diagnosis is confirmed. Direct caregiver costs would be similar to patient costs except that they are calculated based on the proportion of patients who reported to have used care givers. On average ACF and HCI patients would spend $4.29; this applies only to those who would need to travel to the clinic for a chest x-ray.

Patient and care giver indirect costs: Patient indirect costs are estimated based on patient time spent in travel, waiting time, the diagnostic evaluation process at the clinic visit and lost days of work. In ACF and HCI, very minimal or no indirect costs are incurred since people are evaluated in their homes. Based on survey results, patients and caregivers in PCF lost a total of 73.5 hours on average during the diagnostic evaluation process. The time lost was multiplied by Uganda's minimum hourly wage of $0.15 per hour (Uganda, Bureau of Statistics 2011) to obtain the indirect cost. We valued patients' and caregivers' time using the minimum wage in Uganda as a proxy for the value of time for a person who is a non-wage earner (Gold, 1996).

Effectiveness Measure

The main effectiveness measure is the number of true TB cases detected. This intermediate outcome is of interest to the TB program health providers involved in case detection. A numeric counter (payoff) of 1 was assigned for a true TB cases detected in each strategy. A payoff of zero was assigned for a true negative, false positive or false negative case. For the PCF+HCI strategy, a payoff of 2 was assigned for any true positive case to reflect an additional case detected through HCI efforts; a payoff of 1 is assigned if an additional case is detected from HCI following a false positive case in PCF.

Incremental Cost-effectiveness Analysis

We conducted an incremental cost-effectiveness analysis of PCF+ACF and PCF+HCI strategies compared to PCF alone in terms of cost in 2003 US dollars per additional case detected. Incremental cost costs and incremental effectiveness were calculated based on the expected values of true TB cases and the expected costs for each strategy obtained from the decision model. The incremental cost effectiveness ratios (ICERs) are obtained by dividing the incremental cost by the incremental effectiveness. We compared ICERs to thresholds of cost-effectiveness defined in reference to the country's annual gross domestic product (GDP) per capita following standard benchmarks proposed in international work on cost-effectiveness (Hutubessy, Chisholm, & Edejer, 2003; Shillcutt, Walker, Goodman, & Mills, 2009). When ICERs fall within the range of one to three times the annual GDP per capita, the interventions are considered cost-effective. This range is generally assumed to encompass the decision makers' willingness- to- pay for an additional unit of effectiveness (Shillcutt et al., 2009). Much debate still surrounds the use of GDP as an acceptable threshold for the valuation of a unit of health gains. Standard thresholds are often set based on a QALY saved as the generic outcome; however in situations where the outcome of interest is not a QALY, it's plausible to use a slightly lower cut-off such as one-two times GDP. To-date there is no strict decision making criterion but the benchmarks are used as a guide.

According to the World Bank, Uganda's estimated GDP per capita was US$ 405.40 in 2012 (World Bank, 2013).

Data Sources

For this study, the effectiveness data are obtained from three main sources: a primary study for ACF, program data for PCF and published studies for HCI (Lodi et al., 2012; Morrison et al., 2008; A. E. Shapiro et al., 2012). Expert opinions were elicited in case data were unavailable from the main sources.

Description of Data Collection in Primary Studies

Primary data were collected during a community active case finding survey and a patient cost survey conducted in Kampala, Uganda. A cross-sectional survey was conducted in 2008-2009 to detect active TB cases in urban communities in persons aged 15 years and older. Trained research nurses and social workers visited homes, administered questionnaires, identified persons with chronic cough, collected sputum specimens for laboratory examinations, returned results and referred patients for appropriate care. On average, three visits were made to the patient homes by the study teams.

Over the 18-month study period 5,102 participants were enrolled from nearly 4,400 households. The prevalence of chronic cough was 3.9%. Among chronic coughers who were tested for TB, 39 (24.4%) had TB disease detected through ACF. Patients were referred to the public health clinics for treatment. Detailed results of the study are published elsewhere [Sekandi, et al, IJTLD, 2013 in press]. The results of this primary study were used to generate path probabilities and effectiveness data for the ACF strategy in the model.

Description of TB Patient Cost Survey

This patient cost survey is an addition to the literature on costs associated with the case detection phase for a PCF patient as there is no published primary study for urban Ugandan TB patients. Adult patients 15 years and older, with a confirmed TB diagnosis and already receiving treatment were selected to participate in the cost survey. The survey was conducted in two TB clinics in Kampala; a referral

hospital clinic where most of the national TB program data were obtained and another public health center IV (designated clinic for comprehensive TB patient management). The selection was based on the logic that a high patient load is served at these urban clinics. Patients who had at least completed two weeks of TB treatment were recruited from November to December 2012.

A structured questionnaire was used to collect detailed information regarding all costs incurred by the TB patients and their care givers for each diagnosis related visit during the period when the patient was being evaluated for TB up to the time of initiating treatment (see questionnaire in Appendix D). Information about direct and indirect costs was gathered. Direct costs were defined as out-of-pocket expenditures, including transportation fees, food and drinks for the patients and their caregivers. Indirect included travel time, waiting time and absence from work by the patient or caregivers. Caregivers time was estimated from time spent when a family member/friend escorted the patient to the outpatient clinic visits. A summary of the cost survey results are provided (see Appendix E).

TB Program Data

The national TB program collects routine data on number of people screened, TB tests performed and number of active TB cases diagnosed. These were used to calculate most path probabilities for PCF. We extracted necessary information from clinic registries and laboratory database for the period of January 2008 to June 2009. There was some missing information on patient demographics and classification of TB disease category. In order to fill gaps, other available source documents such as laboratory registers, pharmacy registers and duplicate copies of patient treatment cards were used. Overall the aggregate data quality was good; we obtained most of the information needed for this analysis. Some details of the information on chest x-rays taken for the patients who did not produce sputum was missing so we relied heavily on expert opinion.

Published Literature

We utilize published medical literature to obtain parameter values that were not available from the primary data and the national TB program database. Most of the parameter estimates for HCI studies were obtained from published studies performed in Uganda (Guwatudde, Nakakeeto, et al., 2003; Whalen et al., 2011) and elsewhere in Africa (A. E. Shapiro et al., 2012). Ranges of values used in sensitivity analyses were also obtained from published literature. Estimates from higher order studies such as randomized trials, meta-analyses and prospective observational studies were preferred and, priority given to those conducted in Uganda or in African settings when available.

Expert Opinion

In situations when data were insufficient from the primary sources and/or good quality published literature studies were not available, expert opinions were elicited. This approach to estimating probability values and other study parameters is well established (Gold, 1996). A team of 5 clinical experts were used to estimate the probability of a positive chest x-ray when a person has chronic cough but fails to produce sputum in PCF, the probability of detecting a case from a false positive smear index, true positive chest X-ray index and false positive chest X-ray index. The level of uncertainty around these values is therefore likely to be very high. More details of the process of generating estimates by the expert panel and the experts' credentials are provided (see appendix G).

Decision Model

In structuring the decision model we considered the detection phase of TB disease which involves presentation and diagnosis. The decision tree begins with a choice of three strategies for TB case detection: PCF alone, PCF+ACF and, PCF+ HCI. In PCF, we assume that 57% of potential suspects are accessing the public health system based on the estimated case detection of Uganda. The HCW screens the patients for chronic cough and identifies 97.5% of them with cough >=2weeks (Fig 4.1). Of those,

88.9% are able to produce sputum and hence have a TB test, about 60% will have TB disease but based on the sensitivity of the test 77.6% will test true positive and others will test false negative.

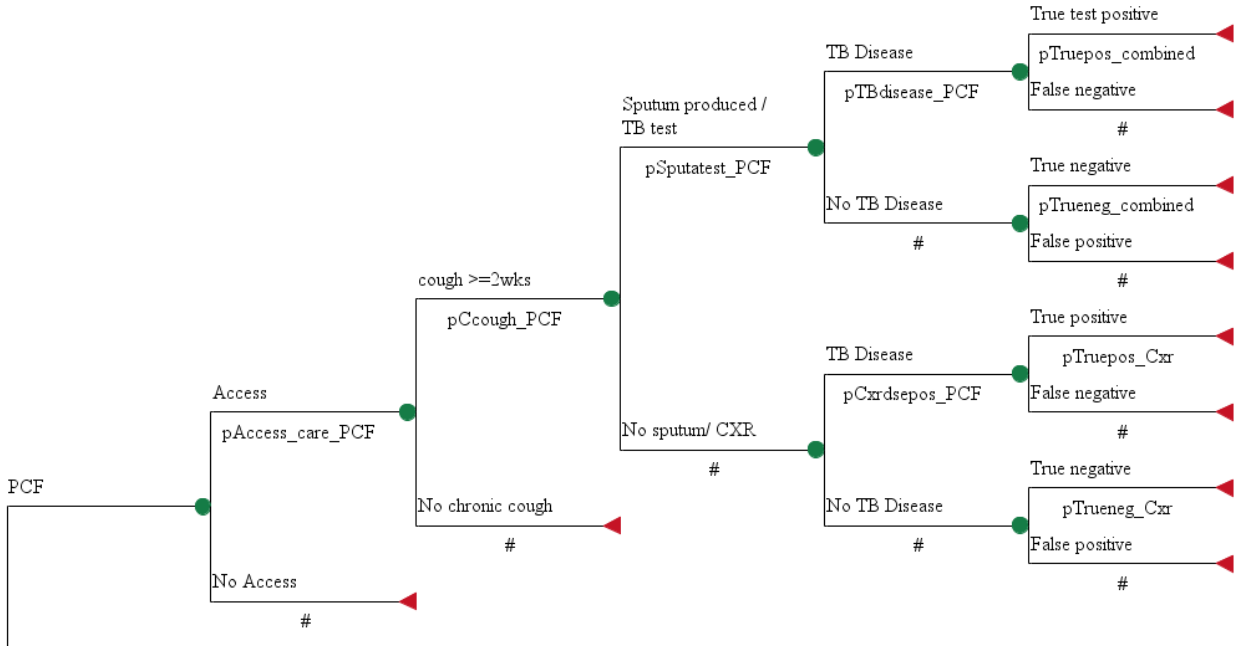


Figure 4.1. Partial Decision Tree for Passive Case Finding

In PCF+HCI, a person enter the pathway with a probability of accessing care in the same was as in PCF alone (Figure 4.2). Once a true or false positive case is detected in PCF then a decision is made to follow the index case and conduct HCI. For simplicity, the set of events in HCI is summarized into a dichotomy of detecting one or more cases, or not detecting a case. The probability that one TB case or more TB are detected in HCI is 19% when a sputum smear true positive index is followed (Table 4 1). We assume that the probability of one or more cases detected from a false smear positive index is 2%. From chest x-ray true positive index, we assume the probability of detecting a case is 10% and 1% if the chest x-ray index is false positive. The implicit assumption is that each case detected through HCI will be a true TB case.

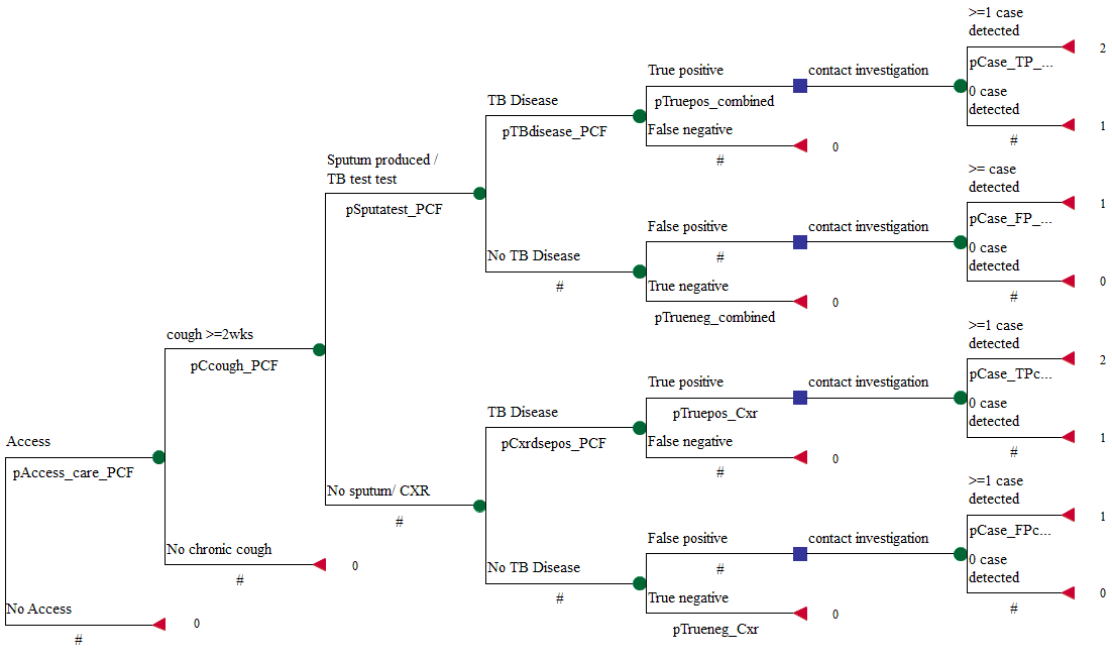


Figure 4.2. Decision Tree for Passive Case Finding and Household Contact Investigations

In PCF+ACF there are two unique pathways through which a TB suspect can be screened, the PCF path is the same as described above and the ACF path. We assume that the 43% who do not access PCF are subjected to ACF. The health care workers in ACF have a chance of accessing 69% of the population for screening (Figure 4.3). However, there is a chance that some people will still not be accessed by the HCWs during ACF. Once accessed by a health care worker, a person is screened for chronic cough, 3.9% of community members would have chronic cough, of those 80.4% are able to produce sputum for bacteriologic testing. The probability of TB disease is 24.4% have TB disease but based on the test sensitivity of 77.6%, some will be true positive and others false negative. Those who are unable to produce sputum receive a chest x-ray evaluation, we assume that 19.6% will have disease but 92% will be true positive and the rest false negative (Table 4.1).

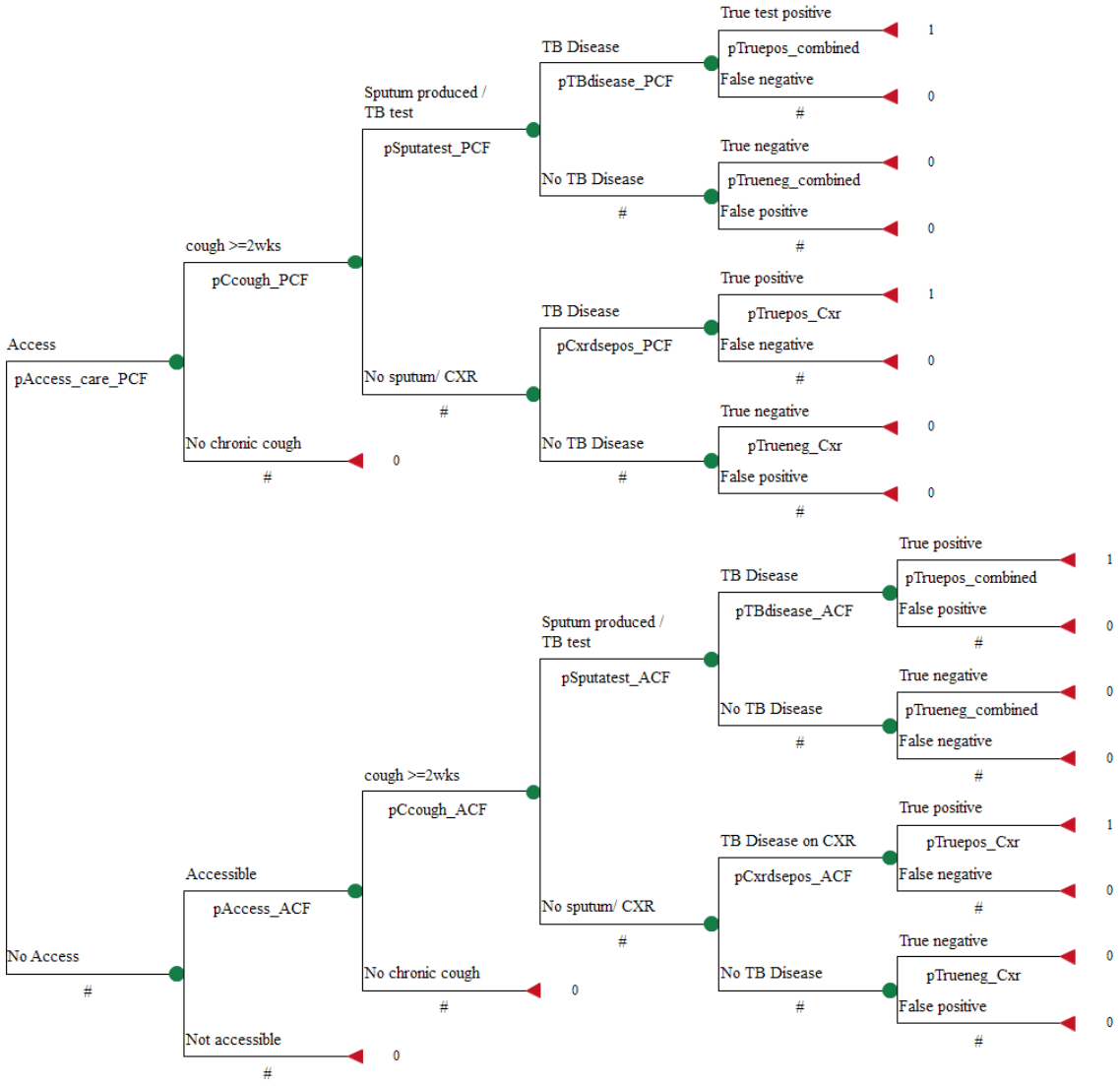


Figure 4.3. Decision Tree for Passive Case Finding and Active Case Finding

Even though the best estimates available in the published literature were used, we anticipate a high potential for uncertainty in the sensitivity and specificity of chest x-rays in persons who are unable to produce sputum because there were no published studies and the number of TB cases that can be detected from a true positive chest x-ray index case or a false smear positive case. The combined sensitivity of smear and culture test of sputum was also obtained from a relatively old study with no clear information

on how it was calculated (Levy et al., 1989). The analysis was performed using TreeAge Pro 2012 software.

Model Assumptions

In this model we assume that all persons who present to the clinic without chronic cough do not have TB disease. They receive initial screening by interview but no diagnostic evaluation is done. This is assumption can hold true based on our knowledge that chronic cough is by far the commonest symptom among TB patients presenting at health facilities. According previous studies, nearly 100% of TB patients attending the Kampala referral clinic have reported chronic cough (Guwatudde, Zalwango, et al., 2003; Nakiyingi et al., 2012). However, we know that a very small proportion of people with exclusively extra-pulmonary TB may not have chronic cough, in this case they would be excluded since they are least likely to be infectious (Nakiyingi et al., 2012).

We also assume that any patient with a TB test negative will have no TB disease; this assumption is based on the fact that we consider a combination of smear and culture tests therefore there is a very low likelihood of cases being missed. False negative cases do not have a chance of being detected by the system as TB cases and no cost penalty is imposed for false negative cases. Our model assumes an ideal situation where 100% of all the index TB cases are followed with contact investigations. This kind of situation can be achieved with a very well organized health system that follows patients in a timely manner.

Table 4.1: Probabilities Estimates Used in Decision Analytic Model

Model parameter	Description of parameter	Baseline value	Source of base value	Range for sensitivity analysis	References
	Passive Case Finding				
pAccess_care_PCF	Probability of accessing care in PCF	0.57	(World Health Organization, 2012)	0.25-1.00	, Estimated
pCcough_PCF	Probability of chronic cough given access	0.975	Uganda TB program records 2008-09	0.78 - 1.00	(A. E. Shapiro et al., 2012) (Guwatudde, Nakakeeto, et al., 2003)
pSputatest_PCF	Probability of sputum production & TB test given chronic cough	0.899	Uganda TB program records 2008-09	0.75-0.95	Kiwuwa, 2005, Estimated upper value
pTBdisease_PCF	Probability of TB disease given chronic cough with sputum production	0.60	Uganda TB program records 2008-09	0.20-0.75	(Dasgupta & Menzies, 2005), (Nakiyingi et al., 2012) (Eang et al., 2012)
pCxrdsepos_PCF	Probability of TB disease detected by positive CXR given chronic cough without sputum production	0.40	Expert opinion	0.30-0.70	(van Cleeff et al., 2005)
	Active Case Finding				
pAccess_ACF	Probability of being accessed by HCW	0.69	Primary study, 2008-2009	0.25-100	(J. N. Sekandi, List, J.,Luzze,H., Yin, X., Dobbin,K., S. Corso, P.S, Oloya, J., Okwera,A., Whalen, C.C,, 2013), Estimated
pCcough_ACF	Probability of chronic cough given being accessed	0.039	Primary study, 2008-2009	0.02-0.40	(Ayles et al., 2009; J. N. Sekandi et al., 2009; van't Hoog et al., 2011)
pSputatest_ACF	Probability sputum production & TB test given chronic cough	0.804	Primary study, 2008-2009	0.65-0.90	(Tadesse et al., 2011); (J. N. Sekandi et al., 2009)
pTBdisease_ACF	Probability of TB disease given chronic cough with sputum production	0.244	Primary study, 2008-2009	0.028-0.30	(Corbett et al., 2010; J. N. Sekandi et al., 2009)
pCxrdsepos_ACF	Probability of TB disease detected by positive chest x-ray given chronic cough without sputum production	0.196	Primary study, 2008-2009	0.10- 0.30	Expert opinion

	Household Contact Investigations				
pCase_TP_HCI	Probability of TB case detected from true positive smear index case	0.19	(A. E. Shapiro et al., 2012)	0.06-0.24	(Guwatudde, Nakakeeto, et al., 2003; Morrison et al., 2008)s)
pCase_FP_HCI	Probability of TB case detected from false positive smear index case	0.02	Expert opinion	0 -1.0	Decision to examine full range of values
pCase_TPcxr_HCI	Probability of TB case detected from true positive CXR index case	0.10	(Dasgupta et al., 2000)	0-1.0	Decision to examine full range of values
pCase_FPcxr_HCI	Probability of TB case detected from false positive CXR index case	0.01	Expert opinion	0-1.0	Decision to examine full range of values
	Sensitivity and Specificity of Tests				
pTruepos_TBtest	Sensitivity of smear test	0.609	Primary study, 2008-2009	0.30- 0.80	(Aber, 1980, Levy, 1989, Dasgupta, 2005)
pTrueneg_TBtest	Specificity of smear test	0.883	Primary CF study, 2008-2009	0.80-0.97	(Aber, 1980, Levy, 1989)
pTruepos_combined	Combined sensitivity of Smear and culture	0.776	(Levy et al., 1989)	0.61-1.0	(Primary study 2008-2009, Estimated upper value)
pTrueneg_combined	Combined specificity of Smear and culture	1.00	(Levy et al., 1989)	0.883-1.00	Primary study 2008-2009 (Levy et al., 1989),
pTruepos_Cxr	Sensitivity of CXR	0.920	(van Cleeff et al., 2005)	0.70- 0.95	lower value estimated, (Tattevin et al., 1999)
pTrueneg_Cxr	Specificity of CXR	0.630	(van Cleeff et al., 2005)	0.52-0.99	(Cohen, Muzaffar, Capellan, Azar, & Chinikamwala, 1996; Tattevin et al., 1999)

Table 4.2: Summary of Cost (in 2013US$) Estimates Associated with TB Detection

Cost category	Cost, $	Range (+/-50%)	Source of data
Program costs[a]			
PCF	7.71	3.86-11.57	Uganda TB program records 2008-09
ACF	26.88	13.44-40.32	
HCI	26.31	13.16-39.47	Primary study research budgets
PCF+ACF	34.59	17.30-51.89	Primary study research budgets
PCF+HCI	34.02	17.01-51.03	TB program records & study
			TB program records & study
Direct Medical [b]			
PCF	47.14	23.57-70.71	Uganda TB program records 2008-09
ACF	47.38	23.69-71.07	
HCI	46.37	23.19-69.56	Primary study research budgets
PCF+ACF	93.52	47.26-141.78	Primary study research budgets
PCF+HCI	92.51	46.76-140.27	TB program records & study
			TB program records & study
Total Patient &Caregiver Costs [c]			
PCF	28.88	14.44-43.32	TB patient cost survey
ACF	4.76	2.38-7.14	Primary study
HCI	4.76	2.38-7.14	Estimated from primary study
PCF+ACF	33.64	16.82-50.46	TB patient cost survey
PCF+HCI	33.64	16.82-50.46	TB patient cost survey
Total per Patient Costs[d]			
PCF	83.73	41.87-125.60	
ACF	79.02	39.51-118.53	
HCI	77.44	38.72-116.16	

a. Program costs include administration, transport, communication & health personnel
b. Direct medical costs include Smear tests, culture tests, CXR & consumable supplies
c. Total patient and care giver costs include direct (transportation& meals) and, Indirect costs (productivity/wages lost)
d. Estimated total per patient costs are a summation of program, direct medical and total patient-caregiver costs estimated

The costs estimates for each strategy were obtained through both macro-and micro-costing approaches. The program costs for ACF and HCI are much higher than the costs for PCF; however, the total patient costs are highest for PCF and low in both ACF and HCI strategies. The medical costs contribute the most

to overall cost in three strategies and are very similar because the same diagnostic tests are used across strategies. Detailed ingredient costing for each category and strategy is provided in Appendix F.

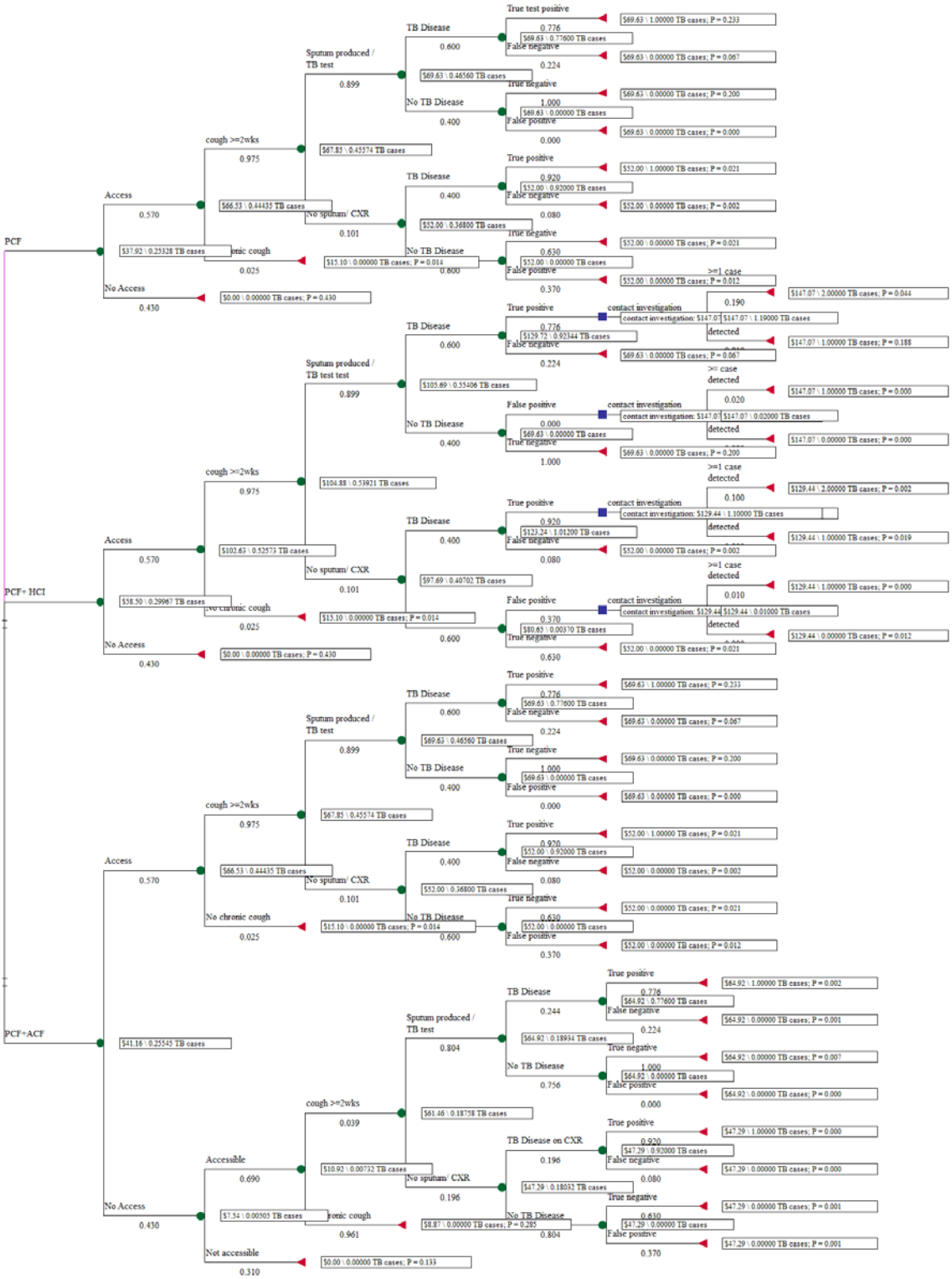
Results

Base Analysis

In this section, results of the base analysis are drawn from the decision model analysis representing calculations of expected values for each course of actions along a given event pathway for screening people in the alternative strategies (Figure 4.4). These values are obtained by from right to left multiplying each of the quantities at the terminal node by all probabilities preceding and summing up the products for each set of events a common chance node in a process of folding back the tree. For instance in PCF, after multiplying all the probabilities and pay offs and summing up the products for a person who follows the event path of access or no access to care the expected value for TB cases detected is 0.253 and the expected cost is $37.92. The strategy that generates the highest expected value of cases detected is considered the optimal strategy.

When comparing the additional benefit of HCI or ACF by itself, we can subtract the effectiveness of PCF alone from the combined strategies. The marginal effectiveness of HCI is an additional forty seven new cases detected while ACF is expected to detect two additional cases. This shows that HCI is more valuable for detecting new cases. Two analytic approaches are used 1) a comparison with PCF alone as a common reference since it is the standard of care 2) a comparison of strategies to the next more effective alternative.

Fig 4.4. Decision Model Showing Expected Values and Optimal Case Finding Strategy


PCF
PCF+ HCI
PCF+ACF
Access
No Access
Accessible
Not accessible
cough >=2wks
No chronic cough
No sputum/ CXR
Sputum produced / TB test
TB Disease
No TB Disease
TB Disease on CXR
True positive
False negative
True negative
False positive
contact investigation
detected
>=1 case
>= case

Cost-effectiveness Analysis from the Societal Perspective

The expected number of true TB case per 1000 persons screened in PCF alone is 253 at a total average cost of $37,920, in PCF+ACF is 255 at $41,160 and in PCF+HCI is 300 at $58,500 (Figure 4.4).The baseline average and incremental cost-effectiveness analysis of the three alternative case detection strategies comparing PCF alone with PCF+ACF and PCF+ HCI are calculated from the expected costs and expected effects (Table 4.3). These results inform decision makers whether to add either ACF or HCI to the existing standard PCF.

Average Cost per True TB Case Detected

The average cost effectiveness ratios (ACERs) show the cost per case detected in each of the strategies compared to doing nothing at zero cost. The average cost of detecting a true TB case in PCF alone is US$ 149.73, in PCF+ACF the cost is US$ 161.41 and is US$ 195.00 in PCF+HCI (Table 4.3).

Table 4.3: Incremental Cost-effectiveness Analysis from the Societal Perspective Referencing PCF as a Common Baseline

Strategy	Total cost (US$)[a]	Incremental cost	Total effects [a]	Incremental effects	Total cost/total effect (ACER)	ICER [b] (cost per additional case detected)
PCF	37920	-	253	-	149.73	-
PCF+ACF	41160	3240	255	2	161.41	**1492.95***
PCF+HCI	58500	20580	300	47	195.00	**443.62***

a. Effects are rounded to the nearest whole number per 1000 person screened in the target population
b. ICER- incremental cost-effectiveness ratio/*calculation are based on 5 significant digits for effects to increase precision and minimize rounding errors

Incremental Cost-effectiveness of Strategies

The incremental cost-effectiveness analysis shows the expected benefit and the cost for a unit of additional effectiveness from ACF and HCI as an add-on strategy to PCF. The incremental benefit of adding ACF is 2 cases of TB and costs US$1492.95 per case detected. The incremental benefit of HCI is

47 cases and costs of US$443.62 per case detected (Table 4.3). These results inform decision makers of whether to perform PCF alone or to add either ACF or HCI the alternative strategies. In reference to the set decision threshold of one to three times Uganda's GDP per capita ($405.40 to $1216.20), the ICER for PCF+HCI falls within the set range of values therefore it is a cost-effective strategy.

Incremental Cost-effectiveness Analysis Comparing PCF+ACF and PCF+HCI Strategies

Compared to PCF+ACF, 45 extra TB cases would be detected by choosing to use the HCI strategy over ACF as the add-on to PCF; this would cost $392.11 per additional case detected. (Table 4.4) The results show that the PCF+HCI strategy is cost-effective because the ICER value lies within the range of the decision threshold. This analysis informs decision makers who want to choose from the two competing alternatives, without consideration of PCF alone as an option.

Table 4.4: Incremental Cost-effectiveness Analysis from the Societal Perspective Comparing PCF+ACF and PCF+HCI

Strategy	Total cost (US$)[a]	Incremental cost	Total effects [a]	Incremental effects	Total cost/total effect (ACER)	ICER [b] (cost per additional case detected)
PCF+ACF	41160	-	255	-	161.41	-
PCF+HCI	58500	17340	300	45	195.00	**392.11***

a. Effects are rounded to the nearest whole number per 1000 person screened in the target population
b. ICER- incremental cost-effectiveness ratio/*calculation are based on 5 significant digits to increase precision and minimize rounding errors

Cost-effectiveness Analysis from the Provider Perspective

In this analysis, only costs borne by the provider were included when evaluating the expected total cost of detecting true TB cases. The expected number of true TB case per 1000 persons screened in each strategy is similar to those from the societal perspective (Figure 4.5). The results in figure 4 show that the PCF+ACF strategy would potentially be eliminated by extended dominance, meaning that a linear combination of PCF and PCF+HCI would outperform it. But, we ignore this aspect and include it in the

analysis because in reality, the linear combination is not a potential option. For PCF alone the total average cost of detecting 253 cases is US$21,690, in PCF+ACF for 255 cases is US$24,880 and in PCF+HCI for 300 cases is US$41010.The baseline average and incremental cost-effectiveness analyses of the three alternative case detection strategies comparing PCF alone with PCF+ACF or PCF+ HCI were calculated from the expected costs and expected effects (Table 4.4). These results inform a decision maker of whether to add either ACF or HCI to the existing standard PCF.

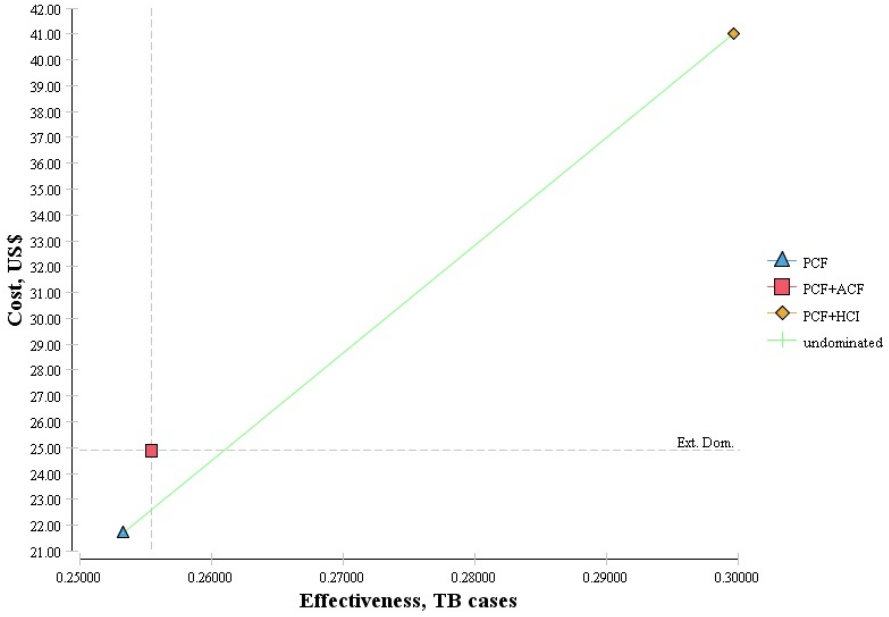


Figure 4.5. Cost Effectiveness Analysis-Health Provider Perspective

Average Cost per True TB Case Detected

The average cost of detecting a true TB case in PCF alone is US$ 85.73, in PCF+ACF the cost is US$ 97.37 and is US$ 136.70 in PCF+HCI (Table 4.5).

Table 4.5: Incremental Cost-effectiveness Analysis from the Provider Perspective Referencing PCF as a Common Baseline

Strategy	Total cost (US$)[a]	Incremental cost	Total effect [a]	Incremental effect [a]	Total cost/total effect (ACER)	ICER [c] (cost per additional case detected)
PCF	21690	-	253	-	85.73	-
PCF+ACF	24880	3190	255	2	97.37	**1467.57***
PCF+HCI	41010	19320	300	47	136.70	**416.35***

a. Effects are rounded to the nearest whole number per 1000 person screened in the target population

b. ICER- incremental cost-effectiveness ratio/*calculation are based on 5 significant digits to increase precision and minimize rounding errors

Incremental Cost-effectiveness of Strategies

From the provider perspective, the expected costs to detected true TB cases are lower than the costs estimated from the societal perspective. The incremental benefit of adding ACF to PCF is 2 more cases and it costs US$1467.57 per additional case detected. When HCI is added to PCF the expected benefit is 47 TB cases detected at a cost of US$416.35 per additional case. These results inform a decision maker of whether to perform PCF alone or to add one of the alternative strategies. In reference to the set decision threshold of $405.40 to $1216.20 (1-3 times Uganda's GDP per capita), the ICER for PCF+HCI falls within range of these values therefore it is a cost-effective strategy.

Model Validation

We validated our decision model using the Number-Needed-to-Screen (NNS) and Number-Needed-to-Test (NNT) obtained from the primary ACF study and directly calculated the cost per TB case detected. The NNS was 131 people and the NNT was 5 to detected one TB case (Table 4.6). From our data, only 4% of the people screened had chronic cough and therefore needed a TB test, this results in 5 chronic coughers screened and tested while 126 people did not

have chronic cough and therefore were only screened not tested. The full program costs were incurred by the 5 chronic coughers and specifically the TB test cost were incurred by 4 of them who produced sputum. Using this direct calculation, we obtain $1371.93 as the cost per TB case detected in ACF. Similarly, from the decision model, we found that the cost per case detected was $1381.84. These two costs being nearly the same provides support for validity of our model.

Table 4.6. Model Validation Using ACF Primary Data

Strategy	NNS	Cost per person screened	Cost/TB case	NNT	Cost per case tested	Cost/TB case	Average total cost/case detected
ACF	131						
Apply 4 %	126	8.87	1117.67	-	-		
chronic cough	5	26.88	134.40				1252.07
Apply 80%	4 sputum	-		4	26.44	105.76	
sputum exam	1 no sputum			1	14.10	14.10	119.86
Total			1252.07			119.86	1371.93

NNS- Number-Needed-to-Screen, NNT- Number-Needed-to-Test

Sensitivity Analysis

We performed one-way and two-way sensitivity analyses to explore the impact of uncertainty in the probability and cost estimates on the base analysis. In one-way sensitivity analyses each model probabilities and costs were varied one at a time over a range of predefined plausible values (Table 4.7& 4.8). We varied probabilities over extreme ranges of zero to one for cases detected from a true positive smear index or positive chest X-ray index in PCF+HCI due to greater uncertainty in the base values.

Costs were varied over a 50% reduction and increase in the base values for the lower and upper range respectively as one of the recommended approaches (Gold, 1996).

In the one-way sensitivity analysis, the model was most sensitive to changes in probability of one or more cases detected from HCI following a true smear positive index and chronic cough in ACF because the model conclusions were altered. When the probability of one or more cases detected from HCI was varied to its lowest plausible value of 0.06, the ICER increased to $1274.43, changing the conclusion of the analysis that PCF+HCI is no longer a cost-effective strategy based on the set decision threshold (Table 4.7). When the probability of chronic cough in ACF was varied from 0.02 to 0.40, the ICERs widely varied from $2644.88 to $398.61 per additional case detected (Table 4.7). The reduction in ICER to $398.61 makes PCF+ACF a cost-effective because it even falls below the defined threshold range of $405.40 to $1216.20 per additional case detected. The model was also sensitive to changes in the program cost of ACF. When costs were varied, a 50% reduction in the base program costs for ACF resulted in a large reduction in the ICER to $838.66 per additional case detected such that PCF+ACF became a cost effective strategy (Table 4.8). The rest of the model parameters did not have a meaningful impact on the conclusion of the analysis.

Table 4.7 One-way Sensitivity Analysis for Cost-effectiveness of TB Case Finding Strategies Varying Probabilities

Strategies Compared	Incremental Cost Effectiveness Ratios (US$/ TB case detected)			
	PCF + ACF vs. PCF		PCF +HCI vs. PCF	
Base ICER[a]	1492.95		443.62	
Probability parameters Base (Ranges: low, high)[b]	For low value	For high value	For low value	For high value
Access to persons by HCW in ACF 0.69 (0.25,1.0)	1492.95	1492.95	443.62	443.62
Access to health service in PCF 0.57 (0.25, 1.0)	1492.95	0.00	443.62	443.62
Chronic cough in ACF 0.039 (0.02, 0.40)	2644.88	**398.61**[c]	443.62	443.62
Chronic cough in PCF 0.975 (0.78,1.0)	1492.95	1492.95	443.62	443.62
Produce sputum in ACF 0.804 (0.65, 0.86)	1488.51	1495.07	443.62	443.62
Produce sputum in PCF 0.899 (0.75,0.95)	1492.95	1492.95	505.43	424.90
TB Disease given sputum test in ACF 0.244 (0.028,0.30)	**5302.58**[d]	1258.53	443.62	443.62
TB Disease given sputum test in PCF 0.60 (0.20,0.75)	1492.95	1492.95	506.37	436.69
Combined TB test sensitivity 0.776 (0.61,1.0)	1808.59	1209.58	452.85	432.85
CXR positive in ACF 0.40 (0.10,0.30)	1644.74	1357.25	443.62	443.62
CXR positive in PCF 0.40 (0.30, 0.70)	1492.95	1492.95	443.20	444.82
CXR sensitivity 0.92 (0.70,0.95)	1563.39	1483.83	440.06	444.10
Case detected from true positive smear index in HCI 0.19 (0.06,1.0)	1492.95	1492.95	**1274.43**[e]	87.67

[a] ICER= Incremental Cost- Effectiveness Ratio
[b] Ranges obtained from published literature, expert opinion, or full ranges used
[c] PCF+ACF becomes a cost-effective strategy at ICER $398.61
[d] Large change, > 3 times increase from base ICER
[e] PCF+HCI is no longer cost effective at ICER 1274.43

Table 4.8 One-way Sensitivity Analysis for Cost-effectiveness of TB Case Finding Strategies Varying Costs

Strategies Compared	Incremental Cost Effectiveness Ratios (US$/ TB case detected)			
	PCF + ACF vs. PCF		PCF +HCI vs. PCF	
Base ICER[a]	1492.95		433.62	
Cost parameters	For low value	For high value	For low value	For high value
Base (Ranges low, high)[b]				
Program costs in PCF	1492.95	1492.95	443.62	443.62
7.71 (3.86,11.57)				
Program costs in ACF	**838.66**[c]	**2147.23**	443.62	443.62
26.88 (13.44,40.32)				
Program costs in HCI	1492.95	1492.95	368.29	519.01
26.31 (13.16,39.47)				
Medical cost in PCF	1492.95	1492.95	443.62	443.62
46.14 (23.57,70.71)				
Medical cost in ACF	**1366.66**[d]	**1619.24**	443.62	443.62
47.38 (23.69, 71.07)				
Medical cost in HCI	1492.95	1492.95	310.83	576.47
46.37 (23.19,69.56)				
Total patient costs in PCF	1492.95	1492.95	443.62	443.62
28.88(14.44,43.32)				
Total patient costs in ACF	1480.26	1505.64	443.62	443.62
4.76 (2.38,7.14)				
Total patient costs in HCI	1492.95	1492.95	429.99	457.25
4.76 (2.38,7.14)				
Cost of TB test	1523.17	1462.73	443.62	443.62
31.72 (15.86,47.58)				
Cost of CXR	1509.53	1476.39	443.62	443.62
14.10 (7.05,21.15)				

[a] ICER= Incremental cost- effectiveness ratio
[b] Range estimated as +/-50% of base values in the model
[c] PCF+ACF becomes cost-effective at ICER 838.66
[d] More than $200 change in ICER when medical costs in ACF vary

Two-way Sensitivity Analysis

In a two-way sensitivity analysis, we examined the joint effect of uncertainty on the cost-effectiveness of the strategies when two variables are varied simultaneously while all other parameters constant. We selected, the probability of chronic cough in ACF and the probability of TB disease given that a person produced sputum for a TB test in ACF because of their strong influence on the model results as shown in the one-way sensitivity analysis (Table 4.7). Any intersection of values on the x-axis and y-axis will fall into one of the two zones, blue or yellow (Figure 4.6). For example, the base probabilities of chronic cough in ACF and of TB disease in ACF (0.039 and 0.244); intersect in the blue zone, so PCF alone is the dominant strategy. But if these values simultaneously varied to at least 24% and 30% respectively these points intersect in the yellow zone, and PCF+ACF becomes cost-effective.

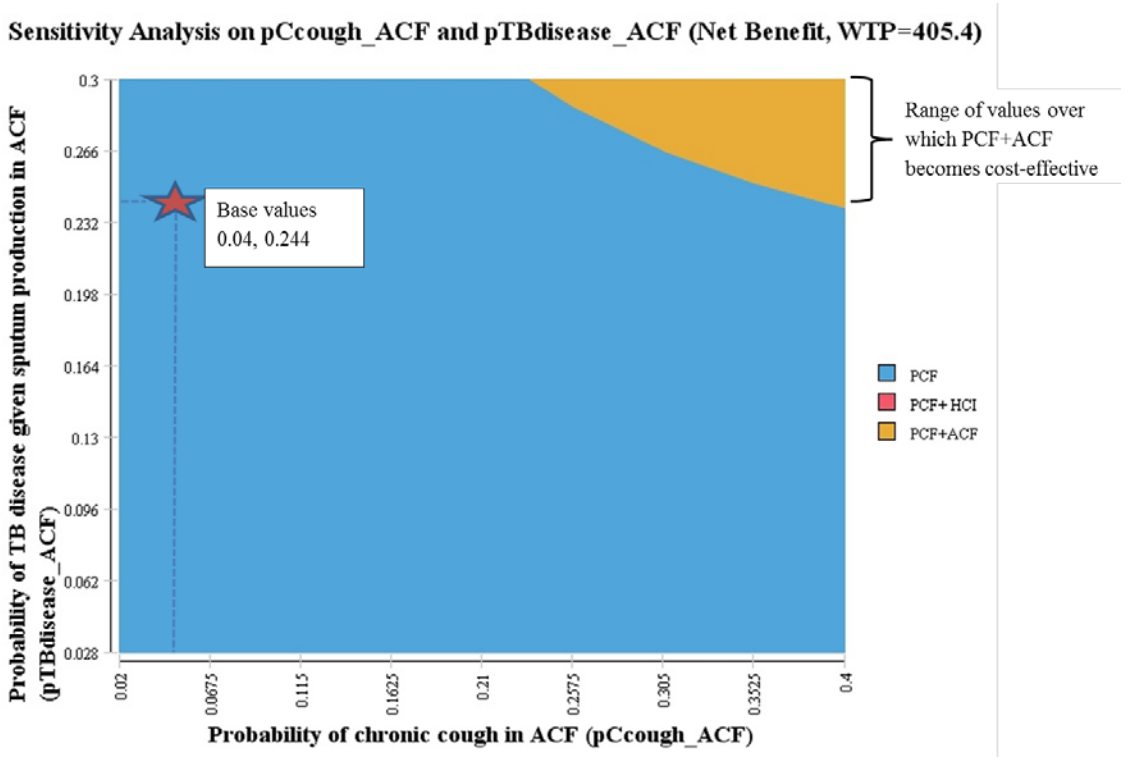


Figure 4.6. Two-way Sensitivity Analysis of Probability of Chronic Cough and TB disease in ACF

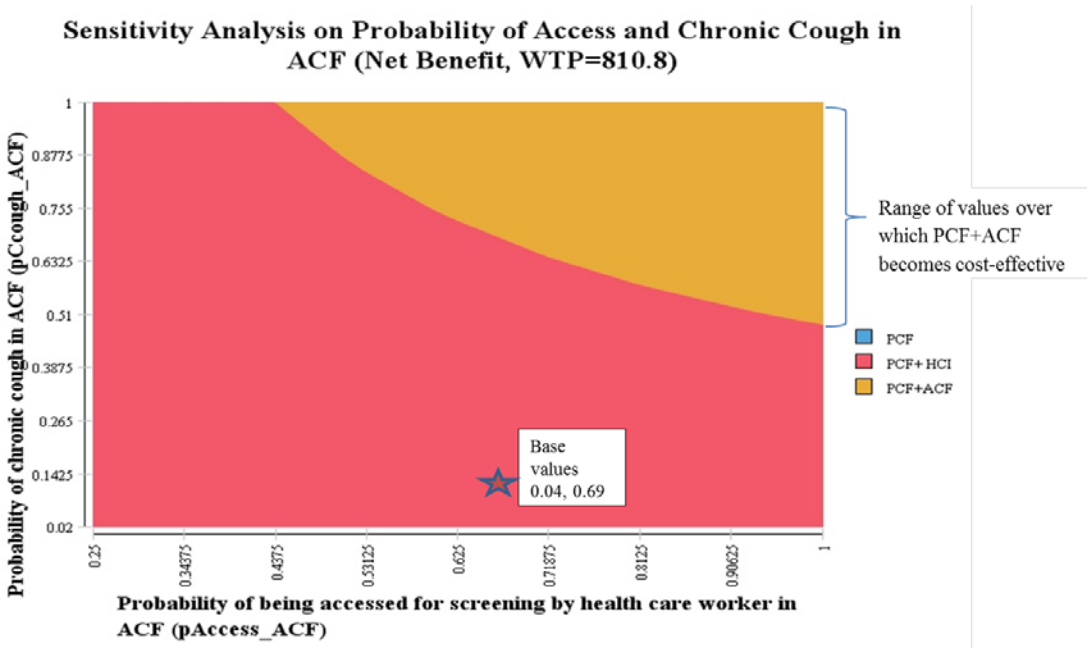


Figure 4.7. Two-way Sensitivity Analysis of Probability of Access and Chronic Cough in ACF

In another two-way sensitivity analysis, we simultaneously varied the probability of health workers accessing people during a community ACF program and the probability of chronic cough in the ACF population over a range including the highest possible value of one (Figure 4.7).The high values allow us to simulate a scenario where, for instance, a whole community would be mobilized through awareness campaigns to identify most if not all of the people with chronic cough that need to screened thus creating an enriched sample. Over a wide range of values for both parameters, the PCF+HCI remains the dominant strategy case detection**.** But, when the level of access to the people to be screened increases to 100%, then even a just having at least 51% level of chronic cough in the enriched sample would make PCF+ACF strategy more cost-effective than PCF+HCI.

Discussion

We conducted an incremental cost-effectiveness analysis to compare PCF+ACF and PCF+HCI with PCF alone from the societal and health provider perspectives in an African city context. The results indicate that PCF+HCI is cost-effective for detecting TB cases compared to PCF alone from both perspectives. The cost per additional TB case detected was $443.62 for PCF+HCI. The model conclusions were sensitive to uncertainty in several parameters; varying the probability of detecting one or more TB cases from a true smear positive index case in HCI changed the decision to PCF+HCI not being cost-effective. This is not surprising because the detection of the majority of cases in HCI is driven by the infectious status of the index. In fact, this finding lends internal validity to our study since it is well-known that smear positive index cases are more likely to infect the contacts than smear negative cases (Eang et al., 2012; Whalen et al., 2011). Varying the probability of chronic cough in ACF to its high plausible value and reducing the program costs in ACF made PCF+ACF a cost-effective strategy. It is important to note that the cost-effectiveness of a strategy involving HCI would be highly dependent on a well-functioning PCF program to which it is tied; it's ability to detect index cases and follow them up to reach all the household contacts in a timely manner. In Uganda and much of Africa, the lack of well-organized health systems, a shortage of health care personnel and limited adequate health resources pose practical barriers to implementation of household contact investigations.

A major strength of this study is that most of the probability and cost parameter estimates used in the decision model were largely drawn from actual data in the Uganda National TB Program and primary studies conducted in urban Uganda. Therefore, most of the model assumptions are close to the real world situation. Second, we conducted a full economic analysis comparing all the currently available TB case detection strategies from the societal perspective as recommended by the panel on cost-effectiveness in health and medicine (Gold, 1996). Third, the costs borne by patients were evaluated directly from a cost

survey of patients receiving TB services from the PCF system in Kampala, Uganda; this is an addition to the existing literature. Finally, our decision model was validated when we found that the estimated cost per case detected as calculated directly using NNS and NNT in the primary epidemiologic study and from the model was very similar. The advantage of using the decision analytic model is to be able to compare the costs and effects of the strategies simultaneously while taking into account the specific diagnostic event pathways that are unique to each patient being screened.

The average cost of detecting a true TB casein Kampala using the alternative strategies ranged from $149.73 to $195.00 with PCF alone having the lowest of the three strategies; this is expected since PCF is the least labor intensive. However, we note that one would have expected ACF and HCI to be much more costly than PCF but this is not case. A plausible explanation is that that taking the societal perspective levels the playing field such that the low program costs of PCF are offset by the higher patient costs and vice versa for the ACF and HCI thus resulting in average cost that is similar across the three strategies. The average cost for detecting a TB cases compared reasonably with those obtained from similar settings. The median cost was $132.00 (range US$60.00-1626.00) per TB case detected as reported from eight ACF projects in high TB burden countries including Uganda, the projects were conducted under the Fund for Innovative DOTS Expansion through Local Initiatives to Stop TB (Hinderaker, 2011). This suggests that our study cost estimates are likely to be within the ball pack of costs that could be reasonable for case detection.

Our study findings contrast with those from a recent study on cost-effectiveness of active case finding conducted in Kampala, Uganda that found PCF+ACF to be more cost-effective (Mupere et al., 2013). The differences between the two studies can easily be explained by the choice of model, the effectiveness measures, the perspective of the analysis and the strategies that were compared. Mupere and colleagues (2003) used a Markov model to capture the dynamic events related to treating a TB case,

evaluated the cost per additional quality adjusted life years (QALYs), life years gained and new cases averted when comparing PCF+ACF to PCF alone from a provider perspective (Mupere et al., 2013). Our study compared a broader range of alternatives including PCF+HCI and considered the costs borne by both the health provider and, the patients and care givers in the analysis.

Our study indicates that the PCF+ACF strategy can become a cost-effective strategy under a number of certain conditions. From the one-way sensitivity analysis, a ten-fold increase in the probability of chronic cough in ACF from 0.04 to 0.4 makes the ACF +PCF strategy also cost-effective. However, given the set threshold PCF+HCI would still be the preferred strategy because it more effective in detecting additional cases. In the real world, achieving a prevalence of chronic cough as high as 40% may be unlikely but it can be encountered in rare situations where access to PCF services is very poor. Furthermore, results from the two-way sensitivity analysis highlighted that when the likelihood of chronic cough in ACF and that of TB disease in ACF increased simultaneously from 4% to 24% and, from 24.4% to 30% respectively then PCF+ACF becomes cost-effective, suggesting that ACF may have a greater role to play in high disease prevalence settings. A study conducted in rural Kenya found a 39% prevalence of chronic cough and 64% of TB prevalence of undetected when using ACF within a setting with very poor health care access (van't Hoog et al., 2011). In order to increase the likelihood of chronic cough and perhaps TB disease in the screening sample, extra efforts to mobilize persons with chronic cough through community mass campaigns would have to be undertaken by the health care workers. This approach may be performed as periodic health outreach programs for greater sustainability and has been shown to be efficient in previous ACF studies (Shargie et al., 2006). The prevalence of chronic cough in ACF emerged as an important variable in this analysis, supporting the idea that enriching screening samples with chronic coughers could improve the efficiency of ACF.

The cost and affordability of performing ACF programs has always been a subject for debate. Our study highlighted that program costs including personnel time, administration and transportation drive the

overall cost. From the sensitivity analysis, a 50% reduction in the base program costs would dramatically reduce the incremental cost per additional case detected by nearly US$650 in PCF+ACF thereby making the strategy cost-effective. A close examination of how program costs can be reduced to improve the efficiency of ACF is therefore warranted. For example, in order to cut back on personnel costs, trained lay health volunteers could be recruited to work in their local communities as frontline cough monitors that detect suspect cases using ACF methods. Datiko and colleagues (2010) conducted a cost-effectiveness study of PCF+ACF using trained health extension workers in Ethiopia; they found that this approach was more cost-effective and reduced the program costs by 61% compared to employing trained nurses to do the field work (Datiko & Lindtjorn, 2010). Others have developed systems of periodic mobile health campaigns that gather all people with chronic cough in a common location for screening (Corbett et al., 2010).

In Uganda, integrating TB screening services with existing outreach health programs such as child immunization and family planning could be a good way to maximize the use of scarce resources. Targeting screening to religious gatherings or market places may be yet another low cost approach to finding persons with symptoms for further medical evaluation. Finally, in the era of explosive growth of mobile phone technology use, there is a great opportunity to reach millions of people in diverse populations with health interventions than never before. Mass campaigns for cough screening could be easily accomplished via text messaging but whether this approach would be more cost-effective remains an open question. No single approach is ideal for all settings but the goal should be to find as many new TB cases early enough at the lowest cost possible and place them on effective therapy.

Policy decision makers should view cost-effectiveness results in light of other related factors, such as case the burden of disease, the patient mix in the target population, ethical and equity concerns. If access to health care is deemed to be a serious problem in a given setting, then community ACF may be the only equitable way to reach the undetected cases. For example, in Kampala city there are five

administrative divisions all of which at least have a densely populated slum with poor and vulnerable populations, with potentially a high likelihood for TB and lack of access to health care, such settings could greatly benefit from ACF. A study conducted in one of the slums in Kampala found a high prevalence of previously undetected TB cases among people who reported chronic cough (J. N. Sekandi et al., 2009). In theory, having all the three of the current case finding strategies in place to maximize the benefit of cases detection would be ideal. But in the real world, even the chosen optimal strategy has to be revaluated regularly for its efficiency due to the changing dynamics of the population. New ways to find all cases must continually be sought in order to address the public health challenge.

Mathematical modeling work has consistently highlighted the importance of case detection and the economic benefit of ACF under certain conditions (Borgdorff, Floyd, & Broekmans, 2002; Currie, Floyd, Williams, & Dye, 2005; Dowdy & Chaisson, 2009; Murray & Salomon, 1998b). It is not possible to make fair comparisons between our study results and findings from mathematical modeling studies because of differences between the static and dynamic model capabilities, outcome measures and the fact that none of the previous models considered household contact investigations among the alternatives for case detection. Murray and Salomon (1998) modeled the maximum costs per DALY at which ACF strategies would be cost-effective when compared to the standard PCF in the different global regions over a 30 year period. In the Sub-Saharan Africa region, the willingness-to-pay for a person detected by ACF using symptomatic screening was US$56 per DALY gained. The strategy could reduce the number of new cases of TB and deaths by 17 million and 7 million respectively between 1998 and 2050 (Murray & Salomon, 1998b). Currie and colleagues (2005) also evaluated the cost-effectiveness of seven strategies to control TB in Kenya and found that improving case detection was very cost-effective at US$ 22 per DALY gained and US$329 per TB case averted compared to the baseline scenario over a period of 20 years. We learn from these findings that ACF is indeed associated with remarkable future health benefits which were not demonstrated by our study because of the limited scope (Currie et al., 2005).

Limitations

The findings in our study are subject to some limitations. First, we used a static model to estimate the number of true TB cases detected; hence it was not possible to account for ongoing TB transmission and the future benefits such as the new cases and deaths that would be averted by implementing each of the alternative strategies. This limitation could lead to underestimation of the long-term health benefits that would accrue from early detection particularly for the ACF and HCI strategies. Mathematical modeling would be required to overcome this limitation.

Second, we did not use Quality-Adjusted life Years (QALYs) as the measure of effectiveness although it's the widely recommended metric; therefore this limits the comparison of our results to other the cost-effectiveness studies that used QALYs and to other health programs. However, the choice to use the number of true TB cases detected as the effectiveness measure was guided by its relevance to answering the research question posed and was also deemed as being of immediate interest to decision makers with regard to TB case finding.

Third, our model does not explicitly account for the prevalence of TB disease in the general population; this limits the evaluation of the effect of varying levels of prevalence on the model results. Indeed we can speculate that the effectiveness of ACF strategies will greatly depend on the prevalence of disease in the general population, such that at very low prevalence levels conduction ACF may be worthless. The results obtained are assumed to hold true for the currently high TB prevalence in Uganda and other high disease burden settings in Africa. One way, to evaluate the potential cost-effectiveness of the case detection strategies in other settings with lower TB prevalence would be to perform sensitivity analyses around key parameters using estimates from those settings. Alternatively, we could design a completely different decision model structure that accounts for population prevalence of disease. We attempted this approach but it turned out to be challenging because of the need to account for different levels of disease prevalence in the subpopulations being reached by each of the strategies (clinic patients

vs. household contact vs. general community). An example of a decision model that includes population prevalence is provided (see Appendix I).

Finally, cost-effectiveness studies are prone to selection bias and/or publication bias because of a heavy reliance on the published literature for model parameter estimates and the ranges of values used in sensitivity analyses. In our study, these biases were substantially minimized because most of the estimated were obtained from real data in Uganda.

Conclusions

Under our baseline assumptions, HCI is more cost effective than ACF when implemented in the context of the existing TB control program that uses PCF for case detection. PCF+HCI cost US$1049 less than PCF+ACF to detect one additional true TB case. However, PCF+ACF has the potential to become cost-effective when the prevalence of chronic cough in ACF increases to 40% in the screened population or if TB disease and chronic cough prevalence simultaneously increase to at least 30% and 24% respectively. Additionally, a 50% reduction in the program cost of ACF makes the strategy cost-effective strategy at a decision threshold of one to three times Uganda's annual GDP per capita.

CHAPTER 5

SYNTHESIS OF RESULTS, PUBLIC HEALTH IMPLICATIONS AND CONCLUSIONS

In this final chapter of the dissertation, we review and synthesize some of the important findings from this body of work in the broader context of TB control, discuss potential public health implications and to provide general conclusions.

Synthesis of Results in the Context of Global TB Control and Elimination

As the world begins to embrace an ambitious goal to eliminate the deadly TB epidemic, it is worth emphasizing that interruption of transmission is the key to successful TB control. Therefore improvement in case detection coupled with several interrelated facets such as development of innovative diagnostics, new drugs and vaccines should ultimately lead to elimination of TB transmission (World Health Organization, 2013a). In most of Africa, case detection has lagged far behind (Obermeyer, Abbott-Klafter, & Murray, 2008); due to significant patients' delays leading to transmission of infection prior to diagnosis and treatment in PCF (Sendagire et al., 2010; Sreeramareddy, Panduru, Menten, & Van den Ende, 2009). From a public health, the greatest population benefit will accrue from early detection and timely initiation of effective therapy for all active TB cases. Active case finding by household contact investigation is cost-effective and lends itself well to early detection while improving access to TB services. Indeed, most TB programs recommend case finding in household contacts, but it is not done in practice (World Health Organization, 2012). For Sub-Saharan Africa, where the high burden of TB

persists and healthcare access is still poor, we argue that HCI should be implemented as an integral part of the TB control strategy.

Notwithstanding the results from our analysis that community ACF is not a cost-effective strategy, the primary study showed that it was beneficial for identifying previously unknown active TB cases and TB-HIV coinfected persons in the city. Multiple studies have shown that supplementing the existing standard PCF with community ACF provides good value for money when they considered long-term benefits such as gains in quality and length of life as measured in QALYs, new TB cases averted and deaths prevented (Dasgupta et al., 2000; Dodd et al., 2011; Mupere et al., 2013; Murray & Salomon, 1998a).Therefore, from a broader public health perspective ACF counts as a beneficial health intervention.

No single strategy is sufficient for detecting all existing TB cases in any given population. The conceptual model for TB case detection (Figure 5.1) shows what would happen in the real world setting. We recognize that each strategy may be well suited for detecting different groups of patients with respect to age, stage of disease and propensity to seek care. For instance, PCF most detects adults who have access to care, good health seeking behavior and are therefore able to present themselves to the health system. However, some of these cases may have advanced stages of disease as a result of diagnostic delays (Sreeramareddy et al., 2009). Household contact investigation is the logical next step to expand case detection because it focuses on recently exposed children and adults who are at-risk of TB infection and disease. Moreover, it has been shown to be cost-effective in our analysis. It is important to note that the majority of TB cases detected by HCI are children below 15 years who are less likely to transmit disease because they typically suffer from extra-pulmonary TB and when they have pulmonary TB they rarely are able cough up the infectious droplets into the air (Guwatudde, Nakakeeto, et al., 2003). The majority of adult cases detected through HCI are likely to be in the early stages of disease. On the other hand, community ACF often targets adults who may have several barriers to healthcare access, or those

who do not perceive their symptoms as serious enough to need medical attention. Indeed, even if all current strategies were in place some cases would potentially remain undetected suggesting the pursuit for new strategies for case detection or improving existing ones should be an ongoing process.

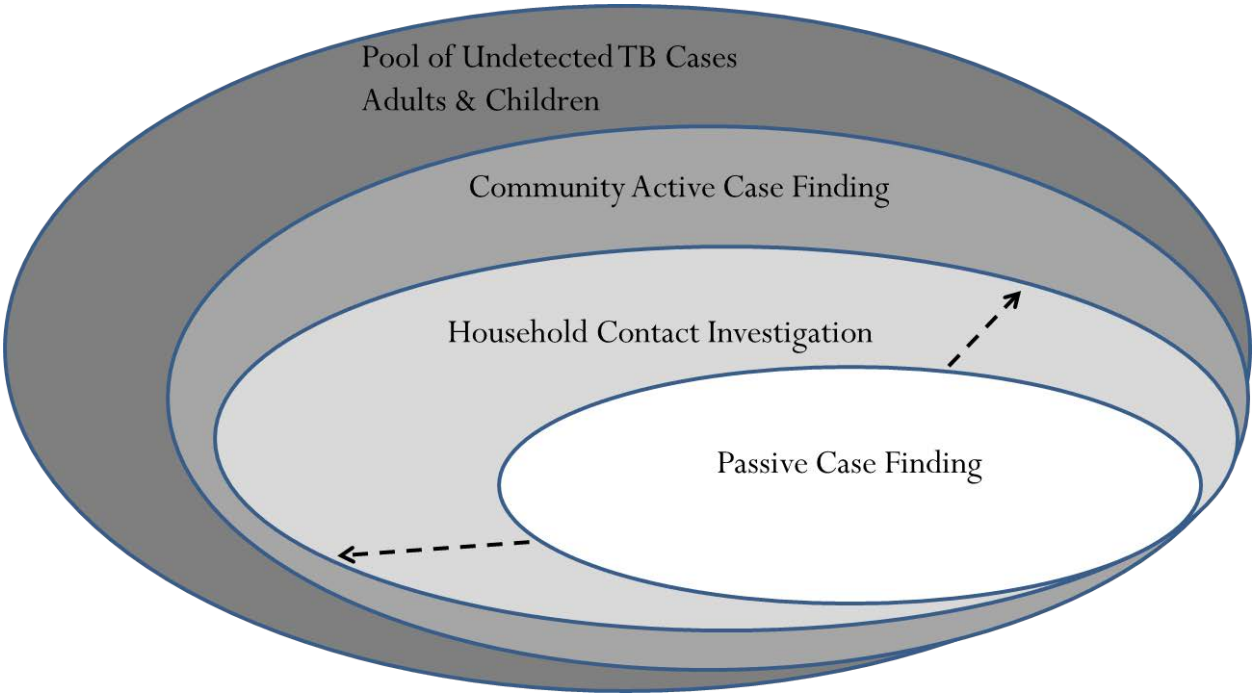


Figure 5.1. Conceptual Model of TB Case Detection

Role of ACF and the Potential Influence of TB Transmission Locale on Policy Decisions

In order to achieve the broader public health goal of TB control and elimination, case detection strategies should not only identify new cases but also interrupt disease transmission. Although our study did not evaluate disease transmission, an important question that must be posed is *"Do the majority of TB transmission occurs in the household or in the wider community (non-household) setting?"* If for instance, the highest proportion of TB transmissions occur within households and only very few occur in the non-household community setting, then conducting HCI may interrupt transmission and benefit

individual contacts in terms of early detection. Indeed a policy decision that targets households will be the optimal strategy for TB control (Figure 5.2). However, if the reverse situation is true and the highest proportion of the transmissions occurs in the community rather than the household, then it means that although HCI is cost-effective, it will have limited impact on transmission and ultimately the TB epidemic. Therefore, a policy decision to perform community active case finding may be beneficial for achieving the public health goal of TB control.

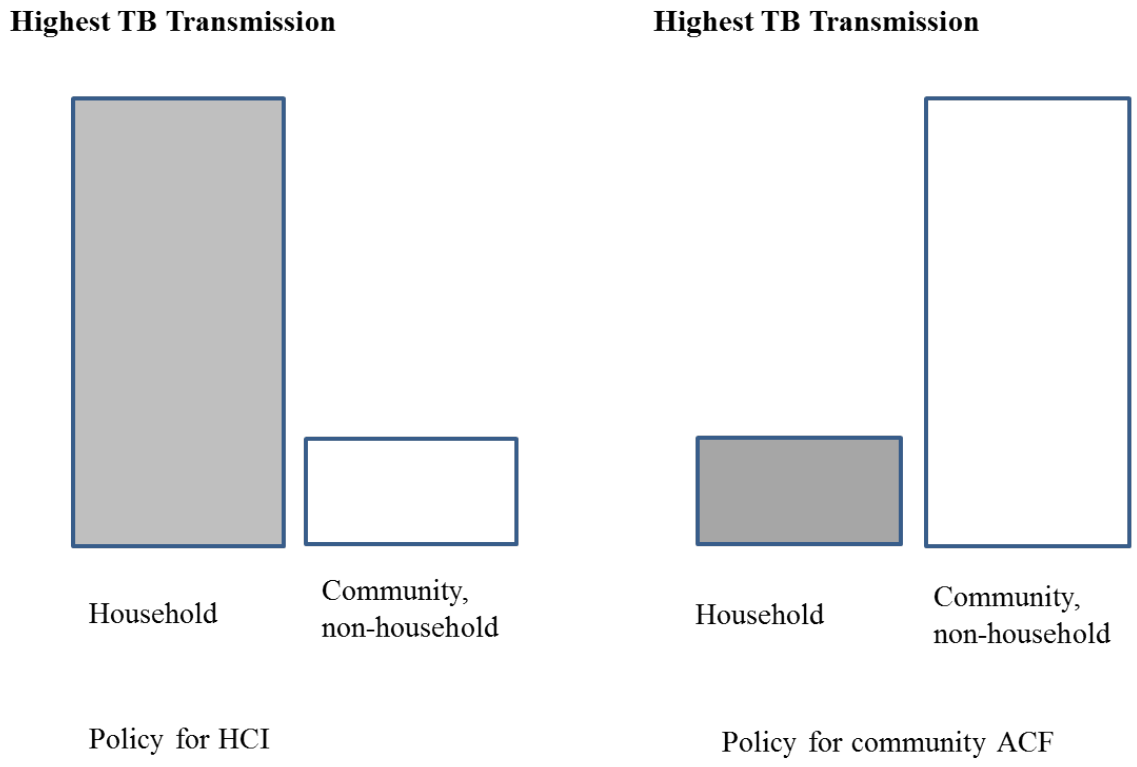


Figure 5.2. Influence of Locale of TB Transmissions on Case Finding Policy Decisions

Studies that have examined transmission dynamics using molecular techniques are still inconclusive, one study conducted in Kampala, Uganda reported that 25% of contacts had acquired disease from a non-household source (Whalen et al., 2011), while another study done in rural Vietnam found that 83% of contacts with TB had been infected by strains from non-household sources, this finding argues against case finding among household members (Buu et al., 2010). There is evidence to suggest that social networks methods could play an important role in identifying complex transmission patterns of *M. Tuberculosis* or other infectious diseases such as HIV/AIDs and provide insights for prioritizing contact investigations (Cook et al., 2007; L. K. Fitzpatrick et al., 2001; Klovdahl et al., 1994). This area of research lends itself to context-specific features such as places of social aggregation between cases and contacts, and socio-cultural behavior within subpopulations. More research is needed to help refine our understanding of where to target the contact investigations in order to achieve the greatest public health impact.

Screening High-risk Populations

Screening for active TB defined as "*systematic identification of people with suspected active TB, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly"* (K. Lonnroth, Corbett, E., Golub, J., Godfrey-Faussett, P., Uplekar, M., Weil, D., Raviglione, M.,, 2013) embodies active case finding activities. In revisiting ACF, it is important to apply screening discriminately by careful selection of high-risk groups that might benefit the most from screening while balancing the risk of doing social harm (stigma) and the related costs. A recent systematic review showed that the number-needed-to-screen varies widely depending on risk group but the greatest gains in efficiency are obtained from targeting the screening to high risk-populations (A. E. Shapiro, Golub, J. E., 2012). Lesson learned from earlier studies in the 1960s and 1970s led to the conclusion that

indiscriminate screening is worthless and the recommendation to abandon the mobile mass radiography (Bleed, Dye, & Raviglione, 2000).

The known high-risk groups include close contacts, immigrants from high prevalence regions, people living with HIV/AIDS, prison populations, refugees, persons with diabetes, the homeless but there is growing interest in health care workers (World Health Organization, 2013b). Important decisions on why, when and how to screen these high risk populations must be made in light of the epidemiologic situation, the acceptability of the screening approach, the availability of resources and the capacity of the health system to handle additional cases. According to new recommendations for systematic screening for active TB disease, priority should be given to household or any close contacts, people living with HIV and current or former workers in workplaces with silica exposure (World Health Organization, 2013b). Additional recommendations that are relevant to Uganda's situations include a high prevalence (1% or greater) of undetected active TB or where people have poor access to health care or live in urban slums. In an earlier study conducted in a Kampala city slum, the prevalence of undetected TB was 3.5% (J. N. Sekandi et al., 2009) suggesting potential value of ACF.

Screening Algorithms

The sensitivity of the screening algorithms used influence the effectiveness of ACF. Highly sensitive screening tools are needed for initial screening in order to identify TB suspects that require further diagnostic testing. In ACF strategies, four screening algorithms have commonly been employed depending on their sensitivity, feasibility and the available resources. These include: Inquiry about cough lasting 2 weeks or more has a low sensitivity (35%), inquiry about any TB symptoms (70%), symptoms inquiry plus chest x-rays (90%) and chest x-ray alone (87%) (World Health Organization, 2013b). Currently, no standard algorithm has been recommended for use in practice. Using both symptom and chest x-ray screening was shown to be the most cost-effective screening algorithm in Cambodia (Nishikiori & Van Weezenbeek, 2013) but, its practical application may be limited in many African

settings. For example, our study and others done in Africa have used chronic cough and any other TB symptoms because of simplicity of application. Trade-offs should be made between gains in sensitivity and feasibility of applying the algorithm in different contexts. With the development of highly sensitive rapid point-of-care diagnostics, a greater yield should be expected upfront thus minimizing the need for initial screening steps.

Impact of New Rapid Diagnostics on Case Detection and Cost-effectiveness

High quality diagnostics are expected to contribute to greater success of TB control. Smear microscopy, a century old TB test is still used in many TB programs in Africa because it's cheap and simple to perform. However, its sensitivity is low at 61% (31-89%) and the average turnaround of test results is 24 hours; these aspects hamper timely diagnosis and impact negatively on case detection (K. Lonnroth, Corbett, E., Golub, J., Godfrey-Faussett, P., Uplekar, M., Weil, D., Raviglione, M.,, 2013). As new diagnostics replace the smear test, the gap in sensitivity and result turn around will be closed. GeneXpert molecular technology is a highly sensitive rapid test that requires more technical expertise, has a 2 hours result turnaround but it's still costly $41.00-$60.00 for most TB programs in Africa (Meyer-Rath et al., 2012).

In our analysis, increasing the sensitivity of the TB test did not seem to add much to the number of cases detected per ser most likely because the sensitivity in our model was already high since we considered parallel TB testing that combined both smear and culture tests. But, supposing the current TB test was replaced with GeneXpert at least two things could happen: 1) the number of TB cases detected will increase especially those that are smear negative, resulting in increased effectiveness for all three strategies 2) the cost of TB diagnosis will likely increase. A recent study conducted to assess the impact and cost of scaling up GeneXpert in South Africa showed that the number of new case detected increased by 30-37% while the cost of diagnosis increased by 55% (Meyer-Rath et al., 2012). The replacement of the smear test with GeneXpert was also shown to be very cost-effectiveness at US$137-US$151 per TB

case detected in three high burden countries including Uganda (Vassall et al., 2011). However, we argue that for some patients, the added cost of the GeneXpert test could be offset by the reduced patients' travel costs since there will not be need from the reduction in clinic visits and the faster turnaround of results. Overtime, the cost of the new test is expected to fall and this may result in cost savings particularly from the patient perspective.

Latent TB Infection and Implication on TB Control

One third of the world's population is estimated to harbor latent TB infection (LTBI). The public health goal of TB elimination will not be achieved in the near future without detection and treatment of LTBI. Even after all infectious cases have been removed and new transmissions have stopped, new cases of TB disease will continue to be generated from the latently infected population due to TB reactivation. HIV infection is the strongest risk factor for reactivation TB (Whalen et al., 2011). In Africa, where the prevalence of both LTBI and HIV infection is high, screening and treating for LTBI should be the ideal standard for TB control (K. Lonnroth et al., 2010). In the context of household contact investigation, screening for LTBI should be done because of the known recent exposure and the risk of progression to primary TB disease for contacts.

Noteworthy are the prevailing drawbacks to screening and treating for LTBI. First, the diagnosis using the current tuberculin skin test (TST) cannot be made with complete accuracy in BCG-vaccinated populations (Kleinert et al., 2012). Although newer, Interferon-Gamma Release Assay (IGRA) tests such as T-Spot hold promise, they have been tested with varying results in developing countries (Kleinert et al., 2012; Knappik et al., 2012; Nienhaus et al., 2011). Second, ruling out active TB in those with LTBI remains a real challenge in developing countries where the laboratory infrastructure is limited. Third, teasing apart individuals at highest risk of progression to active disease in order to balance the benefits and the risk of harm remains an active area for research especially for predictive biomarkers (Diel et al., 2011).

Case Detection and Access to Healthcare

In Africa, access to health care remains a significant challenge to TB case detection efforts. Geographical and financial barriers to access are well-documented factors impeding utilization of health care (Mauch et al., 2013). In order to make progress, governments will have to commit more resources to improving health access for their populations. In Uganda, the poor experience a greater burden of disease yet they encounter the greatest barriers to access to health care (Kiwanuka et al., 2008). The use of active case finding approaches is one way to promote access and remove barriers related to travel and knowledge about health.

The Frequency and Length of Periodic Cycles of Active Case Finding

There is a need to examine the role of continuous or periodic ACF cycles with regard to the optimal frequency and length. There is limited evidence to suggest that comprehensive on-going ACF is effective for TB screening in the short-term but its effect may wane over time. When ACF was conducted under a controlled trial in Rio de Janiero, Brazil, cases were detected over the 8 months intervention period but the effectiveness did not endure in the extended period of 60 days (Miller et al., 2010). This suggests that there may be a saturation point at which all available active TB cases will have been detected either through the passive or the active case finding approaches. Dodd et al (2010) used mathematical modeling to demonstrate that frequent (at least yearly) periodic cycles of ACF may be cost-effective averting a large cumulative TB case load over a period of 10 years (Dodd et al., 2011).

Implication for Scale-Up of Active Case Finding

In the past five years ongoing debate about scale-up active case finding has intensified with a call to communities to act (Getahun & Raviglione, 2010). Evidence of potential beneficial effects of ACF to individuals and communities have been enlisted (Kranzer et al., 2013) and should form basis for scale up.

These benefits include: 1) detecting additional cases with particular interest in the risk group and the number-needed-to-screen should be considered. Current evidence strongly supports screening household contacts and HIV-infected individuals therefore these groups of individuals should be given priority. 2) Earlier detection, a key consideration since it is presumably an intermediate step to interrupting transmission and reducing morbidity. It is important to note that ACF efforts would have limited worth if the patients identified are already experiencing advanced disease. The existing evidence to support the claim that cases identified by ACF strategies are generally still early in the course of disease is based on duration of symptoms, severity of chest x-ray abnormalities or degree of smear grade. However, cautious interpretation should be taken owing to the limited understanding of the relationship between the presence of symptoms and the duration of infectiousness (Dodd et al., 2011). 3) Better treatment outcomes in detected case which should warrant the effort in ACF. In keeping with established principles of mass screening, early case detection should only be undertaken when effective therapy is available to patients (Wilson & Jungner, 1968). Comparisons of treatment completion, default and death in patients detected by PCF and ACF are inconclusive but point to a higher mortality rate in PCF patients (Kranzer et al., 2013). 4) Impacting on TB epidemiology in the community should be a long term goal of ACF; ideally, measures of prevalence and incidence of TB should be undertaken to assess the true effect of ACF on transmission. Very few studies have assessed the effect of ACF on prevalence and/or on transmission (Ayles et al., 2013; Corbett et al., 2010) in Africa.

Recommendation for Future Research

Given the paucity of cost-effectiveness evidence, more studies are still needed to examine the lifetime health benefits and costs that accrue from active case finding strategies in various local contexts in Africa. Future cost-effectiveness studies should specifically account for the impact of active case

finding on the reduction in TB transmission and new TB cases. Additionally, more research to understand where the most TB transmissions occurs, will broaden the understanding of how best to prioritize active case finding, whether to target case finding within household or outside the household. There is also a great need for research to expand our understanding of the patients' health care seeking and diagnostic pathways is needed in order to guide the design of effective interventions to back stop detection gaps. Finally, the exponential growth of mobile technology worldwide offers a great opportunity for developing more innovative and efficient strategies to improve TB case detection using the available mobile phone infrastructure in Africa.

Conclusions

In summary, this body of work provides consistent evidence of that undiagnosed infectious TB cases in high burden settings can be detected by some form of active case finding is an effective strategy, whether community or household contact investigations. Importantly, the study has shown that HCI is a cost-effective alternative for improving case detection when added to the existing PCF programs; the caveat is that the PCF programs should be well-functioning and able to follow up index cases and their contacts in a timely manner. Policy decision makers should therefore recommend the implementation of HCI as part of the TB program activities in Uganda and the rest of Africa. The effectiveness and cost-effectiveness of HCI will depend on the burden of TB disease in the population, the access to health care and on the ability of TB control programs to deliver treatment successfully (Borgdorff et al., 2013). Community ACF might be the only available option for the poor and vulnerable that lack access to health care but low cost innovations that make ACF cost effective must be sought.. Before active case finding of any form is undertaken, careful considerations should be given to ensure the right target group is screened while weighing the benefits and risks of doing harm.

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APPENDICES

A Definitions of TB Cases

Box 1
Definitions of TB cases

Definite case of TB: A patient with *Mycobacterium tuberculosis* complex identified from a clinical specimen, either by culture or by a newer method such as molecular line probe assay. In countries that lack laboratory capacity to routinely identify *M. tuberculosis*, a pulmonary case with one or more initial sputum specimens positive for acid-fast bacilli (AFB) is also considered to be a "definite" case, provided that there is functional external quality assurance with blind rechecking.

Case of TB: A definite case of TB (defined above) or one in which a health worker (clinician or other medical practitioner) has diagnosed TB and decided to treat the patient with a full course of anti-TB treatment.

Case of pulmonary TB: A patient with TB disease involving the lung parenchyma.

Smear-positive pulmonary case of TB: A patient with one or more initial sputum smear examinations (direct smear microscopy) AFB positive; or one sputum examination AFB-positive plus radiographic abnormalities consistent with active pulmonary TB as determined by a clinician. Smear-positive cases are the most infectious and thus of the highest priority from a public health perspective.

Smear-negative pulmonary case of TB: A patient with pulmonary TB who does not meet the above criteria for smear-positive disease. Diagnostic criteria should include: at least two AFB-negative sputum smear examinations; radiographic abnormalities consistent with active pulmonary TB; no response to a course of broad-spectrum antibiotics (except in a patient for whom there is laboratory confirmation or strong clinical evidence of HIV infection); and a decision by a clinician to treat with a full course of anti-TB chemotherapy.

A patient with positive culture but negative AFB sputum examinations is also a smear-negative case of pulmonary TB.

Extrapulmonary case of TB: A patient with TB of organs other than the lungs (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges). Diagnosis should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active extrapulmonary disease, followed by a decision by a clinician to treat with a full course of anti-TB chemotherapy. A patient in whom both pulmonary and extrapulmonary TB has been diagnosed should be classified as a pulmonary case.

New case of TB: A patient who has never had treatment for TB or who has taken anti-TB drugs for less than one month.

Retreatment case of TB: There are three types of retreatment case: (i) a patient previously treated for TB who is started on a retreatment regimen after previous treatment has failed (treatment after failure); (ii) a patient previously treated for TB who returns to treatment having previously defaulted; and (iii) a patient who was previously declared cured or treatment completed and is diagnosed with bacteriologically-positive (sputum smear or culture) TB (relapse).

Note: New and relapse cases of TB are incident cases. Cases of TB started on a retreatment regimen following treatment failure or treatment interruption are prevalent cases.

1 See *Treatment of tuberculosis guidelines*, 4th ed. Geneva, World Health Organization, 2010 (WHO/HTM/STB/2009.420).

B Consent Form

UNIVERSITY OF GEORGIA
CONSENT FOR INVESTIGATIONAL STUDIES

Project Title: COMMUNITY CASE FINDING OF PULMONARY TUBERCULOSIS AND HIV CASES IN KAMPALA, UGANDA.

Principal Investigator: Christopher Whalen, MD, MS

DESCRIPTION OF STUDIES

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INTRODUCTION

This form gives you information about a research study that will be explained to you. This research project wants to ask people about chronic cough and how they seek health care in your community. You were selected as a possible participant because we are recruiting people who live in this area. Once you have had all your questions answered about the study, and if you agree to be in the study, you will be asked to sign this form. You will be given a copy of these forms to keep.

PURPOSE

The study will primarily look for people with chronic cough who have not sought health care, examine their sputum for TB, test for TB infection and also test for HIV infection and then refer them for appropriate treatment. Researchers from Makerere University, the University of Georgia, Case Western Research Collaboration, Makerere University School of Public Health are working with sponsors from the Doris Duke Charitable Foundation to find out how they can improve health service to evaluate and treat people with chronic cough in this community and others in Uganda. About 10,000 people from Kampala will participate in this study.

STUDY PROCEDURES

You will be asked several questions about cough, other symptoms of TB and HIV testing. You are free to decline from answering any questions you do not want to answer.

If you have cough for two (2) weeks or more, your blood will be tested for HIV infection with a rapid HIV test using blood from a finger prick. A tuberculin skin test (TST) will also be placed on your left forearm, in order to do this TST; we will use a small needle to inject a little amount

of liquid solution under your skin. You may experience a little pain from the two procedures above. You will also be asked to provide two (2) to three (3) sputum samples to be tested for TB germs. One will be collected after the interview; the remaining specimens will be collected two days after the interview. The sputum samples will be sent to the National TB Reference Laboratory at Wandegeya for examination. Even if you feel well, you may still be requested to cough and spit into a cup. If you are unable to produce sputum you will be evaluated with a physical exam and a chest X-ray which will be done at the TB treatment center at Mulago Hospital and if your X-ray is abnormal then a sputum induction procedure may be performed to help you to produce for sputum smear examination.

If you do not have chronic cough but would like to have an HIV test, you will be offered counseling and testing with same day results.

RECEIVING TEST RESULTS AND REFERRAL FOR CARE

You will be informed of the test results from the sputum examinations 3-5 days after this interview. You will receive your HIV test results on the same day of the test except if we are uncertain of the result. In case of uncertainty, blood (about 4 teaspoons) will be drawn from your arm into a tube and taken to the laboratory for a confirmatory HIV test. The HIV test result that you receive will be repeated at the clinic where you will be referred for care, this is done for purposes of double checking your result. All results will be given to you in private but within your home environment unless you agree to share your test results with your family members. The TST reading will be taken by a home health visitor 2-3 days after its placement on your left forearm.

If you are found to have TB or HIV infection or both, you will be referred to one of the following places; the TB Research Unit at Uganda CWRU Collaboration or the TB Clinic or TB/HIV clinic or the HIV clinic which are all located in the Mulago Hospital Complex, or a public health clinic near your residence where you will receive all the usual care and free treatment for tuberculosis and /or HIV as recommended by the Uganda National Tuberculosis Control Program.

DURATION OF INVOLVEMENT

The study procedures described above should take only about 1 hour of your time on the first day of our visit to your home. We will make a second visit 2-3 days later to take the TST reading and collect the second sputum specimen; this will take no more than 20 minutes of your time. We will make our third visit to you in order to bring back your sputum test results and refer you to one of our clinics in Mulago for appropriate care, this will take about 30 minutes of your time. The study staff will explain your results to you and help you to access appropriate treatment. If you have negative smear results or do not have

tuberculosis after the initial evaluation, we will visit you again only within 6 months to re-evaluate you for tuberculosis. We will use the smear tests as before to evaluate for tuberculosis.

RISKS

You may be asked some questions that may make you feel shy or uncomfortable; however you do not have to answer any question you do not want to answer. Testing whether you have TB or not, and testing for HIV infection or learning that you have TB or HIV or both may cause you to become anxious. If you tell others, you may have problems being accepted in your family and community. You may also experience minor pain and slight swelling or redness at the site of the TST placement on your left forearm.

BENEFITS

By taking part in this research study, you will help the study personnel to identify those with chronic cough who might need further medical evaluation. If you are found to have TB or HIV or both diseases, you will be given appropriate health education about TB and HIV and will be referred for treatment at a health center of your choice.

Finding people with active TB or HIV or both diseases that are not on treatment in this community and referring them for appropriate care will help reduce the risk of death and the spread of TB infection to their contacts. This information will also help the Ministry of Health officials in Uganda to plan better TB/ HIV control programs for many similar communities in Uganda, which may benefit society in the future.

ALTERNATE OPTIONS

Your participation in this study is voluntary. If you choose not to take part in this study, or if you decide to leave this study, your medical care will not be affected. You are also able to seek health care from a private doctor. If you wish, you can be referred to another health care facility. You are free to stop the interview at any point in the process and withdraw at any time.

CONFIDENTIALITY

You need to understand that all individually-identifiable information collected from this study, such as answers you give to us and test results from your specimens, will be kept confidential to the extent allowed by law. Both your HIV and TB test results will be reported to you in private within your home unless you choose to share the report with a family member. Test results will only be written down on a slip for purposes of referral for appropriate clinical care. By participating in this research study, you are giving permission to certain agencies to review your records for safety reasons. These agencies include, the Uganda National Council for Science and Technology, the Makerere University School of Public Health, the University of Georgia, University Hospitals Case Medical Center (UHCMC), the Doris Duke Charitable Foundation and the professional staff working on this study. You understand that in order to protect your privacy, information about you will be coded with a number. This number will be shared only with those individuals who need to know because they are working on this study. The code of numbers will be stored in a safe place. This code will be destroyed at the end of the study, or about six months after the last person is enrolled in the study. Your name will never be used in any of the databases where this information is stored or in connection with any scientific papers or reports published, which may result from the study findings.

COSTS AND REIMBURSEMENT

You will not receive any payment and there will be no charge to you for participating in this study. Transportation reimbursement will be given if you require visiting the TB clinic at Mulago for further evaluation. The medical examination and chest X-ray done as part of your evaluation for chronic cough will be free of charge.

RESEARCH RELATED INJURIES

Treatment will be made available to you if a medical problem occurs as a result of participation in this study. This treatment will be at no cost to you and will include any emergency treatment and follow-up at a government hospital. If you choose to have further treatment at a private hospital or clinic, payment for these services will be your responsibility. You are not giving up any of your legal rights by signing this informed consent document.

SUMMARY OF YOUR RIGHTS AS A PARTICIPANT IN A RESEARCH STUDY

Your participation in this research study is voluntary. Refusing to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed. In the event that new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

AUTHORIZATION TO USE AND DISCLOSE YOUR INFORMATION

You authorize Dr. Christopher Whalen and Dr. Juliet Sekandi, the Principal Investigators and other investigators at the University of Georgia (UGA), Case Western Reserve University (UHCMC), and Makerere University School of Public Health, and their employees to use and disclose information concerning you, medical history and information collected during this study for the following purposes: Medical evaluation of chronic coughers, HIV test, tuberculin skin test for latent TB infection and making appropriate referral for treatment in a public health center. Such information may also be disclosed or used by others involved in or overseeing the study including the UGA Institutional Review Board, UHCMC Institutional Review Board, Doris Duke Charitable Foundation (the study sponsor) and its agents, as well as U.S., European, and other governmental, regulatory and accrediting agencies. In all disclosures outside of UGA, UHCMC, and Makerere University, you will be identified by the number code and not by your name or any other direct personal identifier unless required by law. Foreign laws governing privacy, use and disclosure of health information may provide less protection than the laws of your country. Once disclosed your information may be re-disclosed by others who are not required to maintain the privacy of your information. You may withdraw authorization to collect additional information about you at any time by writing to the local Principal Investigator, but information already collected may continue to be used and disclosed. This authorization has no expiration date.

CONTACT INFORMATION

_____ has described to you what is going to be done, the risks, hazards, and benefits involved. The researchers conducting this study are Drs. Christopher Whalen and Juliet Sekandi. You may ask any questions you have now. If you have any questions, concerns or complaints about the study in the future, you may contact Dr. Juliet Sekandi at the Makerere School of

Public Health, Mulago Hospital Complex (256-77-411-118 or 256-0414-533-531). If the researchers cannot be reached, please contact Christopher Whalen, M.D., M.S., at the University of Georgia at (706) 227-4736 or Professor Fred Wabwire-Mangen, the chairman of the MUSPH, Higher Degrees Research Committee, at 256-041-4532-207.

Questions or concerns about your rights as a research participant should be directed to the Chairperson, University of Georgia Review Board, 612 Boyd GSRC, Athens, GA, 30602-7411; telephone (706) 542-3199; email address irb@uga.edu or to Professor Fred Wabwire-Mangen at the telephone number above.

SIGNATURE

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

I agree to:

	Yes	No
1. participate in the study	☐	☐
2. Have an HIV test	☐	☐
3. Have a Tuberculin Skin Test	☐	☐
4. Have my sputum examined for TB	☐	☐

Printed Name of participant _____ (First, Surname)

Signature /Thumbprint _____

Date _____ / _____ / _____ (DD / MM / YY)

Printed Name of Interviewer or Health Home Visitor _____ Signature: _____

First, Surname

Date _____ / _____ / _____

DD MM YY

Study ID: | | | | | | | | |

I have explained the purpose of this study to the volunteer. To the best of my knowledge, this volunteer understands the purpose, risks, and benefits involved in taking part in this study.

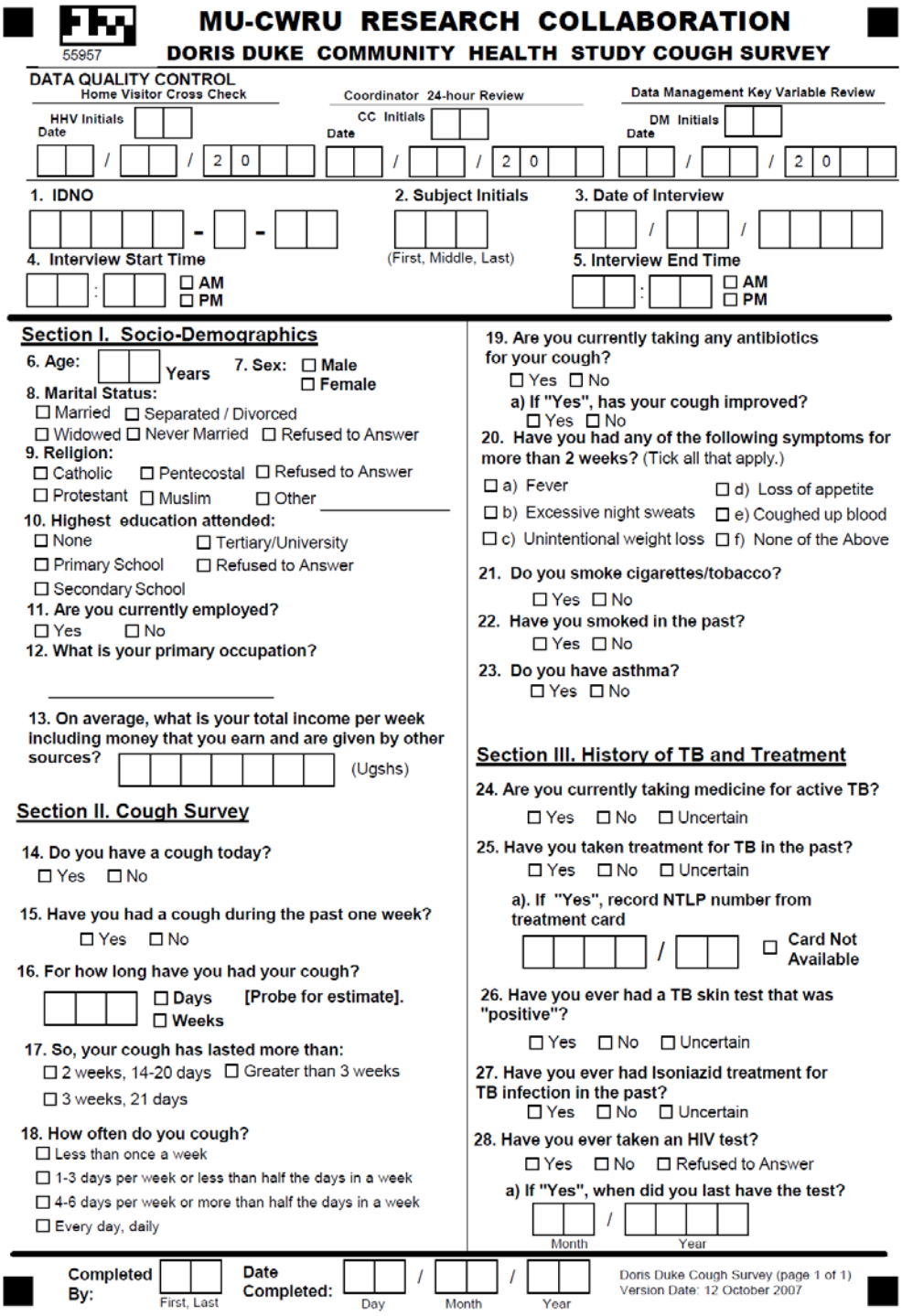
Printed Name of Investigator _____ Signature: _____

First, Surname

Date _____ / _____ / _____

DD MM YY

C Cough Questionnaire



MU-CWRU RESEARCH COLLABORATION

55957

DORIS DUKE COMMUNITY HEALTH STUDY COUGH SURVEY

DATA QUALITY CONTROL

Home Visitor Cross Check — HHV Initials ☐☐ Date ☐☐/☐☐/20☐☐

Coordinator 24-hour Review — CC Initials ☐☐ Date ☐☐/☐☐/20☐☐

Data Management Key Variable Review — DM Initials ☐☐ Date ☐☐/☐☐/20☐☐

1. IDNO ☐☐☐☐☐-☐-☐☐

2. Subject Initials ☐☐☐ (First, Middle, Last)

3. Date of Interview ☐☐/☐☐/☐☐☐☐

4. Interview Start Time ☐☐:☐☐ ☐ AM ☐ PM

5. Interview End Time ☐☐:☐☐ ☐ AM ☐ PM

Section I. Socio-Demographics

6. Age: ☐☐ Years

7. Sex: ☐ Male ☐ Female

8. Marital Status:
☐ Married ☐ Separated / Divorced
☐ Widowed ☐ Never Married ☐ Refused to Answer

9. Religion:
☐ Catholic ☐ Pentecostal ☐ Refused to Answer
☐ Protestant ☐ Muslim ☐ Other _____

10. Highest education attended:
☐ None ☐ Tertiary/University
☐ Primary School ☐ Refused to Answer
☐ Secondary School

11. Are you currently employed?
☐ Yes ☐ No

12. What is your primary occupation?
_____

13. On average, what is your total income per week including money that you earn and are given by other sources? ☐☐☐☐☐☐☐ (Ugshs)

Section II. Cough Survey

14. Do you have a cough today?
☐ Yes ☐ No

15. Have you had a cough during the past one week?
☐ Yes ☐ No

16. For how long have you had your cough?
☐☐☐ ☐ Days ☐ Weeks [Probe for estimate].

17. So, your cough has lasted more than:
☐ 2 weeks, 14-20 days ☐ Greater than 3 weeks
☐ 3 weeks, 21 days

18. How often do you cough?
☐ Less than once a week
☐ 1-3 days per week or less than half the days in a week
☐ 4-6 days per week or more than half the days in a week
☐ Every day, daily

19. Are you currently taking any antibiotics for your cough?
☐ Yes ☐ No
a) If "Yes", has your cough improved?
☐ Yes ☐ No

20. Have you had any of the following symptoms for more than 2 weeks? (Tick all that apply.)
☐ a) Fever ☐ d) Loss of appetite
☐ b) Excessive night sweats ☐ e) Coughed up blood
☐ c) Unintentional weight loss ☐ f) None of the Above

21. Do you smoke cigarettes/tobacco?
☐ Yes ☐ No

22. Have you smoked in the past?
☐ Yes ☐ No

23. Do you have asthma?
☐ Yes ☐ No

Section III. History of TB and Treatment

24. Are you currently taking medicine for active TB?
☐ Yes ☐ No ☐ Uncertain

25. Have you taken treatment for TB in the past?
☐ Yes ☐ No ☐ Uncertain
a). If "Yes", record NTLP number from treatment card
☐☐☐☐/☐☐ ☐ Card Not Available

26. Have you ever had a TB skin test that was "positive"?
☐ Yes ☐ No ☐ Uncertain

27. Have you ever had Isoniazid treatment for TB infection in the past?
☐ Yes ☐ No ☐ Uncertain

28. Have you ever taken an HIV test?
☐ Yes ☐ No ☐ Refused to Answer
a) If "Yes", when did you last have the test?
☐☐ (Month) / ☐☐☐☐ (Year)

Completed By: ☐☐ (First, Last) Date Completed: ☐☐ (Day) / ☐☐ (Month) / ☐☐ (Year)

Doris Duke Cough Survey (page 1 of 1)
Version Date: 12 October 2007

D Patient Cost Survey

64337

MAKERERE UNIVERSITY - UNIVERSITY OF GEORGIA RESEARCH COLLABORATION

COMMUNITY HEALTH AND SOCIAL NETWORKS OF TUBERCULOSIS

TB PATIENT COSTS SURVEY FORM

Part ID# ☐☐☐

Qn.1. Sex ☐☐ 01=Male 02=Female

Qn.2. Age(Yrs) ☐☐ *Code 77 for Dont Know*

Qn.3. Residence ☐☐ 01=Rubaga 02=Nakawa 03=Central 04=Kawempe 05=Makindye 88=Other

Qn.4. Are you receiving TB treatment?

☐☐ 01=Yes 02=No

Qn.5. When did you start your TB treatment?

☐☐ / ☐☐ / 2 0 ☐☐

Day / Month / Year

Qn.6.How long have you been taking TB treatment?

☐☐ Weeks

☐☐ Months

Code 77 for Dont remember

Qn.7 At what clinic were you diagnosed with TB?

☐☐ 01= Mulago TB Clinic 02=KCCA clinic 03=Private Clinic 04=Lubaga hospital 88=Other

Cost Information:The questions below refer to visits associated with your TB diagnosis

Qn.8. How many times did you travel to this clinic for diagnostic evaluation of your current TB episode (Here, I mean when you had the sputum exam and/chest x-ray)?

☐☐ Times *Code 77 for Dont remember*

Qn.9.What means of transportation did you use to travel to the clinic for diagnostic evaluation of your current illness?

- ☐ Public Taxi
- ☐ Private Taxi (Hired)
- ☐ Walked/Foot
- ☐ Boda boda
- ☐ Personal Car
- ☐ City bus
- ☐ Other Specify

Qn.10.Approximately, how much money did it cost you to travel from your home to the clinic for the TB diagnostic evaluation (one way fare)?

☐☐☐☐☐ Uganda Shillings

Qn 11. Approximately,how much time did you spend traveling to the clinic for diagnostic evaluation visit?

☐☐ Hours ☐☐ Minutes

Qn 12. Approximately,how much time did you spend waiting in line to see the health provider at the diagnostic evaluation visit?

☐☐ Hours ☐☐ Minutes

Qn 12a. Did you have a chest X-ray taken?

☐☐ 01=Yes 02=No

Qn 12b. If "YES" how much money did you pay for the chest X-ray?

☐☐☐☐☐ Uganda Shillings

Qn 13. Did you spend money on food/snack/drinks while on any of the diagnositic evalaution clinic visits? ☐☐ 01=Yes 02=No

Qn 14. If yes, estimate how much money you spent on food/snacks/drinks while on any of the diagnostic visits for your current illness.

☐☐☐☐☐ Uganda Shs

Qn 15. Do you think you would have spent the same money on food were you not attending a diagnostic clinic visits?

☐☐ 01=Yes 02=No *Code 88 for Dont know*

Qn 16.Are you currently employed? ☐☐ 01=Yes 02=No

Qn 17. What is your occupation?

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MAKERERE UNIVERSITY - UNIVERSITY OF GEORGIA RESEARCH COLLABORATION
COMMUNITY HEALTH AND SOCIAL NETWORKS OF TUBERCULOSIS
TB PATIENT SURVEY FORM

Qn 18.On avarege, how much money do you earn in a month from all you jobs?

☐☐☐☐☐☐☐ Uganda Shs

Qn 19. Did you take off days from work to come to the clinic for diagnostic evaluation of your current illness?

☐☐ 01=Yes 02=No *Code 77 for Dont remember*

Qn 20.If yes, approximately how much time did you spend while seeking medical evaluation at the clinic?

☐☐ Hours
☐☐ Days *Code 77 for Dont remember*

Qn 21.Did you hire someone short-term to manage your business when seeking diagnostic evaluation?

☐☐ 01=Yes 02=No

Care giver Infromation

Qn 22. Did you have any person accompanying you to any of the diagnostics clinic visits? ☐☐ 01=Yes 02=No

Qn 23.If yes, how many people accompanied you on the diagnostic visits?

☐☐

Qn 24. How many of your care givers were employed?

☐☐

Qn 25. Did you **specifically** hire someone to take care of you children or your home while you were away attending the clinic visits for diagnosis?

☐☐ 01=Yes 02=No

Qn 26. How much roughly did you pay this person on the days you were away for clinic visits?

☐☐☐☐☐ Uganda shs

Int Initials: ☐☐ Comp Date: ☐☐ / ☐☐ / 20☐☐
Day / Month / Year

Rev Initials: ☐☐ Rev Date: ☐☐ / ☐☐ / 20☐☐
Day / Month / Year

E Summary Results from Patient Cost Survey

Patient Characteristics N=103	Frequency (percent)
Sex	
Male	60 (58)
Female	43 (42)
Mean Age (SD)	32 (10.04)
Division of Residence	
Rubaga	36 (35)
Nakawa	9 (9)
Central	8 (8)
Kawempe	26 (25)
Makindye	9 (9)
Other	15(14)
Clinic of diagnosis	
National TB clinic, Mulago	75 (73)
Other	28 (27)
Chest X-Ray	
Yes	94 (91)
No	9 (9)
Employed	
Yes	59(57)
No	44(43)
Patient costs	
Median monthly income (IQR) in US$[a]	2.8 (0-120)
Mean monthly income (SD) in US$[b]	76 (132)
Mean number of clinic visits (SD)	2.5 (1.16)
Mean travel cost (SD) in US$[c] One way	1.21 (0.94)
Mean travel time in minutes (SD)	58 (44)
Mean waiting time (SD) in hours	5.4 (4.7)
Mean expense on meals	0.99 (1.12)
Mean hours of work (SD)	6.2 (6)
Mean days off work (SD)	1.1 (1.5)
Transportation type	
Public transport	54 (52)
Private	10 (10)
Boda boda	34 (33)
Other	5 (5)
Caregivers	
Company of care givers	
Yes	28 (27)
No	75(72)
Median number of caregivers	1 (0-1)
Help with childcare while away at clinic visit	
Yes	9 (9)
No	94(91)
Hired help while away at clinic visit	
Yes	16 (17)
No	81 (83)
Mean total cost of help/chilcare (SD)	4.55 (11.49)

a. US$2.8 =7,000 Uganda Shillings [1US$=2500Ugshs]

b. US$75.69=189,233 Ugshs

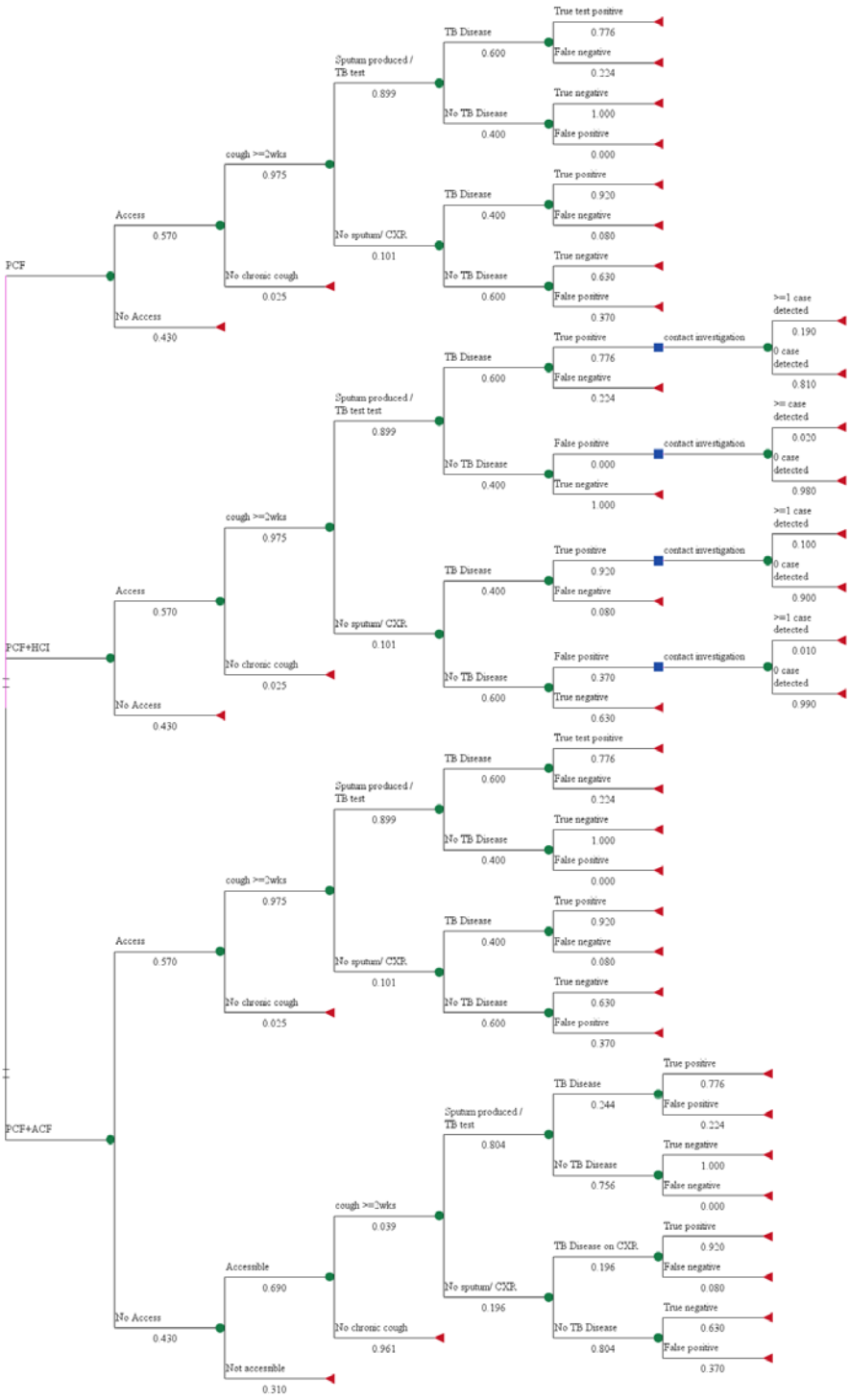
F Detailed of Cost Estimation and Valuation of Resources for PCF, ACF and HCI Strategies Based on ACF and National TB Program Data

Program Costs	**PCF**	**ACF**	**HHCI**	**PCF+ACF**	**PCF+HHCI**
Personnel	2.55	11.33	7.94	13.88	10.49
Admin supervision	0.6	0.71	0.01	1.31	0.61
Field transport	0.45	1.76	0.62	2.21	1.07
Training	0	0.1	0.03	0.1	0.03
Community sensitization	0	0.35	0.06	0.35	0.06
Phone communication	0.032	0.423	0.1	0.455	0.14
Printing, copying, office supplies	0.748	0.882	0.311	1.63	1.06
Community volunteers	0	0.35	0	0.35	0.00
Total	4.38	14.74	9.071	20.285	13.46
Total adjusted for inflation to 2013US$	7.71	28.02	15.95	35.73	23.66
Direct Medical Costs					
2 smear tests	3.00	3.00	3.00	6.00	6.00
2 culture test	15.00	15.00	15.00	30.00	30.00
Chest X-ray	8.00	8.00	8.00	16.00	16.00
Consumable supplies	0.75	0.88	0.31	1.63	0.48
Total	26.75	26.88	26.31	53.63	52.48
Total adjusted for inflation to 2013US$	47.17	47.38	46.37	94.55	92.50
Direct Patient Costs					
Avg Transportation for 2.3 visits @ $1.58, 2-way	3.63				
Avg Transportation for 1 visits @ $1.58, 2-way		1.58	1.58	5.21	5.21
Meals for 2.3 visits @ $0.99	2.28				
Meals for 1 visit @ $0.99		0.99	0.99	3.27	3.27
Avg care giver costs	5.91	0	0		5.91
Child care/hired help/day	4.55	1.5	1.5	6.05	6.05
Total	16.37	4.07	4.07		20.44
Indirect Patient Costs /Productivity Losses					
Avg total patient time lost in outpatient care (36.75)					
Avg total patient &C/giver time lost (73.5hrs)	11.03	0.45	0.45	11.48	11.48
Avg total patient &C/giver time lost in ACF/HHCI (3 hrs)					
Min. wage hourly rate in Uganda ($0.15)					
Total	27.4	4.52	4.52	31.92	28.87
Patient total cost adjusted for inflation to 2013US$	28.88	4.76	4.76	33.64	33.64

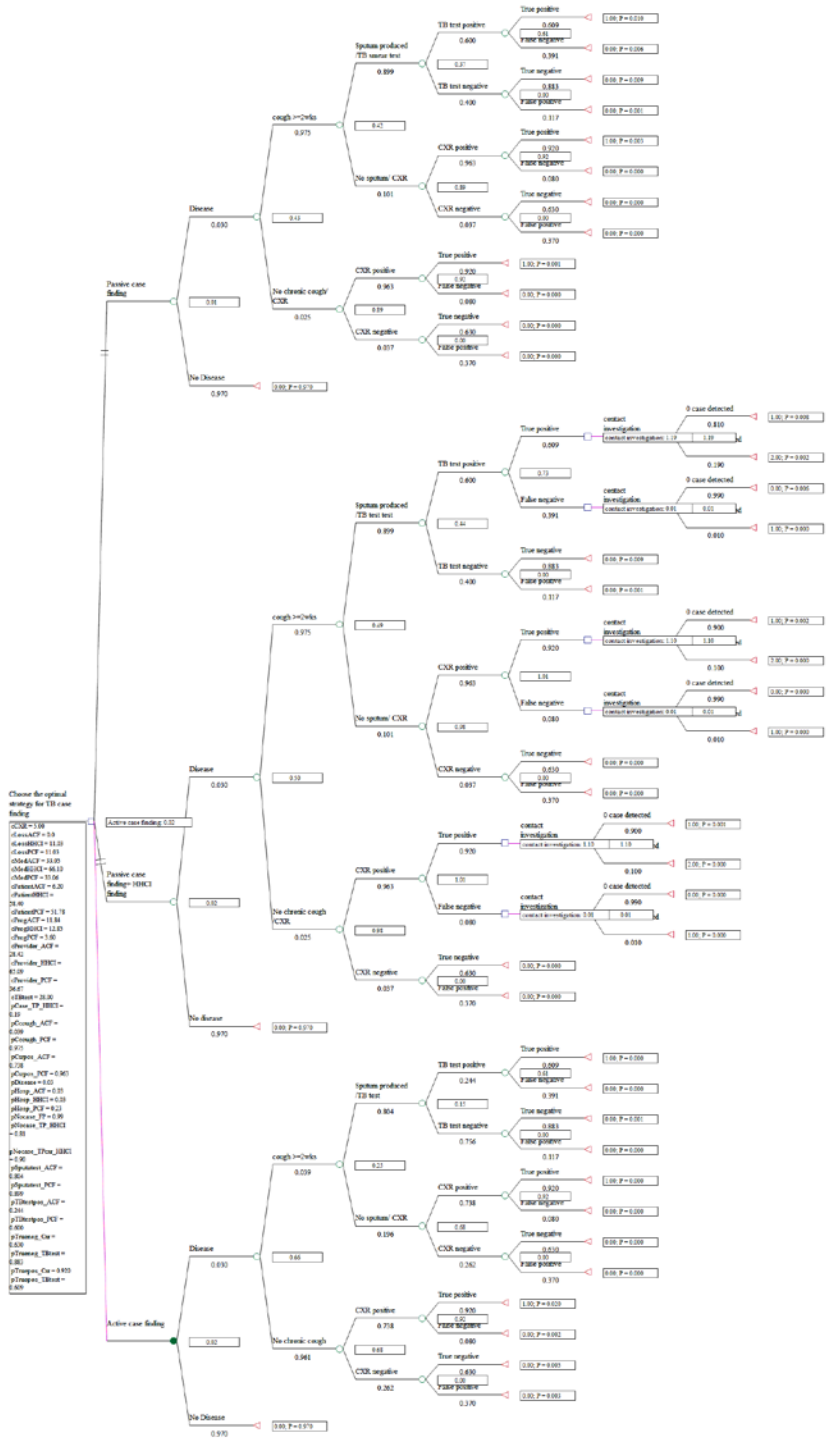
G Composition and Credentials of Expert Opinion Team

Expert	Qualifications	Area of Expertise	Work Setting
Dr. Christopher Whalen	M.D, MS	TB & HIV Epidemiology research	U.S & Uganda
Dr. Juliet Sekandi	MBChB, MS	TB health services research	Uganda
Dr. Achilles Katamba	MBChB, MS, PhD	TB program and surveillance	Uganda
Dr. William Worodria	MBChB, MMED, PhD	TB clinical research	Uganda
Dr. Sarah Zalwango	MBChB, MPH	TB clinical & community research	Uganda
Dr. Jonathan Golub	PhD	TB and HIV epidemiologic research	U.S, Brazil, South Africa

H Full Decision Tree Showing Case Detection Strategies and Probabilities

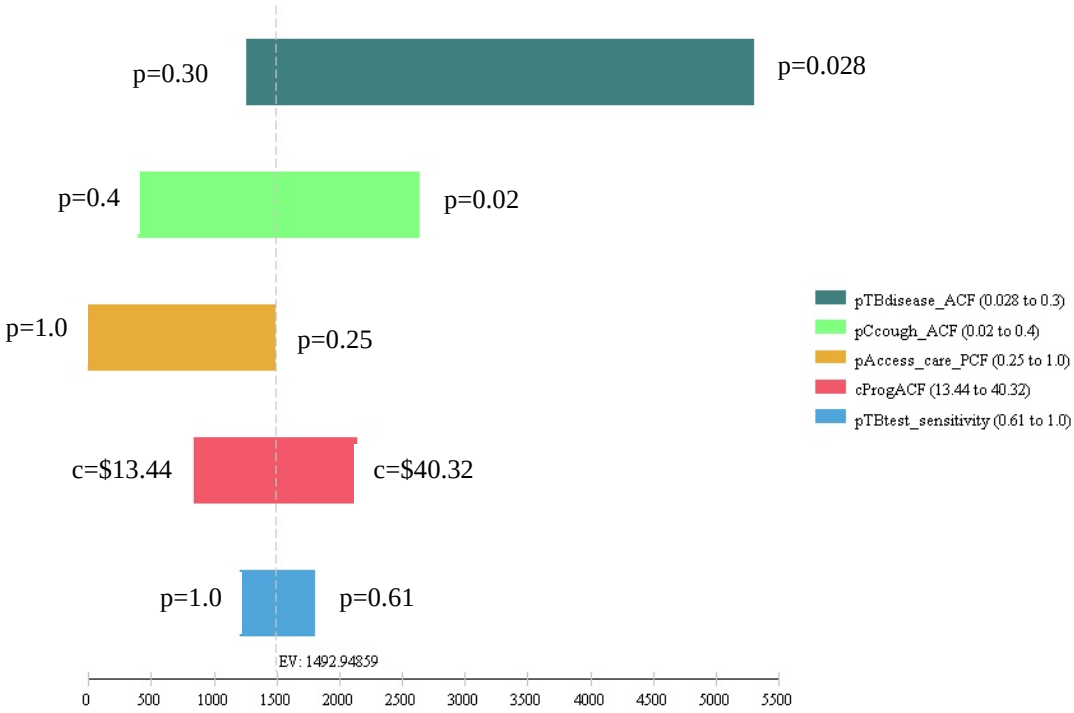


I Example of Decision Model with Population TB Prevalence



J Tornado Analysis

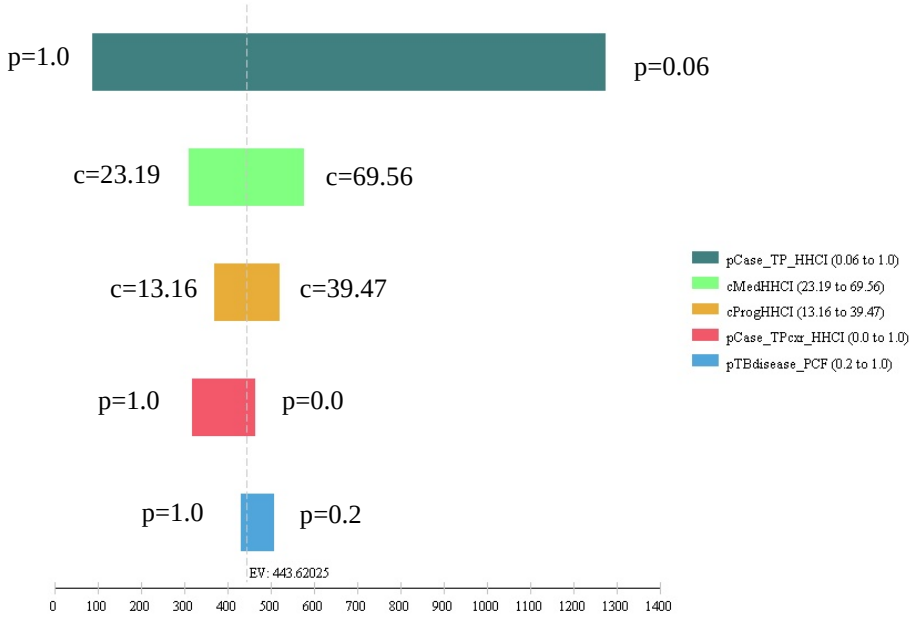
The tornado analysis was performed to get a better idea of which variables exert the most influence on the incremental cost-effectiveness ratio (ICER) in each of the two new strategies being tested in the decision analysis model. Each bar represents results of a single one-way sensitivity analysis. The variables that have the greatest influence on the ICER appear at the top of the graph. Each variable is then ranked for its overall influence from top to bottom giving it the appearance of a tornado. In Figure 4.6, the expected value (x-axis) indicates the base ICER for the PCF+ACF strategy ($1492.95). As one moves from the left to right side of the graph there is an inverse effect; the probabilities decrease from the high to low value, the ICERs increase making the strategy less favorable. However, we observe the opposite effect with cost, as the cost increase from a low to a high value the ICERs increase making the PCF+ACF strategy less favorable. The five variables which exert the most influence are 1) probability of TB disease in ACF (pTBdisease_ACF) 2) probability of cough in ACF (pCcough_ACF) 3) probability of access to care in PCF (pAccess_care_PCF) 4) program costs in ACF (cProgACF) and 5) the sensitivity of the TB test (pTBtest_sensitivity).



p=probability parameter estimates, varied across high and low range of values result in change from lower to higher ICER respectively

c=cost parameter estimates, varied across low and high range of values result in change from lower to higher ICERs respectively

Figure 1. Tornado Diagram of Selected Variables and Influence on ICER in PCF+ACF



p=probability parameter estimates, varied across high and low range of values result in change from lower to higher ICER respectively

c=cost parameter estimates, varied across low and high range of values result in change from lower to higher ICERs respectively

Figure 2. Tornado Diagram of Selected Variables and Influence on ICER in PCF+HCI

In Figure 4.7, the vertical line is the expected value (x-axis) indicating the base ICER for the PCF+HCI strategy ($443.62). We see that the five variables which exert the most influence are 1) probability of one TB case or more found from a true positive index case household in HCI (pCase_Tp_HHCI) 2) medical costs in HCI (cMedHHCI 3) program costs in HCI (cProgHHCI) 4) probability of one TB case or more found from a true positive chest X-ray index household (pCase_Tpcxr_HHCI) 5) probability of TB disease in patients given sputum examination in PCF (pTBdisease_PCF).

K Expected True TB Cases Detected and Costs by Strategy in Screened Population over 18 Months Period (Jan 2008- June 2009)

Strategy	Expected True TB case/1000 persons screened	Expected Cost of detection/1000 persons screened	Population screened [a]	Expected total true TB cases	Total Program Cost for TB cases detected
PCF	253	37,920	6020[a]	1520	227,819
PCF+ ACF	255	41,160	11122[b]	2836	457,763
PCF + HCI	300	58,500	20,468	6140	1,197,300