Tuberculosis Stigma, AIDS Stigma, and Tuberculosis Control in Southern Thailand

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ABSTRACT

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Tuberculosis Stigma, AIDS Stigma, and Tuberculosis Control in Southern Thailand
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Tuberculosis (TB) remains one of the most important infectious diseases
worldwide, with approximately one-third of the world's population infected with the
Mycobacterium tuberculosis bacillus and more than 9 million new cases and 1.7 million
deaths annually. Stigma may act as a barrier to TB care, treatment, and control in areas
where quality services are available. Health-related stigma is defined as "a social process
or related personal experience characterized by exclusion, rejection, blame, or
devaluation that results from experience or reasonable anticipation of an adverse social
judgment" because of specific health problem. Few measures of TB stigma exist, making
it difficult to understand its determinants and effect on health behaviors.

Data were collected in southern Thailand where culturally relevant TB and AIDS
stigma scales were developed. Using these scales, a survey of 300 healthy community
members, and a cohort of 480 newly diagnosed TB patients, the aims of this dissertation
were to 1) to identify socio-demographic, TB knowledge, and clinical factors associated
with TB stigma, 2) to estimate the association between stigma and patient delay in
seeking care for TB symptoms, and 3) to estimate the effect of stigma on adherence to
TB treatment.

We found high levels of both TB and AIDS stigma, but few factors were
identified that could contribute to TB stigma. Knowledge of the link between TB and

AIDS, higher AIDS stigma, and knowing someone who died of TB were consistently associated with TB stigma. However, neither TB nor AIDS stigma had an overall effect on delay in seeking care for TB symptoms or adherence to treatment. Effects were observed within sub-groups of gender, HIV status, and presenting symptoms, where higher stigma increased delay and non-adherence among some, while decreasing delay and improving adherence among others.

These findings have important implications for future stigma research and interventions. Specifically, stigma research conducted at the general population level (community or patient) may miss important effects. Future research should recognize that stigma may serve as a motivator or barrier, and therefore identify specific sub-groups in which stigma has an adverse effect and who would therefore benefit from stigma reduction interventions.

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CHAPTER 1

INTRODUCTION

Tuberculosis (TB) remains one of the most important infectious diseases worldwide

with approximately one-third of the world's population estimated to be infected with the

Mycobacterium tuberculosis bacillus, and more than 9 million new cases and 1.7 million

deaths annually (Dye, Scheele et al. 1999; WHO 2006; WHO 2008). In 1993, the World

Health Organization (WHO) declared TB a global emergency and recommended that

countries implement the DOTS strategy as a cost effective way of managing and controlling

the TB epidemic (WHO 1999). DOTS is based on five key components: 1) government

commitment, 2) passive case detection by sputum smear microscopy, 3) standardized

treatment for six to eight months incorporating directly observed treatment, 4) regular,

uninterrupted supplies of anti-TB drugs, and 5) standardized recording and reporting. A

target of detecting 70% of new infectious cases and successfully treating 85% of those

detected was established, with the expectation that incidence rates would decline 10% per

year in areas where rates were already stable and HIV co-infection was absent (Dye, Garnett

et al. 1998; Dye, Maher et al. 2006). While 93% of the world's population is living under

DOTS coverage, it is estimated that only 61% of new smear-positive cases are detected, with

85% of these being treated successfully. Among the 22 high burden countries, only five

(China, Indonesia, Myanmar, the Philippines, and Viet Nam) had achieved the WHO targets for case detection and successful treatment (WHO 2008).

The dynamics of TB disease and control have changed, however, with the onset of the HIV/AIDS pandemic. In the absence of HIV co-infection, a person infected with TB has a - 10% *lifetime* risk of developing active disease, with the greatest risk of active disease occurring in the first two years after infection (Harries and Dye 2006). In contrast, individuals living with HIV who are not receiving antiretroviral therapy have a 5-15% *annual* risk of developing active TB disease and up to a 50% lifetime risk of disease. Approximately 8% of new TB cases worldwide are co-infected with HIV and 12% of TB deaths are among those infected with HIV (WHO 2008). This increase in incident disease can place additional strain on national TB control programs, making it difficult to reach the WHO targets (Lienhardt and Rodrigues 1997).

With its focus on passive case detection, diagnostic techniques, and directly observed therapy, DOTS has been criticized as a treatment guideline and biomedical strategy that does not account for social factors related to TB control, rather than a comprehensive control plan (Lienhardt and Ogden 2004; Whalen 2006). The new WHO Global Plan to Stop Tuberculosis (WHO 2006) recognizes that DOTS will not control TB in areas of HIV and drug resistant TB. It therefore enhances the DOTS strategy, creating a more comprehensive approach that addresses poverty and other social factors. One of these factors is stigma, which may act as a barrier to appropriate care and treatment in areas where quality services are available.

CHAPTER 2

REVIEW OF THE LITERATURE

BACKGROUND OF HEALTH-RELATED STIGMA

In recent years, there has been increasing interest in the role of stigma in affecting

public health issues (Van Brakel 2006). Erving Goffman is credited with writing the seminal

work on stigma, published in 1963 and entitled Stigma: Notes on the Management of Spoiled

Identity (Goffman 1963). Observations on a broad range of conditions and behaviors form

the basis of his work, including physical deformities, hearing loss, epilepsy, schizophrenia,

sexual orientation, and conviction for criminal acts. Through interviews, observation, and

research, he formalized the concept of stigma and described how it affects those who are

stigmatized, particularly as they work to manage their personal and social identity in relation

to that which stigmatizes them. He defines stigma as "an undesirable or discrediting attribute

that an individual possesses, thus reducing that individual's status in the eyes of society".

This "discrediting attribute" can fall into one of three categories: abominations of

body (e.g. physical defects), blemishes of character (e.g. behavioral defects), or tribal

attributes (e.g. race, ethnicity, religion) which can be passed on through lineage. He further

separates stigma in discredited (or visible) and discreditable (or hidden) forms. Discredited

attributes refer to those which are known or evident to the observer. Many physical

deformities, race and ethnicity constitute this form of stigma. Discreditable attributes refer to

those that are unknown or hidden from the observer. These can be behavioral attributes or physical attributes that can easily be hidden. The form of stigma that a person has will influence how he or she interacts with society. Those who are discredited will tend to avoid social situations or seek to lessen the impact of their attribute when going out in public. Those who are discreditable will try to manage their stigma. They will expend time and energy keeping the attribute hidden while deciding to whom they will disclose it. Additional energy is spent as they anticipate and react to the response of the observer upon disclosure.

Stigma research has blossomed since Goffman's publication. An unfortunate result has been the multiple definitions and ambiguous concepts of stigma that have emerged in the literature (Link and Phelan 2001; Deacon 2006). Ambiguity in the term has important implications for stigma research and interventions. It is imperative that, when stigma is discussed and measured, there be little confusion about its concept, underlying mechanisms, and observable outcomes. Weiss and Ramakrishna define health-related stigma as "a social process or related personal experience characterized by exclusion, rejection, blame, or devaluation that results from experience or reasonable anticipation of an adverse social judgment about a person or group identified with a particular health problem" (Weiss and Ramakrishna 2006). They draw attention to the need for formal research on the role of stigma in the burden of illness and propose six research objectives:

1) Document the burden of stigma for serious health problems
2) Compare stigma for different health problems and in different settings
3) Identify determinants of stigma and their effect on health policy, illness experience, and behavior

4) Evaluate changes in stigma over time and in response to interventions and social change

5) Improve knowledge about the nature and risk of target health problems so that laws and health policy minimize stigma

6) Develop clear, simple, and unambiguous messages about the complicated health problems of stigma

Accomplishing these objectives requires a clear understanding of the occurrence of stigma. As identified in the definition by Weiss and Ramakrishna, stigma can be a social process (i.e. present in the community) or personal experience, both of which can be perceived or real effects. Recent literature on health-related stigma has identified five broad components that incorporate both community and patient perspectives (Nyblade 2006; Van Brakel 2006). These include:

1) Stigmatizing attitudes toward affected persons. This component can involve feelings and attitudes of blame, shame, fear, disgust, and prejudice directed at the affected person.

2) Stigmatizing practices and actions toward affected persons. This component can involve avoidance, rejection, and discrimination directed at affected person.

3) Perceived stigma by the affected person. This component can involve fear of what others think or will do because of what they know or suspect about the affected person.

4) Experienced stigma by the affected person. This component can involve actual experiences of rejection, isolation, and discrimination by the affected person.

5) Internalized stigma by the affected person. This component can include feelings of shame, guilt, loss of esteem or dignity, and social isolation or withdrawal by the affected person.

The first two components relate to stigma as it exists in the general population or community. This includes health care workers, which, while members of the general population, are in a unique position to interact with persons that have a potentially stigmatizing health condition, while also having the potential to positively or negatively impact the stigma perception of the patient (Dodor, Kelly et al. 2009). The latter three components relate to the person with the stigmatizing attribute.

As identified by Goffman, stigma can occur with many conditions and characteristics. A recent review of health-related stigma identified leishmaniasis, lymphatic filariasis, Buruli ulcer, onchocerciasis, leprosy, tuberculosis, and HIV/AIDS as communicable diseases that carry a stigma (Van Brakel 2006). Of these, stigma associated with HIV/AIDS has perhaps been the most studied and has contributed significantly to the understanding of health-related stigma. The literature includes both qualitative and quantitative studies, including published scales for measuring HIV/AIDS stigma, and reports of the negative impact it can have on testing, treatment, and risk behavior (Mahajan, Sayles et al. 2008). In contrast to the HIV/AIDS literature, research on TB stigma is less developed.

QUALITATIVE REPORTS OF TUBERCULOSIS STIGMA

Reports of TB stigma come from Asia (Liefooghe, Michiels et al. 1995; Johansson, Diwan et al. 1996; Long, Johansson et al. 1999; Johansson, Long et al. 2000; Ngamvithayapong, Winkvist et al. 2000; Long, Johansson et al. 2001; Ali, Rabbani et al. 2003; Balasubramanian, Garg et al. 2004; Sengupta, Pungrassami et al. 2006; Baral, Karki et al. 2007; Daftary, Padayatchi et al. 2007), Africa (Liefooghe, Baliddawa et al. 1997; Eastwood and Hill 2004; Daftary, Padayatchi et al. 2007), the Americas (Jaramillo 1998; Macq, Solis et al. 2005), Europe (Dimitrova, Balabanova et al. 2006), and among immigrants and minorities (Gibson, Cave et al. 2005; Nnoaham, Pool et al. 2006). These use interviews and focus groups with TB patients, family members, providers, and community members to explore the stigma associated with TB. Some also included patients co-infected with HIV (Ngamvithayapong, Winkvist et al. 2000; Nnoaham, Pool et al. 2006; Sengupta, Pungrassami et al. 2006; Daftary, Padayatchi et al. 2007).

Tuberculosis is reported to have negative social consequences. This includes family members requiring the patient to use separate utensils or eat and sleep in a different room (Long, Johansson et al. 2001) as well as outright avoidance and isolation (Johansson, Diwan et al. 1996; Long, Johansson et al. 2001). In some studies, women stated their husbands might leave them if they were diagnosed with TB, while those who were not married feared their marriage prospects would decrease (Liefooghe, Michiels et al. 1995; Long, Johansson et al. 1999; Long, Johansson et al. 2001; Balasubramanian, Garg et al. 2004). Some TB patients feared losing their jobs (Demissie, Getahun et al. 2003). Occasionally, the negative social consequences of TB continued beyond the period of infectiousness, and in some cases beyond completion of treatment (Liefooghe, Michiels et al. 1995; Long, Johansson et al. 2001). Fear of being isolated or rejected was reported to cause persons with prolonged cough

to try to conceal their disease, withdraw from others, and avoid seeking care for fear of officially being diagnosed as a TB patient (Johansson, Diwan et al. 1996; Johansson, Long et al. 2000; Long, Johansson et al. 2001; Demissie, Getahun et al. 2003).

The reasons for stigmatizing attitudes vary, but generally fall into three categories: inadequate or incorrect knowledge of TB, association of TB with poverty, poor hygiene, or particular behavior among marginalized populations, and association of TB with the occurrence of HIV/AIDS. Some reports identified fear of infection and transmission as sources of stigma (Liefooghe, Baliddawa et al. 1997; Jaramillo 1998). This was compounded by incorrect knowledge about transmission of TB, including being hereditary (Long, Johansson et al. 1999; Balasubramanian, Garg et al. 2004) or from smoking (Eastwood and Hill 2004; Sengupta, Pungrassami et al. 2006). Others reported incorrect knowledge of treatment and curability (Liefooghe, Baliddawa et al. 1997; Johansson, Long et al. 2000; Long, Johansson et al. 2001), including viewing a TB diagnosis as a death sentence. When isolation and rejection were reported to continue beyond the period of infectiousness, it was due to an incorrect knowledge of treatment and curability and therefore a source of stigma, rather than a public health measure (Long, Johansson et al. 2001; Baral, Karki et al. 2007).

Tuberculosis stigma may also exist due to the people, circumstances, or behaviors it is associated with. Some view TB as a dirty disease, and one that is associated with poverty or poor hygiene (Johansson, Diwan et al. 1996; Eastwood and Hill 2004; Dimitrova, Balabanova et al. 2006). Additionally, its association with prostitution (Eastwood and Hill 2004; Baral, Karki et al. 2007), immigration or ethnic minorities (Gibson, Cave et al. 2005), and substance abuse, prison, or unemployment (Dimitrova, Balabanova et al. 2006) means

that stigma associated with these groups is transferred onto TB patients or that the diagnosis makes existing stigma greater.

Finally, there is growing concern that existing TB stigma is compounded and complicated by the role HIV infection plays in the occurrence of TB. While stigma exists with both diseases, it is generally recognized that HIV/AIDS is more stigmatizing due to moral judgments on its mode of transmission (Ngamvithayapong, Winkvist et al. 2000; Sengupta, Pungrassami et al. 2006). In some cases, patients co-infected with TB and HIV prefer to disclose their TB status rather than their HIV status knowing that the social response will be less severe. The effect of HIV on TB stigma appears to occur in two ways. First, symptoms of TB and AIDS are very similar, leading people to think a person has AIDS when they may have TB (Nnoaham, Pool et al. 2006; Sengupta, Pungrassami et al. 2006). Secondly, as the knowledge of the interaction between TB and HIV grows, some feel that a diagnosis of TB means a concurrent diagnosis of HIV (Godfrey-Faussett and Ayles 2003; Nnoaham, Pool et al. 2006). Fear of being dually diagnosed can have a negative impact on patients seeking TB care (Ngamvithayapong, Winkvist et al. 2000; Godfrey-Faussett and Ayles 2003).

QUANTITATIVE MEASURES OF TUBERCULOSIS STIGMA
Background

In contrast to the amount of quantitative data for HIV-related stigma, specifically in the area of stigma measures, there is a paucity of published, quantitative measures and research for TB stigma (Macq, Solis et al. 2006). Attempts to quantify TB stigma have been made and are reported in the literature (Table 2.1). These include both the general

population and patients with TB, and have focused on some of the stigma components within each population. However, few have been developed specifically for TB stigma and subsequently evaluated for validity and reliability of the underlying stigma construct. They therefore provide little additional understanding beyond qualitative findings of what factors contribute to stigma and what the impact of stigma is on TB control.

Before continuing with a review of published TB measures, however, a brief overview of scale development is provided along with general requirements for evaluating a scale provided by DeVellis (DeVellis 1991). Psychometric scales are developed to identify and measure underlying phenomena, called constructs, that are not directly observable. In this case, stigma is the underlying construct of interest. There are two primary concerns with any scale that is developed: validity and reliability. Validity relates to whether or not the underlying construct gives rise to the scale items, and can include content and construct validity. Content validity is the extent to which the items selected for a scale are a valid sample of all possible items that could be included in the scale. While it is impossible to measure content validity, the use of focus groups, interviews, expert review, and relevant literature in the development of scale items will enhance the likelihood that a valid sample of all possible items is used. Construct validity refers to the theoretical relationship between the behavior of the scale and the underlying construct. Construct validity can be assessed two ways. First, factor analysis can identify sets of items that are related and therefore likely to measure the same construct, while excluding items that may be unrelated. Second, the correlation between the scale and other related scales can be measured, with the assumption that related constructs are well correlated. Social support and self-esteem are constructs expected to be inversely correlated with stigma.

Reliability of a scale refers to how much of the variance is attributable to the underlying construct, rather than random error. The primary measure of reliability is Cronbach's alpha, which ranges from zero to one. It is generally accepted that an alpha of at least 0.70 is good to excellent, while an alpha <0.65 is less acceptable (DeVellis 1991; Bland and Altman 1997). Another way to assess reliability is to have participants test and then re-test the scale within a short period of time. A correlation between paired scores suggests that item responses truly measure the underlying construct rather than varying randomly. However, test/re-test results may be invalid if the construct is believed to change over time.

In summary, a well-developed scale should have evidence of content validity, a measure of construct validity, and a measure of reliability. Below is a review of published TB stigma measures (also see Table 2.1).

Review of quantitative measures of tuberculosis stigma

Jenkins (1966) (Jenkins 1966) appears to be the first to measure TB stigma as part of a study to obtain data on beliefs and attitudes towards TB in the United States of America. A probability sample of 436 adults from a large urban city were enrolled, with 76% being White, 12% Latino, and 11% Black. Sixteen items were developed that addressed perceptions and feelings about TB, including susceptibility, prominence, severity, prevention, and social impact. Participants were asked to respond on a continuum ranging from 0 to 20, with higher scores indicating more negative attitudes. Factor analysis of the items was performed by racial group and items were considered to contribute to a specific factor if loadings were > 0.30.

The only stigma-related factor identified occurred among Blacks and was termed "escape from social damage". It contained six items with elements of stigma such as viewing TB as a dirty disease, affecting bad people, and the willingness to give up a portion of income to avoid contracting TB. A seventh item indicating that TB was embarrassing did not meet the factor loading criteria, but loaded more strongly on the "escape from social damage" factor than on any other. No similar factor was identified among Whites or Latinos, and Jenkins concludes that Blacks view TB as "a common disease with social stigma".

Unlike stigma scales developed more recently, the scale identified by Jenkins was not intended to measure stigma specifically. Rather, in the context of understanding broader beliefs about TB, a specific measure of stigma was identified. The measure is relatively rigorous in that it used factor analysis to group related items. However, no measure of reliability (e.g. Cronbach's Alpha) was reported and no summary stigma score for the population is provided.

Westaway (1989) (Westaway 1989) developed a measure of TB stigma as part of a study to obtain information on knowledge, beliefs, and feelings about TB and to evaluate the usefulness of social stigma in understanding TB attitudes in South Africa. A convenience sample of 211 healthy adults was enrolled from urban health clinics. Five items were developed to specifically measure TB stigma, three of which were taken from Jenkins' "escaping from social damage" scale. Participants responded to each item on a three point scale and the responses were summed to create a stigma score. Results indicated that individuals with a family history of TB reported lower stigma than those with no family history. Knowledge of TB including signs and symptoms, cause, transmission, diagnosis, cure, and treatment was not found to be related to stigma.

While this study specifically set out to measure TB stigma and discover how TB knowledge affected stigma, no information is reported on scale characteristics. Given the small number of items, a factor analysis would likely not have been informative. However, no measure of reliability was reported. Additionally, no summary stigma score was reported and it is not clear what statistical methods were used for the analysis.

Jaramillo (1999) (Jaramillo 1999) developed a set of items to measure prejudice towards people with TB as part of a study to learn whether beliefs about TB transmission predict prejudice in Colombia. A random sample of 399 adults was surveyed. A social distance scale consisting of five items was developed to measure prejudice. It included asking about the respondent's ability to kiss, share meals with, have sex with, work/study with, and hug people with TB. Participants responded by indicating strongly disagree, don't know, or strongly agree with each item. A prejudice score ranging of 5 – 15 was created by summing item responses, with lower scores indicating more prejudice. Cronbach's alpha was reported to be 0.70. An additional four items were developed to measure feelings toward people with TB but were not combined in a scale because Cronbach's alpha was unacceptably low (0.50). These included fear, loathing, anger, and sorrow. Respondents indicated very strong, some/don't know, or none to each of the emotions.

Prejudice scores were normally distributed and reported by gender, age group, education level, and socio-economic status, but never collapsed across groups. An overall mean prejudice score of 8.68 was estimated using the assumption of normality within strata and the reported stratum specific scores. Multivariable linear regression with forward selection was used to identify predictors of prejudice. Beliefs about TB transmission (Estimate: 0.25; 95% CI: 0.19, 0.31), fear of persons with TB (0.55; 0.28, 0.82), age (-0.22; -

0.36, -0.08), socio-economic status (0.32; 0.08, 0.56), and educational and health care institutions as sources of TB information (0.62; 0.11, 1.13) were retained as candidate predictors.

The primary criticism of the Jaramillo scale is that prejudice is only one component of stigma (Link and Phelan 2001; Weiss, Ramakrishna et al. 2006), and provides limited insight into TB stigma. Furthermore, the prejudice was measured using social distance and did not incorporate other emotions (e.g. fear, anger) to create a more comprehensive scale.

Godfrey-Faussett et al. (2002) (Godfrey-Faussett, Kaunda et al. 2002) developed a stigma index as part of a study to evaluate the extent and causes of delay among patients with cough seeking health services in Zambia. A convenience sample of 427 patients were surveyed from two urban health clinics. A number of questions were asked to assess how comfortable patients were with different levels of social contact with former TB patients and a relative or spouse who was on treatment. Forms of contact included sharing utensils, working together, marriage, shaking hands, and sharing a bed. Participants were also asked if undergoing a TB test would make others think a person also has AIDS. A summary indicator was created ranging from 1 – 15, with no stigma defined as scores 1 – 4, moderate stigma as scores 5 – 8, and high stigma as scores 9 – 15. It was not clear how many questions were used, what the response options were, and no measure of reliability was reported.

Stigma scores were normally distributed, but no mean score was reported. Based on the frequency distribution provided, an estimated mean score of 6.15 was calculated. Using the categories defined in the study, 45% of patients had moderate stigma, while 23% had high stigma. Chi-square analysis indicated that poor knowledge (p=0.004) and gender

(p=0.019) were associated with stigma, but no further information was provided. Godfrey-Faussett and colleagues found no association between stigma and delay in seeking care for cough (see review of TB stigma and delay below).

While great effort was made to develop a comprehensive measure of stigma, no information on the development process or index itself were reported. This makes critiquing the index difficult and hinders interpretation of the results. This is unfortunate, because the authors report that a substantial proportion of participants held stigmatizing attitudes on many of the items, including that 49% felt that undergoing TB testing could indicate to others the presence of AIDS.

Mak et al. (2006) (Mak, Mo et al. 2006) developed a stigma scale for the purpose of comparing TB, HIV/AIDS, and SARS stigma in Hong Kong. Random digit dialing was used to survey 3,011 adults, administering one of the scales to each participant so that each scale had approximately 1,000 respondents. Fourteen items were developed to measure stigma based on focus groups and exiting measures of psychiatric stigma. Items addressed affective (patients are revolting), behavioral (keeping a distance from patients), and cognitive (patients are a burden to society) aspects of stigma. Participants responded on a six point scale ranging from strongly disagree to strongly agree. A summary score ranging from 1 – 6 was created by taking the average response for all items, with higher scores indicating higher stigma. Scale items for each disease were identical, and Cronbach's alpha of 0.85, 0.83, and 0.81 was calculated for the HIV/AIDS, TB, and SARS scales, respectively.

The mean TB stigma score was 1.94, ranking lower than AIDS stigma but higher than SARS stigma. Bivariate analysis indicated that higher stigma was not correlated with knowledge about transmission, symptoms, and treatment (r=0.03).

The scale by Mak and colleagues is a well developed scale with good reliability. It incorporates multiple dimensions of stigma, including affective, behavioral, and cognitive aspects. It is further strengthened by the accompanying parallel scale for AIDS stigma.

World Health Organization Regional Office of the Eastern Mediterranean (WHO/ROEM) (2006) (WHO/ROEM 2006) developed a stigma scale as part of a study to evaluate TB diagnostic and treatment delay and to identify their determinants in seven Eastern Mediterranean countries. A total of 5,053 patients with TB were enrolled as a convenience sample from TB clinics in specific regions of Pakistan (844), Iraq (400), and Somalia (809), and from nationwide random samples in Iran (800), Egypt (802), Syrian Arab Republic (800), and Yemen (598). Fifteen items were developed that addressed social interaction, family and work responsibilities, a woman's ability to decide on treatment, cost, and incorrect beliefs about the effect of TB on female reproductive outcomes and breastfeeding. Participants responded on a five point scale ranging from strongly agree to strongly disagree, with lower scores indicating higher stigma. To create a summary score, items were re-coded so that higher scores indicated higher stigma, then transformed to reflect the percent of the total possible score, ranging from 0 to 100%. Prior to translation into local languages, the scale was pilot tested to assess content validity (expert review) and test/re-test reliability (results not provided). Cronbach's alpha was calculated and found to be acceptable, but no value was reported.

Mean stigma scores were reported by gender, but not collapsed across gender. An overall score was estimated using the assumption of normality within both strata and the reported scores. Mean scores ranged from a low of 50 in Egypt to a high of 71 in Iran.

While considerable effort was made to develop, administer, and evaluate TB stigma in the Eastern Mediterranean region, the scale suffers from two major limitations. First, it could be argued that five of the 15 items are not appropriate for measuring stigma. These include the perceived cost of TB treatment, and the four items addressing incorrect beliefs about the effect of TB on female reproductive outcomes and breastfeeding. While it is possible that poor TB knowledge can lead to higher stigma, poor TB knowledge itself should not be confused or mixed with stigma. Second, the reliability of the scale was assessed prior to its translation into the appropriate languages. It is likely (see Woith and Larson below) that some reliability would be lost after translation. It would have been more informative to calculate and report Cronbach's alphas for the scales actually used in each country.

Macq et al. (2008) developed a stigma scale for the purpose of evaluating an intervention aimed at reducing stigma and increasing treatment outcomes among patients with TB in Nicaragua. A convenience sample of 268 new smear positive TB patients were enrolled from government health centers. Ten items were developed to measure internalized stigma based on a scale used for mental illness. The scale consists of four sub-dimensions that include alienation, perceived discrimination, stereotype endorsement, and social withdrawal. Participants responded on a five point scale ranging from completely disagree to completely agree. A summary score ranging from 10 – 50 was calculated by summing each item response. Chronbach's alpha for the scale was 0.70.

Mean stigma scores were 33.3 and decreased to 30.5 after two months of treatment. The decrease in stigma was greater among patients in the intervention group than those in the control group (p=0.03).

The scale by Macq and colleagues appears to be a good scale with acceptable reliability. It is short and focuses on the experiences of patients with TB and may be more general than just internalized stigma. While the authors mention four sub-dimensions, there was no indication that factor analysis was used to select and group items, and it does not appear that the scale should be administered as four separate scales.

Somma et al. (2008) (Somma, Thomas et al. 2008) developed a stigma scale for the purpose of quantifying the presence of stigma and identifying its socio-cultural determinants, with particular interest in the role of gender as an effect (measure) modifier, in Bangladesh, India, Malawi, and Colombia. A convenience sample of 100 patients from each country undergoing TB treatment were enrolled from health clinics or by community health volunteers. Eighteen items were developed to measure stigma based on local information and previous studies. Items covered aspects of disclosure, shame, social isolation, relations with others, and marriage. Participants responded on a four point scale comprised of no, uncertain, possibly, and yes. A summary score ranging from 0 – 3 was created by taking the average response for all items with higher scores indicating higher stigma. Cronbach's alpha for each scale were 0.85 (India), 0.77 (Bangladesh), 0.65 (Malawi), and 0.63 (Colombia).

Mean stigma scores ranged from 0.85 (Malawi) to 1.17 (India), although scores were not normally distributed. Only in Bangladesh did stigma scores differ between men (0.88) and women (1.12). Multivariable linear regression with normalized stigma scores was performed to identify predictors of stigma. Separate models were built for Bangladesh, India, and Malawi (data not available for Colombia) using forward selection with an entry p-value <0.15. Interactions between gender and each of the explanatory variables were considered. A large number of statistically significant predictors were reported. For

simplicity, only those with associated with increased stigma that had estimates ≥0.20 are presented here: female gender, never married, unskilled labor (women only), social isolation, reduced social status, loss of job and wages (women only), reduced income, physical exertion as a perceived cause, sexual contact as a perceived cause (men only), and seeking care at a private hospital (women only). Similarly, the following characteristics were associated with decreased stigma (estimates ≤-0.20): unskilled labor (men only), trade or business employment, 10 year increase in age, fever, and the climate as a perceived cause. The strongest predictors were being female in Bangladesh (Estimate: 1.07), perceiving the climate to be a cause of TB in India (-0.93), and unskilled labor employment (-0.93) and perceiving sexual contact to be a cause (0.88) in Malawi.

The scale by Somma and colleagues is a well developed scale with good reliability in India and Bangladesh and moderate reliability in Malawi and Colombia. The reported results, however, are nearly impossible to interpret. First, no information is provided about how the scores were normalized. Therefore the estimates indicate the unit increase in the mean score from an unknown transformation. Secondly, only p-values, not standard errors or confidence intervals, are reported for the estimates, making any assessment of precision impossible. Finally, estimates and p-values for the interaction term between gender and explanatory variables are provided, but not for the estimate (and p-value) within strata of men and women. Therefore, stratified results could be misinterpreted as important when the linear combination of main effect and interaction term is, in fact, approximately zero. Because the models were built using different sets of predictor variables, any comparison of the effect of determinants across countries is impossible.

Woith and Larson (2008) (Woith and Larson 2008) used the Social Impact Scale, initially developed in the United States to measure stigma associated with HIV/AIDS and cancer (Fife and Wright 2000), as part of a study to asses the effect of TB stigma on delays in seeking care and treatment adherence in Russia. This was the only study to use a previously developed stigma scale. A convenience sample of 105 patients with TB receiving treatment were enrolled from two outpatient clinics. The Social Impact Scale is a well-developed scale that enhanced content validity by obtaining input from clinical experts and patients with HIV on each item. Construct validity was assessed by factor analysis on the selected items and measuring the correlation with related scales including self-esteem, body image, and personal control. The final scale consisted of 24 items and four subscales measuring social rejection (9 items), financial insecurity (3 items), internalized shame (5 items), and social isolation (7 items). Reliability of the original scale was good with Cronbach's alphas for each scale ranging from 0.85 to 0.90. Participants respond to each item using a four point scale ranging from strongly disagree to strongly agree. A summary score for each subscale was created by summing the item responses, with higher scores indicating higher stigma. Upon translating the scale into Russian, the reliability of the subscales decreased, with Cronbach's alphas between 0.70 and 0.84 for three subscales and 0.50 for internalized shame.

Stigma scores for each subscale were normally distributed. For purposes of reporting here, mean scores were divided by the number of items in the subscale to create a standardized score with a range of 1 – 4. This facilitates comparison of scores across scales. Mean scores for each subscale were, 2.24 (social rejection), 2.62 (financial insecurity), 2.62 (internalized shame), and 2.32 (social isolation). Woith and Larson did not find an association between stigma and delay (see section on TB stigma and delay below), but did

report that higher financial insecurity was associated with lower adherence, while higher internalized shame was associated with higher adherence (see section on TB stigma and adherence below).

Woith and Larson chose a well-developed stigma scale to measure TB stigma. It appears, however, that the combination of changing the disease under investigation and translation to a different language decreased the reliability and validity. The authors did not provide any information about whether or not the concept of stigma among Russians was similar to that measured by the original scale.

Summary of tuberculosis stigma measures

All measures reviewed here included at least one assessment of content validity, construct validity, or reliability. However, none performed all three. One scale was adapted from a well-developed scale for AIDS stigma, but was not fully assessed for its usefulness in measuring TB stigma. The scales developed by Mak et al. and Somma et al. were the most comprehensive, developed specifically for TB. These were informed from the published literature and local research and had good to acceptable reliability. They found low levels of stigma among the general population and patients with TB.

Among those that included some analysis of what factors are associated with stigma, those that reported results for age and gender found associations with stigma. The role of TB knowledge was mixed, with two studies reporting knowledge is not associated with stigma while three found some form of poor or incorrect knowledge associated with stigma.

In conclusion, there remains a need for well-developed measures of TB stigma that address the complex nature of stigma. As these measures are developed, they need to be assessed for their usefulness across populations and cultures.

Table 2.1. Summary characteristics for published measures of tuberculosis stigma.

First author	Year	Country	Population	Measured factors	No. of items	Scale development
Jenkins	1966	United States	General population	• Escape from social damage	6	Performed factor analysis
Westaway	1989	South Africa	General population	• Social stigma	5	Adapted from Jenkins; No assessment of validity or reliability
Jaramillo	1999	Columbia	General population	• Avoidance of persons with TB	5	No assessment of validity; Chronbach alpha for subscales was 0.70, 0.50, respectively
Godfrey-Faussett	2002	Zambia	Individuals with cough	• Social contact	?	No assessment of validity or reliability
Mak	2006	Hong Kong	General population	• Social stigma	14	Item selection informed from published literature and focus groups; Chronbach alpha was 0.83
WHO/ROEM	2006	7 Eastern Mediterranean countries	TB patients	• Social stigma	15	Assessed content validity, test/re-test reliability, and Cronbach's alpha prior to translation
Macq	2008	Nicaragua	TB patients	• Internalized stigma	10	Assessed content validity; Chronbach alpha was 0.70
Somma	2008	Bangladesh, India, Malawi, Colobmia	TB patients	• Social stigma	18	Item selection informed from local interviews a published literature; Cronbach's alpha for each country was 0.77, 0.85, 0.65, and 0.63, respectively
Woith and Larson	2008	Russia	TB patients	• Social rejection • Financial insecurity • Internalized shame • Social isolation	24	Social Impact Scale developed by Fife and Wright(Fife and Wright 2000); Chronbach alpha for subscales was 0.50 to 0.84

TUBERCULOSIS STIGMA AND DELAY IN SEEKING CARE FOR TUBERCULOSIS SYMPTOMS

Background

A common path to TB diagnosis begins with self-medication using home remedies or medication bought at the local pharmacy (Liefooghe, Baliddawa et al. 1997; Jaramillo 1998; Sanou, Dembele et al. 2004). If symptoms persist, patients may consult a traditional healer or visit the village or community doctor. In both cases, a correct diagnosis is rarely made. Only when symptoms persist or become more severe, will the individual seek care at a health facility that has the capability of diagnosing TB (Liefooghe, Baliddawa et al. 1997; Watkins and Plant 2004). Even then a diagnosis may not be made immediately.

Studies on health seeking behavior and diagnostic and treatment delays in the TB literature typically distinguish between patient delay and health system delay. Patient delay refers to the time it takes for an individual to present at a health facility after the onset of TB symptoms. Health system delay refers to the time it takes health providers to diagnose and prescribe treatment once the patient has presented with symptoms. The sum of both delay times equals the total time from symptom onset to treatment initiation. The WHO recommends that individuals with a cough for three weeks or more undergo examination for TB (WHO 2004). Therefore, a patient delay time of up to three weeks may be acceptable programmatically. Nevertheless, any delay can increase morbidity and mortality for the patient and result in an increased number of infections in the community (Madebo and Lindtjorn 1999; Barker, Millard et al. 2006; Golub, Bur et al. 2006; Lin, Chongsuvivatwong et al. 2008). In actuality, the amount of time it takes patients to seek care varies greatly. A study in Tanzania found a median delay of 120 days (17.1 weeks) (Wandwalo and Morkve

2000; Wandwalo, Kapalata et al. 2004) while another found a median delay of 2 days (0.3 weeks) in The Gambia (Lienhardt, Rowley et al. 2001).

There is a large body of quantitative literature on factors associated with delay in seeking care for TB symptoms. A recent review of the literature grouped these factors into access to care, personal characteristics, socioeconomic, clinical, TB knowledge or beliefs, and social support or psychosocial factors (Storla, Yimer et al. 2008). However, it is difficult to draw definitive conclusions about the role of many of these factors because different definitions of delay are used and there are variations in analytic methodologies. Regardless, stigma remains one of the factors that has received little attention.

In qualitative studies, decisions to seek care appear to be guided by fear of being ostracized or isolated due to the potential TB diagnosis. Women in particular were found to conceal their symptoms to avoid seeking a diagnosis (Johansson, Long et al. 2000). Patients also mentioned the similarity in symptoms between TB and AIDS as a concern (Ngamvithayapong, Winkvist et al. 2000; Nnoaham, Pool et al. 2006). Thus, a person with cough, weakness, and weight loss may avoid seeking care because he or she fears being diagnosed with AIDS, rather than TB. Other participants feared being labeled as having AIDS when only TB had been diagnosed (Godfrey-Faussett, Kaunda et al. 2002). Knowledge of the link between TB and HIV means that a diagnosis of TB is a reason to suspect AIDS in the eyes of family members and the community. Thus, fear of social consequences such being labeled as dirty, dangerous, being rejected by family or the community, losing marriage prospects, or being labeled as an AIDS patient (thus inheriting any existing AIDS stigma), can all be expressions of TB stigma. In spite of these concerns

about the role of TB or AIDS stigma in delays in seeking care for TB symptoms, few studies have quantified the association between stigma and delay (Table 2.2 and below).

Review of quantitative studies of tuberculosis stigma and delay

Auer et al. (2000) (Auer, Sarol et al. 2000) performed a retrospective study of patients with TB in the Philippines to explore how illness experience, perceived causes, and health care experiences affect health seeking behavior. Patients were eligible if they had completed treatment for pulmonary TB. Of 812 eligible patients, 319 (39%) were successfully contacted and interviewed. Delay was defined as >4 weeks between symptom onset and first visit to a health care facility. All patients were interviewed using an extensive questionnaire. While no formal measure of stigma was used, the questionnaire did include questions about the emotional impact of TB including guilt, embarrassment, loss of self-esteem, and feeling ostracized. The Chi-square test was used to analyze the association between each emotion and delay. The authors state that no association was found between guilt, embarrassment, and self-esteem, but no data are provided. Feeling ostracized was associated with delay and an odds ratio could be estimated from the data provided. The crude odds ratio for the association between feeling ostracized and delay in seeking care was 1.69 (95% CI: 0.97, 2.96).

This study was performed prior to the implementation of standardized, directly observed therapy and is therefore not comparable to more recent studies. Less than half of eligible patients were identified, potentially causing selection bias. No attempt was made to control for confounding, and data were only reported for statistically significant results, leaving the magnitude and precision of the crude effects for other emotions unknown.

Godfrey-Faussett et al. (2002) (Godfrey-Faussett, Kaunda et al. 2002) performed a study to identify determinants of delay among patients seeking care for cough at government health services in Zambia. Patients were eligible if they were >15 years old and presented with a cough that had not been previously assessed in a health center. A convenience sample of 427 patients was interviewed from two health clinics. Delay was defined as the time between onset of cough and presentation to that clinic. Data were collected on demographics, socio-economic status, access to the clinic, illness severity, TB knowledge, and TB stigma (see section on measures of TB stigma above). For purposes of analysis, delay was dichotomized as >4 weeks and ≤4 weeks and stigma was categorized as none, moderate, and high. The Chi-square test was used to test for associations between potential determinants and delay, and multivariable logistic regression was used to adjust for factors statistically significant in the bivariate analysis. Delay >4 weeks occurred among 35% of patients. The authors only report the Chi-square p-value for stigma and delay but provide enough data to calculate an odds ratio. The crude odds ratios for high and moderate stigma versus no stigma were 0.86 (95% CI: 0.50, 1.49) and 1.04 (95% CI: 0.66, 1.64), respectively. Stigma was not included in the multivariable model.

The study by Godrey-Faussett and colleagues suffers from less selection bias than other delay studies because it included all patients seeking care for a cough, not just patients with TB. TB stigma is expected to affect everyone developing a prolonged cough and deciding when to receive care, regardless of whether or not TB is ultimately diagnosed. Additionally, great effort was made to develop a stigma index, but it measured degrees of social contact, which is only one component of stigma. It is possible that considerable loss of information occurred due to categorizing both stigma and delay, when they were initially

measured as continuous variables. However, dichotomizing delay at 4 weeks is both common and reasonable given TB policy.

Yimer et al. (2005) (Yimer, Bjune et al. 2005) performed a study to analyze factors affecting delay in seeking care at government health institutions among patients with TB in Ethiopia. Patients were eligible if they were >15 years and had newly diagnosed, smear positive, pulmonary TB. A convenience sample of 384 patients was enrolled from 20 TB management units immediately after diagnosis. Delay was defined as the time from symptom onset to the first visit at a qualified medical provider. Data were collected on socio-demographics, symptoms, TB knowledge, and TB stigma. No information is provided on how stigma was measured. Delay was dichotomized as >31 days and ≤30 days, and stigma was dichotomized as high and low. Crude and adjusted odds ratios were used to assess the association between potential determinants and delay. Median delay time was 30 days. The crude odds ratio for high versus low stigma was 0.87 (95% CI: 0.57, 1.33). When all covariates were included in the model, the adjusted odds ratio was 0.88 (95% CI: 0.54, 1.45).

The major criticism of the study by Yimer and colleagues is that no information was provided on the measurement of stigma. This makes interpretation of the stigma result impossible. Additionally, it is possible that considerable loss of information occurred due to categorizing both stigma and delay, which were initially measured as continuous variables. However, dichotomizing delay at 4 weeks is both common and reasonable given TB policy.

Cambanis et al. (2005, 2007) performed two studies to explore reasons for late presentation to health services in rural Ethiopia (Cambanis, Yassin et al. 2005) and rural Cameroon (Cambanis, Ramsay et al. 2007). Study methodologies were identical for the two

locations. Patients of all ages were eligible if they had been referred to the health center due to suspicion of pulmonary TB. A convenience sample of 243 patients was interviewed. Delay was defined as the time from symptom onset to first health consultation. Information was collected on demographics, socio-economic status, access to care, symptoms, TB knowledge, and whether or not TB was perceived as stigmatizing. No information was provided on how stigma was measured. Delay was dichotomized as > 4 weeks and ≤ 4 weeks, and stigma appears to be dichotomized as yes and no. Crude and adjusted odds ratios were used to assess the association between potential determinants and delay. Variables with $p<0.20$ on bivariate analysis were selected for multivariable logistic regression followed by backwards elimination to retain all variables with $p<0.05$. Median delay time in Ethiopia was 4.3 weeks with a crude odds ratio for perceiving TB as stigmatizing of 1.46 (95% CI: 0.8, 2.5). Median delay time in Cameroon was 2.0 weeks with a crude odds ratio for TB stigma of 2.50 (95% CI: 1.0, 6.1). Stigma was not retained in either of the multivariable models.

The major criticism of the studies by Cambanis and colleagues is that no information is provided on the measurement of stigma. This makes interpretation of the stigma result impossible as well as uninformative if perceived stigma was asked as a yes/no question. Additionally, it is possible that considerable loss of information occurred due to categorizing delay, which was initially measured as a continuous variable. However, dichotomizing delay at 4 weeks is both common and reasonable given TB policy.

WHO/ROEM (2006) (WHO/ROEM 2006) performed a study to identify determinants of delay in diagnosis and treatment among patients with TB in seven eastern Mediterranean countries. Patients with TB were eligible if they were ≥15 years old, had

smear positive pulmonary TB, and had been on treatment less than two weeks. A total of 5,053 patients were enrolled as a convenience sample from TB clinics in specific regions of Pakistan (844), Iraq (400), and Somalia (809), and from nationwide random samples in Iran (800), Egypt (802), Syrian Arab Republic (800), and Yemen (598). Delay was defined as time from symptom onset to first health care provider visit. A comprehensive questionnaire was administered that collected information on socio-demographic characteristics, risk factors for TB, health seeking behavior, TB knowledge, quality of care, and TB stigma (see section on measures of TB stigma above). Delay was dichotomized at the median value for each country, and it was unclear whether stigma was analyzed as a continuous variable or dichotomized at a median value or other cut-point. Supplemental results from Somalia (Maamari 2008) indicated that stigma was dichotomized as high (0-2 from the original response coding) and low (3-4). Multivariable logistic regression with all covariates was performed in each country except for Iran (linear regression) and Iraq (bivariate analysis only). Median delay ranged from 9 days in Pakistan to 53 days in Somalia. In Somalia, the crude odds ratio for stigma and delay was 1.49 (0.77, 2.86), which decreased to 1.06 (0.92, 1.23) in the multivariable analysis. All but one of the countries in the WHO/ROEM report had stigma results that were statistically not significant, but no results were provided. Only the Syrian Arab Republic had a statistically significant finding, with an adjusted odds ratio of 0.64 (0.51, 0.82).

It is difficult to draw conclusions from the WHO/ROEM study about the role of stigma in delays in seeking care, primarily because few of the results are provided. For many of the countries, the analyses found that the association between stigma and total delay (combination of patient delay and health services delay) was statistically significant, and

these are the results that are provided. These are likely not valid, however, because stigma reported by the patient is unlikely to have any affect on how the health system performs its duties. In addition to the questionable validity and reliability of the stigma scale (see the section on measures of TB stigma above), three covariates were used in the analysis that could bias the results. These include the first health seeking behavior, first health facility consulted, and the health facility that made the initial diagnosis. Each of these variables is likely affected by stigma, in addition to having an effect on the delay time. Therefore, the multivariable analysis from the WHO study adjusted for variables that were causal intermediates between stigma and delay, rather than confounders.

Woith and Larson (2008) (Woith and Larson 2008) performed a study of delay in seeking treatment and adherence to treatment (see section on TB stigma and adherence below) among patients with pulmonary TB in Russia. Quantitative measures of illness representation and TB stigma (see section on measures of TB stigma above) were the predictors of interest. Patients were eligible if they were ≥18 years old, diagnosed with pulmonary TB, and had completed at least three months of treatment. A total of 105 patients were enrolled from two outpatient clinics. Delay was defined as the time from symptom onset to the first physician visit. Patients selected one of 14, four-week time frames ranging from <4 weeks to >52 weeks. Patients also responded to the TB stigma scale, which captured four components of stigma: social rejection, financial insecurity, internalized shame, and social isolation. Delay times and stigma scores were both analyzed as continuous variables using multivariable linear regression that also included illness representation scores but no other covariates. Fifty-two percent of patients had a delay time <4 weeks. Stigma was not found to be associated with delay, and no results were provided.

While this is the only study to examine stigma as the primary exposure of interest, it suffers from many methodologic issues. First, delay time was not well measured. Patients had already been on treatment for three months when they were asked to recall the duration of their symptoms and the duration was recorded in four week intervals, rather than a more precise interval such as weeks or days. Second, the linear regression model assumes the outcome is normally distributed, whereas the distribution of delay is reported to be highly skewed with 52% of patients having delay times in the lowest category (<4 weeks). Additionally, the authors report the distribution of demographic and substance use data, but none of these are included as confounders in the analysis. Finally, only parameter estimates for the statistically significant predictors are reported, leaving unknown the magnitude and precision of the crude stigma effects. These issues, along with the poor reliability of the translated internalized shame scale (Cronbach's alpha = 0.50), indicate that the study was not appropriate for determining whether or not TB stigma has any effect on patient delay times.

Summary of tuberculosis stigma and delay

Only seven studies were found that quantified the association between TB stigma and delay in seeking care for symptoms. The study populations differed between each study and there was some variation the definition and categorization of delay. Most studies, however, dichotomized delay at approximately one month. With the exception of Woith and Larson, each study suffers from two major limitations. Either stigma was not the primary exposure of interest so appropriate analyses were not performed, or stigma was not measured using a formally developed scale. The study by Woith and Larson suffers from other methodologic

limitations, primarily in the poor reliability of the internalized shame subscale, and the use of highly skewed delay data in their linear regression model.

In addition to these methodologic issues, it is difficult to summarize the effects of stigma due to publication bias. Results from Woith and Larson and five countries in the WHO/ROEM study were not statistically significant and the authors chose not to present the results. In light of these limitations, the crude odds ratio for the association between stigma and delay >4 weeks from the six studies reporting the results ranged from 0.86 to 2.50 (Table 2.2). While these results are likely biased away from the null, the direction of effect suggests that increased stigma is associated with longer delay. There remains a need for more rigorous research to quantify the effects of TB stigma on delays in seeking care for TB symptoms.

Table 2.2. Summary of quantitative studies on TB stigma and delays in seeking care.

Study	Year	Location	Study pop.	Study size	Median delay	Delay category	Stigma definition	Stigma category	Crude OR (95% CI)*	Adjusted OR (95% CI)
Auer	2000	Philippines	Previously treated PTB	319	Not stated	>4 wks; ≤4 wks	Feeling ostracized	Yes; No	1.69 (0.97, 2.96)	
Godfrey-Faussett	2002	Zambia	Patients with cough	427	2 wks	>4 wks; ≤4 wks	Social contact index	High; Moderate; None	Moderate: 0.86 (0.50, 1.49) High: 1.04 (0.66, 1.64)	
Yimer	2005	Ethiopia	Sm+ PTB	384	30 days	>31 days; ≤30 days	Not reported	High; Low	0.87 (0.57, 1.33)	0.88 (0.54, 1.45)
Cambanis	2005	Ethiopia	TB suspect	243	4.3 wks	>4 wks; ≤4 wks	Perceived as stigmatizing	Yes; No	1.46 (0.8, 2.5)	
Cambanis	2007	Cameroon	TB suspect	243	2.0 wks	>4 wks; ≤4 wks	Perceived as stigmatizing	Yes; No	2.50 (1.0, 6.1)	
WHO	2006	Syrian Arab Republic	Sm+ PTB	800	31 days	>31 days; ≤31 days	Stigma scale	High; Low	1.49 (0.77, 2.86)	1.06 (0.92, 1.23)
		Somalia	Sm+ PTB	809	53 days	>53 days; ≤53 days	Stigma scale	Unclear		0.64 (0.51, 0.82)
		Egypt	Sm+ PTB	802	12 days	>12 days; ≤12 days	Stigma scale	Unclear	Stigma was not statistically significant in the logistic regression analysis; results not presented	
		Iraq	Sm+ PTB	400	31 days	>31 days; ≤31 days	Stigma scale	Unclear		
		Pakistan	Sm+ PTB	844	9 days	>9 days; ≤9 days	Stigma scale	Unclear		
		Yemen	Sm+ PTB	598	28 days	>28 days; ≤28 days	Stigma scale	Unclear		
		Iran	Sm+ PTB	800	24 days	Continuous	Stigma scale	Unclear	Stigma not statistically significant in the *linear regression* analysis; results not presented.	
Woith and Larson	2008	Russia	On treatment for PTB	105	<4 wks	Continuous 4 wk categories	Social Impact Scale	Continuous	Stigma not statistically significant in the *linear regression* analysis; results not presented.	

*OR results from Auer and Godfrey-Faussett estimated from data reported in text. Authors reported Chi-square statistic.

TUBERCULOSIS STIGMA AND ADHERENCE TO TUBERCULOSIS TREATMENT

Background

Adherence to the full course of TB treatment is essential for achieving complete cure and reducing the development of drug resistant TB (Frieden, Sterling et al. 2003). Non-adherence, and not just default, can lead to persistent infectiousness, treatment failure, disease relapse, drug resistance, or death (Chaulk and Kazandjian 1998; Gelmanova, Keshavjee et al. 2007). The development of standardized short course therapy, usually six to eight months, and implementation of directly observed therapy have greatly improved adherence. Typically, patients take four anti-TB drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) either three or seven days a week for two months (WHO 2003). This is referred to as the intensive phase of treatment. It may be extended to a third month if the patient remains smear positive after the initial two months of treatment. This is followed by a regimen of isoniazid and rifampicin taken three, or seven days a week for four to six months. This is referred to as the continuation phase of treatment.

Defaulting from treatment is the most extreme form of non-adherence and is defined by the WHO as two or more consecutive months without treatment (WHO 2003). Default is a common definition of non-adherence because it is a standard treatment outcome recorded in patient records. However, it is not the only form of non-adherence. A recent study found that adherence to less than 80% of the prescribed treatment is associated with poor outcomes including treatment failure, death, or subsequent default (Gelmanova, Keshavjee et al. 2007). Thus, efforts to improve any level of non-adherence will likely improve treatment success and patient outcomes.

A number of barriers to full adherence have been reported. In a recent review of qualitative studies, Munro et al. (Munro, Lewin et al. 2007) identified eight major factors affecting adherence to TB treatment: Organization of treatment and care, including access to care; interpretation of illness and wellness; financial burden; knowledge, attitudes, and beliefs about treatment; law and immigration; personal characteristics; side effects; and family, community, and household influence. These factors have been generally supported through quantitative studies which report that longer distances to the health center (Shargie and Lindtjorn 2007), type of transportation (Shargie and Lindtjorn 2007), travel cost (Mishra, Hansen et al. 2005), perceived health status as good (Lertmaharit, Kamol-Ratankul et al. 2005), HIV infection (Connolly, Davies et al. 1999), young and old age (Connolly, Davies et al. 1999; Santha, Garg et al. 2002; Shargie and Lindtjorn 2007), male gender (Connolly, Davies et al. 1999; Santha, Garg et al. 2002; Lertmaharit, Kamol-Ratankul et al. 2005), low income (Mishra, Hansen et al. 2005), employment (Mishra, Hansen et al. 2005; Hasker, Khodjikhanov et al. 2008), and alcohol or drug use (Santha, Garg et al. 2002; Cayla, Caminero et al. 2004; Gelmanova, Keshavjee et al. 2007; Hasker, Khodjikhanov et al. 2008) were associated with default. As with the studies on delay in seeking care for TB symptoms, it is difficult to draw definitive conclusions about the role of many of these factors because different definitions of adherence are used, there are variations in analytic methodologies, and variation in the designation of directly observed therapy and the overall treatment regimen.

The presence of stigma was identified in half of the qualitative studies and included patients trying to hide their diagnosis from family, friends, or employers. More specifically, stigma may adversely affect adherence because patients do not want others to find out they

have the disease, much the same as when patients delay seeking care in order to avoid being labeled as a TB patient. Patients reported the strain of trying to keeping their disease secret from others (Liefooghe, Michiels et al. 1995; Nair, George et al. 1997), and not complying with treatment visits helped remove some of the suffering because they would no longer be seen going to the clinic (Mata 1985; Barnhoorn and Adriaanse 1992; Johansson, Long et al. 1999; Dimitrova, Balabanova et al. 2006). In other cases, fear of transmission and social consequences led to social isolation at home, rather than being encouraged to seek and continue treatment (Demissie, Getahun et al. 2003). And some patients reported fear that their employer would know of their disease (Johansson, Diwan et al. 1996). In contrast to stigma, family support was overwhelmingly noted as helping patients remain adherent (Munro, Lewin et al. 2007).

Only two studies have quantified the association between TB stigma and adherence to TB treatment.

Review of quantitative studies of tuberculosis stigma and adherence

Comolet et al. (1998) (Comolet, Rakotomalala et al. 1998) performed a case-control study of demographic, knowledge, attitude, and psycho-social factors associated with default from treatment in Madagascar. Patients were eligible if they had pulmonary TB and had either completed treatment or been lost to follow-up. Default was defined as missing more than a month of treatment during the prescribed period. Controls were patients who completed treatment without interruption. Because none of the patients were currently receiving treatment, all eligible participants had to be traced, contacted, and interviewed. Only 38 (40%) of 95 eligible defaulters were traced and interviewed, while 111 (75%) of 150

eligible completers were interviewed. All patients were interviewed using an extensive

questionnaire. While no formal measure of stigma was used, the questionnaire did include

the statement "Felt that TB was a shameful disease". Odds ratios and the Chi-square test was

used to analyze the association between each factor of interest and default. The crude odds

ratio for feeling that TB was shameful and default was 2.97 (95% CI: 1.26, 6.99).

This study was performed prior to the implementation of standardized, directly

observed therapy and is therefore not comparable to more recent studies. Additionally, less

than half of eligible defaulters were included in the study. Selection bias could have been

introduced if feeling shame was related to why they could not be contacted. The authors do

state that bias may have been introduced if defaulters felt shame due to defaulting rather than

from having the disease.

Woith and Larson (2008) (Woith and Larson 2008) performed a study of delays in

seeking treatment (see section on TB stigma and delay) and adherence to treatment among

patients with pulmonary TB in Russia. Quantitative measures of illness representation and

TB stigma (see section on measures of TB stigma) were the predictors of interest. Patients

were eligible if they were ≥18 years old, diagnosed with pulmonary TB, had completed the

intensive phase of treatment, and had received at least four weeks of continuation phase

treatment. A total of 105 patients were enrolled from two outpatient clinics. Adherence was

defined as the proportion of doses taken out of the total doses prescribed from beginning of

the continuation phase until the interview time. Data were collected from the patients'

medical records. Patients also responded to the TB stigma scale, which captured four

components of stigma: social rejection, financial insecurity, internalized shame, and social

isolation. Adherence and stigma scores were both analyzed as continuous variables using

multivariable linear regression that also included illness representation scores but no other covariates. Adherence was highly skewed with 54% of patients having 100% adherence. Financial insecurity was associated with a 2.78 (95% CI: -5.09, -0.47) point decrease in adherence, while internalized shame was associated with a 2.49 (95% CI: 0.51, 4.47) point *increase* in adherence.

This is the only study of adherence where stigma is the primary exposure of interest. However, caution should be taken when interpreting these results for the same reasons mentioned above in their analysis of delay, namely concerns with scale reliability, violation of the assumption of normality in the adherence distribution, lack of covariates to adjust for confounding, and uncertainty of the magnitude and precision of the stigma effects. Therefore, while the results are intriguing, particularly for internalized shame, the methodologic issues suggest that conclusions about the effect of stigma on adherence cannot be made.

Summary of tuberculosis stigma and adherence

Only two studies assessed the quantitative association between stigma and adherence to treatment. One found stigma to be associated with defaulting from treatment, but suffered from poor participant recruitment and potential selection bias. It also was performed in a setting where current recommendations on directly observed therapy had not been implemented. The other found that increased financial insecurity was associated with poor adherence, but that increased shame was associated with better adherence. This study, however, suffered from many limitations including poor reliability of the shame

measurement and violation of linear regression normality assumptions. Conclusions on the effect of stigma on adherence cannot be made based on current literature.

SUMMARY OF LITERATURE REVIEW

Numerous reports suggest that TB is a stigmatizing disease and that it has an effect on patients seeking care and adherence to treatment. Nevertheless, there are very few published measures of TB stigma that can quantify the presence and effect stigma, as well as identify determinants of stigma suitable for intervention. Some measures have been recently published that are well-developed. These indicate relatively low levels of stigma in the study populations and offer conflicting results about determinants of stigma.

There are very few studies that have quantified the association between TB stigma and delay in seeking care for symptoms or adherence to treatment. All of them suffer from methodologic limitations related to measurement of stigma and variation in the study population, definition of delay, and definition of adherence. While it is difficult to make conclusions based on the studies' limitations, the findings suggest that stigma may play a greater role in affecting treatment adherence than patient delay.

CHAPTER 3

SPECIFIC AIMS AND RATIONALE

SPECIFIC AIM 1

To identify potential socio-demographic, TB knowledge, and clinical factors associated with TB stigma. We hypothesize that female sex, severe TB symptoms, and HIV co-infection are associated with higher stigma, while correct TB knowledge and having known a patient with TB are associated with lower stigma.

SPECIFIC AIM 2

To estimate the association between stigma and patient delay in seeking care for TB symptoms while controlling for important confounders. We hypothesize that high TB and AIDS stigma are associated with longer patient delays in seeking care.

SPECIFIC AIM 3

To estimate the effect of stigma on adherence to TB treatment while controlling for important confounders. We hypothesize that high TB and AIDS stigma are associated with low adherence to TB treatment.

RATIONALE

Tuberculosis is reported to be a stigmatizing disease leading to delays in seeking care or difficulty adhering to treatment in an effort to avoid the perceived or actual negative social consequences of being a patient with TB. Most studies of TB stigma have been qualitative and, until recently, there have been no quantitative measures of TB stigma formally developed and published. In the absence of an empirical measure of TB stigma, it is impossible to evaluate the level of stigma present in the community or reported by patients, identify determinants of high TB stigma, assess the effect that stigma has on health behavior, and to evaluate stigma interventions. Additionally, pre-existing TB stigma has likely been compounded by AIDS stigma due to the growing link between TB and HIV. A well developed and comprehensive TB stigma scale is needed. Therefore, a companion AIDS stigma scale is needed to fully understand the impact AIDS and TB stigma have on TB control efforts. Using well-developed stigma scales and data from a study in southern Thailand, this dissertation aims to identify potential factors associated with TB stigma, estimate the association between both TB and AIDS stigma and delay in seeking care for TB symptoms, and estimate the effect of TB and AIDS stigma on TB treatment adherence.

CHAPTER 4

STUDY DESIGN AND METHODS

SETTING AND STUDY DESIGN

Data for this dissertation come from a study in southern Thailand begun in 2003 in response to the reported, negative impact of TB and AIDS stigma and, at the time, the paucity of validated scales for measuring stigma. The purpose was to develop culturally relevant stigma scales in order to quantify TB and AIDS stigma and measure its effect on patients with TB seeking care for their symptoms and during their TB treatment. The study involved four phases which are summarized here and describe in detail elsewhere (Sengupta, Pungrassami et al. 2006; Van Rie, Sengupta et al. 2008). These include scale development (Phase 1), pilot study and scale modification (Phase 2), cohort study and scale validation (Phase 3), and community study (Phase 4).

Phase 1: Scale development

Phase one of the study involved identifying relevant stigma items and holding focus groups (Sengupta, Pungrassami et al. 2006). Relevant literature was reviewed and 42 TB items and 49 AIDS items were selected which reflected many of the components associated with stigma. Because TB and AIDS have similar clinical presentations, a number of the

items selected were parallel items. That is, a TB item and AIDS item had the exact same wording with the exception of the disease.

The content validity of these items was ensured by holding focus groups and in-depth interviews with TB patients, patients co-infected with TB and HIV, family members, community members, religions leaders, and health care workers. As a result of these meetings, the number of TB items increased to 56 while the number of AIDS items decreased to 47. Forty items were parallel items. All items were phrased so that affirmation of the statement indicated stigmatizing beliefs.

Phase 2: Pilot study

Phase two of the study involved administering the preliminary scale items to patients with TB. Eligible patients were at least 18 years old, and had received no more than one month of treatment. Following informed consent, 204 patients responded to the 103 stigma items on a 4-point Likert scale, indicating strongly disagree, disagree, agree, or strongly agree.

Exploratory factor analysis was performed on the responses to identify underlying constructs. Twelve TB items were grouped together as TB stigma from the *community perspective*, while 12 additional items were group as TB stigma from the *patient perspective*. The remaining 32 TB items were removed due to large numbers of missing responses (13) or because they did not load on a single factor (19). Similarly, 12 AIDS items were grouped together as AIDS stigma from the *community perspective* while 10 additional items were grouped together as AIDS stigma from the *patient perspective*. The remaining 25 AIDS

items were removed due to large number of missing responses (5) or because they did not load on a single factor (20). All items retained had a factor loading of at least 0.35.

Phase 3: Cohort study

Phase three of the study involved administering the revised stigma scales to a cohort of 480 newly diagnosed patients with TB. Original power and sample size calculations were based on dichotomizing stigma, delay, and adherence at the mean, five weeks, and 80%, respectively. Given a baseline level of 30% delay and 20% non-adherence, a sample of 460 was expected to have 80% power to detect a ratio effect of 1.5.

Eligible patients were at least 18 years old and newly diagnosed with any type of TB between August 2005 and July 2006 at the regional TB center or seven hospital-based TB clinics in southern Thailand. Patients were enrolled if they had been receiving TB treatment for less than one month and then referred for HIV counseling and testing if their HIV status was unknown or if they had tested negative more than six months prior to enrollment. However, an HIV test was not required for participation.

Baseline demographic, clinical, and TB knowledge data were obtained using a structured questionnaire, and the stigma scales were administered. Patients were followed during the entire course of treatment or until lost to follow-up and stigma scales were re-administered after approximately two months of treatment and at the completion of treatment.

The standard treatment regimen used for new TB cases in southern Thailand is two months of isoniazid, rifampicin, pyrazinamide, and ethambutol taken daily (2HRZE; intensive phase) followed by four months of isoniazid and rifampicin taken daily (4HR;

continuation phase). Directly observed therapy (DOT) is recommended for all patients,

either at the clinic or by a family or community member, but is not required. This decision is

made jointly by clinic staff and the patient, and depends on the patient's access to the clinic

and availability of family or community members to perform observation.

Phase 4: Community study

Phase 4 involved the administration of the stigma scales to healthy community

members. In April 2007, a convenience sample of 300 healthy, adult community members

were invited to participate while visiting friends or family members (admitted for reasons

other than TB or AIDS) at one government and one private hospital from which TB patients

had also been enrolled. To rule out possible TB disease among community participants,

individuals were not eligible if they reported a cough for three weeks or longer. HIV status

was unknown but assumed negative as the adult prevalence of HIV in southern Thailand is

low (0.19% among blood donors and 0.59% among women at ante-natal clinics) (RODPC

2007). Baseline demographics, TB knowledge, and experiences with family, friends, or co-

workers with TB or AIDS were collected. The same stigma scales used in the cohort study

(Phase 3) were administered to community members.

STIGMA SCALES

Baseline stigma data collected from the patient cohort was used to perform a

confirmatory factor analysis and finalize the stigma scales (Van Rie, Sengupta et al. 2008).

The original *community perspective* and *patient perspective* factors were retained for both the

TB and AIDS scales. One item from each of the *community perspective* scales was removed

due to improper wording resulting in a low factor loading. The final four stigma scales

(Tables 4.1 and 4.2) included a total of 44 items: TB stigma from the *community perspective* (11 items) and *patient perspective* (12 items), and AIDS stigma from the *community perspective* (11 items) and *patient perspective* (10 items). Cronbach's alpha for each scale was calculated for both patients with TB and community members. Reliability was good with alphas ranging from 0.79 to 0.91 (Table 4.3). Stigma scales from the *community perspective* were inversely correlated with the O'Brien social support scale. Construct validation with the Rosenberg self-esteem scale could not be performed due to its poor reliability in the study population.

Table 4.1. Final items for the TB stigma scales.

Stigma from the community perspective

1. Some people prefer not to have those with TB living in their community
2. Some people keep their distance from people with TB
3. Some people think that those with TB are disgusting
4. Some people feel uncomfortable about being near those with TB
5. Some people do not want those with TB playing with their children
6. Some people do not want to talk to others with TB
7. If a person has TB, some community members will behave differently towards that person for the rest of his/her life
8. Some people may not want to eat or drink with friends who have TB
9. Some people try not to touch others with TB
10. Some people may not want to eat or drink with relatives who have TB
11. Some people are afraid of those with TB

Stigma from the patient perspective

1. Some people who have TB feel guilty because their family has the burden of caring for them
2. Some people who have TB keep their distance from others to avoid spreading TB germs
3. Some people who have TB feel alone
4. Some people who have TB feel hurt of how others react to knowing they have TB
5. Some people who have TB lose friends when they share with them they have TB
6. Some people who have TB are worried about having AIDS
7. Some people who have TB are afraid to tell those outside their family that they have TB
8. Some people who have TB will choose carefully who they tell about having TB
9. Some people who have TB are afraid of going to TB clinics because other people may see them there
10. Some people who have TB are afraid to tell their family that they have TB
11. Some people who have TB are afraid to tell others that they have TB because others may think that they also have AIDS
12. Some people who have TB feel guilty for getting TB because of their smoking, drinking, or other careless behaviors

Table 4.2. Final items for the AIDS stigma scales.

Stigma from the community perspective

1. Some people prefer not to have those with AIDS living in their community
2. Some people keep distance from people with AIDS
3. Some people think that those with AIDS are disgusting
4. Some people feel uncomfortable being near those with AIDS
5. Some people do not want those with AIDS playing with their children
6. Some people do not want to talk to others with AIDS
7. If a person has AIDS, some community members will behave differently towards that person for the rest of his or her life
8. Some people try not to touch others with AIDS
9. Some people are afraid of those with AIDS
10. Some people think that people with AIDS are unclean
11. Some people think that people with AIDS get what they deserve

Stigma from the patient perspective

1. Some people who have AIDS feel guilty because their family has the burden of caring for them
2. Some people who have AIDS keep their distance from others to avoid spreading the AIDS virus
3. Some people who have AIDS feel alone
4. Some people who have AIDS feel hurt because of how others react to knowing they have AIDS
5. Some people who have AIDS lose friends when they share with them they have AIDS
6. Some people who have AIDS are afraid that other people in the community will talk about them having AIDS
7. Some people who have AIDS will chose carefully who they tell about having AIDS
8. Some people who have AIDS try very hard to keep the issue of having AIDS a secret
9. Some people who have AIDS worry that others will reveal their secret
10. Some people who have AIDS are afraid to tell those outside their family that they have AIDS

Table 4.3. Cronbach's alpha for each stigma scale, by participant group.

	Patients with TB	Community members
TB stigma (community perspective)	0.88	0.85
TB stigma (patient perspective)	0.82	0.79
AIDS stigma (community perspective)	0.91	0.85
AIDS stigma (patient perspective)	0.83	0.87

ANALYTIC METHODS

Stigma scores and other covariates

Stigma was the primary variable of interest in all three aims, either as an outcome or exposure. Both the TB and AIDS stigma scales were used in all analyses. Participants responded to each stigma item on a Likert scale with four levels: strongly disagree, disagree, agree, and strongly agree, which were coded 0, 1, 2, and 3, respectively. Responses were summed for each scale, resulting in possible scores ranging from 0 to 33 for both *community perspective* scales, 0 to 36 for the TB stigma *patient perspective* scale, and 0 to 30 for the AIDS stigma *patient perspective* scale. Higher scores indicate higher stigma. Summed stigma scores were analyzed as continuous variables in all analyses unless otherwise noted. Comparison of summed scores across scales was not possible given different score ranges. Therefore, item-adjusted scores were created by dividing the summed scores by the number of items in the scale, creating an adjusted score ranging from 0 to 3 for each scale.

Information was collected on socio-demographic, TB knowledge, access to care, and clinical factors. These are listed in Tables 4.4 to 4.6 along with the variable categories and the analyses they were included in. In each analysis, linearity of continuous variables with the outcome was assessed to ensure modeling assumptions were met. Additional information on selected variables is found below:

Knowing someone with TB. Community members were asked if they had ever known a family member, friend, or co-worker who had TB. For those that knew someone with TB, they were asked if any of the TB patients they knew had died from TB. Patients with TB were not asked this question.

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Symptoms. Presenting symptoms were recorded for each patient and categorized into a hierarchy of mutually exclusive symptom combinations. *Cough* indicates the presence of cough but absence of hemoptysis, with or without other symptoms. *Hemoptysis* indicates the presence of blood in the cough, with or without other symptoms. *Weight loss* indicates the presence of weight loss and absence of cough, with or without fever or extrapulmonary symptoms. *Fever or Extrapulmonary* indicates the presence of fever and/or extrapulmonary symptoms only with no cough or weight loss. *No symptoms* indicates patients who presented to the clinic for other reasons (e.g. contact of an active case) and were found to have evidence of disease.

HIV status. HIV status was only recorded for patients with TB. Those who had never tested for HIV or who tested negative more than six months earlier were referred for voluntary HIV counseling and testing. *Negative* indicates a patient tested negative within the last six months (including upon presentation to the TB clinic). *Known positive* indicates a patient had previously tested positive for HIV. *New positive* indicates those patients who were referred for testing and found to be HIV co-infected. *Refused* indicates patients who refused to be tested.

TB knowledge (cause). Participants were asked to choose one of nine perceived causes of their TB. Due to conceptual similarities and small numbers, drinking alcohol was combined with smoking, while the belief that TB was a punishment for bad deeds or from God were combined with respondents who chose none of the listed causes.

TB knowledge (transmission). Participants were asked four Yes/No questions about routes of transmission. Routes of transmission were not exclusive, so participants could respond that transmission occurs multiple ways. For each route, those who did not know that

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TB was transmissible were combined with those who believed transmission could not occur via that route. Due to the large number of covariates included in the analysis of aims two and three and concerns about sparse data, transmission via touch, sex, and other routes not listed were combined.

TB knowledge (TB/HIV). Participants were asked three Yes/No questions about the perceived link between TB and HIV. For each question, those who were uncertain about TB/HIV were combined with those who did not think there was a link.

Table 4.4. Definitions of socio-demographic covariates used in the analyses for aims 1 – 3.

Variable description	Categories	Determinants analysis	Delay analysis	Adherence analysis
Gender	Male Female	✓	✓	✓
Age	Continuous years	✓	✓	✓
Religion	Buddhist Muslim	✓	✓	✓
Education	None or Less than primary school Completed primary school Completed secondary school	✓	✓	✓
Income	Continuous 1,000 Baht per month	✓	✓	✓
Children (≤15yrs) in household	Continuous number children		✓	✓
Adults (>15yrs) in household	Continuous number of adults		✓	✓
Personally know someone with TB	No Yes (survived) Yes (died)	✓ (Community members only)		

Table 4.5. Definitions of TB knowledge covariates used in the analyses for aims 1 – 3.

Variable description	Categories	Determinants analysis	Delay analysis	Adherence analysis
Cause	Infection Eating or drinking with patient Smoking or Drinking Hard work Heredity Weak body	✓	✓	✓
Transmission (cough/sneeze)	Yes No or Don't know	✓	✓	✓
Transmission (eating/drinking)	Yes No or Don't know	✓	✓	✓
Transmission (touch)	Yes No or Don't know	✓		
Transmission (sex)	Yes No or Don't know	✓		
Transmission (touch, sex, other)	Yes No or Don't know		✓	✓
Cure	Yes No or Don't know	✓		
TB/HIV (TB increases chance of getting AIDS	Yes No or Don't know	✓	✓	✓
TB/HIV (AIDS increases chance of getting TB	Yes No or Don't know	✓	✓	✓
TB/HIV (Symptoms appear similar)	Yes No or Don't know	✓	✓	✓

Table 4.6. Definitions of access to care and clinical covariates used in the analyses for aims 1 – 3 (only collected for patients with TB).

Variable description	Categories	Determinants analysis	Delay analysis	Adherence analysis
Friend to visit doctor with	Yes No		✓	
Time to first qualified provider	Continuous minutes		✓	
Mode of travel first qualified provider	Car or Motorcycle Bus Walk, Bicycle, or Other		✓	
Symptoms	Cough Hemoptysis Weight loss Fever or Extrapulmonary No symptoms	✓	✓	✓
Ever tested for HIV	Yes No		✓	
HIV status	Negative New positive Known positive Unknown or Refused	✓	✓	✓

Analytic methods for specific aim one

Data from the 480 patients with TB and 300 healthy community members were used in the analysis for specific aim one. The two groups were analyzed separately due to differences in the variables collected. Patients with TB were also expected to differ from community members in regards to TB stigma simply because they have TB. Thus, community members and TB patients have knowledge of stigma from their respective perspectives, but they also have perceptions about stigma in the others' group (Table 4.7). TB stigma from the *community perspective* and *patient perspective* were the two outcomes of interest. AIDS stigma from both perspectives was considered a determinant of interest along with other demographic, TB knowledge, clinical, and TB experience variables (Tables 4.4 – 4.6). Symptoms and HIV status were only collected from patients with TB, while experience of knowing someone with TB was only collected from community members.

Table 4.7. Relationship between stigma perspectives and study participants.

	Stigma from the community perspective	Stigma from the patient perspective
Community members	Item responses based on *membership in* community group	Item responses based on *perception of* patient group
Patients with TB	Item responses based on *membership in* and *perception of* community group	Item responses based on *membership in* patient group

Primary analysis. Continuous scores for TB stigma from the *community perspective* and *patient perspective* were modeled as separate outcomes using multivariable linear regression (SAS 9.1, PROC GENMOD with identity link and normal distribution). Separate regression models were fit for each potential determinant, first among patients with TB, then among community members. Crude and adjusted differences in mean stigma scores were estimated along with 95% confidence intervals. Stigma scores were analyzed as continuous

variables to avoid loss of information due to categorization. Scores were normally distributed and therefore met the modeling assumptions.

Sufficient sets of potential confounders for each covariate-stigma relationship were identified with the aid of directed acyclic graphs (Glymour and Greenland 2008). These schematics provide a visual aid to help identify sets of adjustment variables sufficient to control confounding by measured covariates in studies of causal inference. Using the directed acyclic graphs for the patients with TB (Figure 4.1) and community members (Figure 4.2), we identified no confounders of the relationship between age or religion and stigma, and the following potential confounders for the remaining determinants: for gender, age and religion; for income, age, religion and education; for education, religion and gender; for TB knowledge, age, education, knowing someone with TB (community members only) and income (TB patients only); for AIDS stigma, age, gender, religion, education, income, TB/HIV knowledge, HIV status (TB patients only), and TB symptoms (TB patients only); for knowing someone with TB, age and income; for HIV status, age, religion and income; and for TB symptoms, gender and HIV status. No interactions among potential determinants were considered.

Figure 4.1. Directed acyclic graph for analyzing determinants of TB stigma among patients with TB.
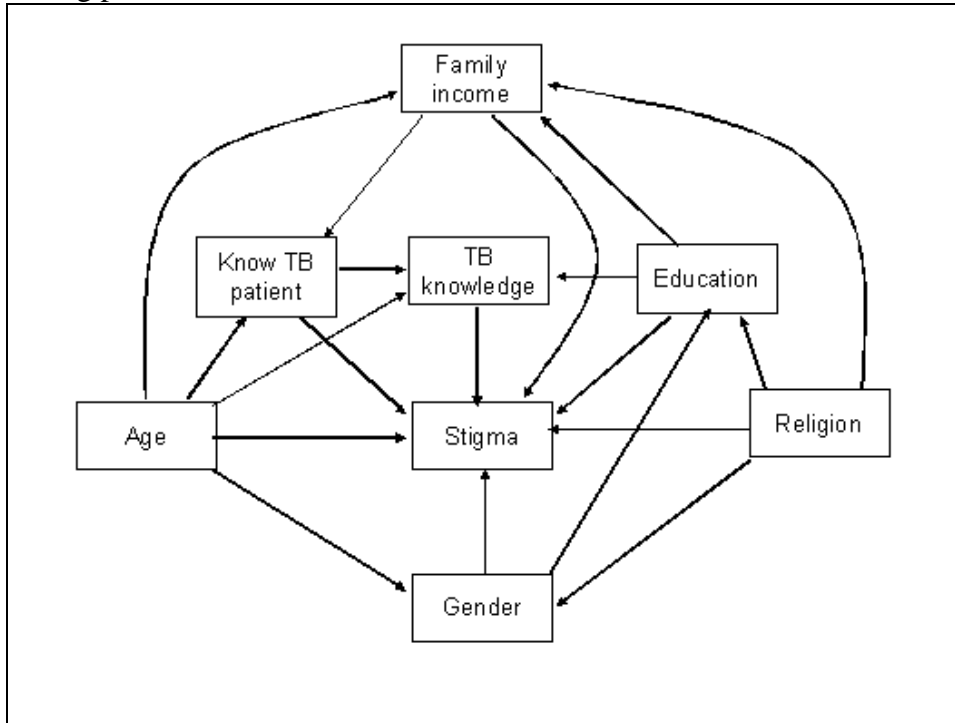
Figure 4.2. Directed acyclic graph for analyzing determinants of TB stigma among community members.
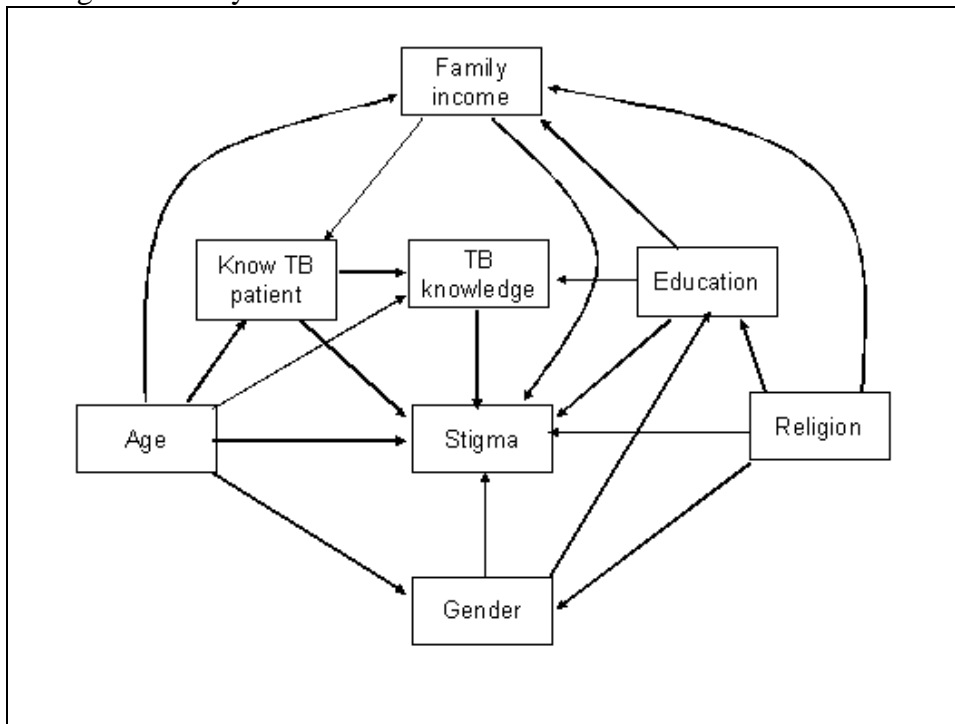
Sensitivity analysis. In addition to the primary analyses just described, three sensitivity analyses were performed to 1) assess the impact of an unmeasured confounder of the association between TB knowledge variables and stigma scores among patients with TB, 2) assess the impact of assuming even spacing between stigma item response options, and 3) to investigate how robust the results were to different cut-points for "high" stigma.

In the first sensitivity analysis, we suspected that knowing someone with TB may be an important determinant of stigma and related to the level of TB knowledge. This information, however, was only collected from community members, and not from patients with TB. A sensitivity analysis was performed to estimate the impact of this unmeasured confounder on the observed association between TB knowledge variables and stigma scores among patients with TB.

To do this, information was needed on the relationship between knowing someone with TB and stigma (the unmeasured confounder and the outcome), and knowing someone with TB and each of the covariates (the unmeasured confounder and the exposures of interest). Thus, two bias parameters were needed, and the adjusted association of each knowledge variable with stigma was obtained using the following equation

$$\beta_{adj} = \beta_{crude} - (p - q)\beta_{conf}$$

where β_{adj} is the updated parameter estimate for the association between TB knowledge and stigma after adjusting for all measured confounders and the unmeasured confounder, β_{crude} is the parameter estimate for the association between TB knowledge and stigma when not adjusted for the unmeasured confounder, *p-q* is the specified difference in proportion

between those with and without TB knowledge who have the unmeasured confounder, and β_{conf} is the parameter estimate for the association between the unmeasured confounder and stigma. The term '$(p - q)\beta_{conf}$' is referred to as the bias factor. That is, the amount by which the observed, crude estimate is biased. To simplify the sensitivity analysis, the unmeasured confounder was collapsed to a dichotomous variable: knowing a TB patient who died vs. knowing a TB patient who lived or not knowing a TB patient.

Information on the frequency of people who knew someone with TB who died was collected among community members. Therefore, both its distribution within TB knowledge categories and its association with stigma obtained in the community member analysis could be used to inform these parameters in the sensitivity analysis. The value of β_{conf} was specified as 2.5 and 2.0 for *community perspective* and *patient perspective* stigma, respectively. The value $p - q$ was calculated for each knowledge variable and rounded to the nearest 0.05. Upper and lower bounds for $p - q$ and β_{conf} were specified at ± 0.15 and ± 2.0 of the observed value, respectively.

Solving for β_{adj} in the preceding equation indicates what the updated association of TB knowledge with stigma would be given each of the two bias parameter specifications. Specifically, it identifies the most probable association and the upper and lower extremes given the specified variation around each parameter. It does not, however, provide uncertainty estimates around the parameter estimate. To do this required using Monte Carlo methods to repeatedly sample from the specified bias parameter distributions. A triangular probability distribution (Greenland and Lash 2008) was specified using the expected value and upper and lower bounds of the two bias parameters. For each parameter repeatedly sampled, the unadjusted estimate was updated by subtracting the bias factor to create an

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adjusted estimate. A final distribution was specified for the adjusted parameter estimate using the mean of the adjusted estimate and the standard error from the observed, crude estimate. This provided an estimate of the adjusted association that accounted for both the simulated systematic error and the standard random error. A fully adjusted parameter estimate with 95% uncertainty limits (reflecting systematic and random error) was obtained by identifying the 50th, 2.5th and 97.5th percentiles from this final distribution of estimates.

In the second sensitivity analysis, we assessed the impact of assuming even spacing between stigma item response options. The original coding of 0 – 3 assumed that the difference between strongly disagree and disagree is equal to the difference between disagree and agree. We repeated the original analyses using item response scoring of 0, 1, 3, 4 (a greater difference between agree and disagree response options), and 0, 2, 3, 5 (a greater difference between strongly disagree and disagree and strongly agree and agree response options).

Finally, as there is no consensus on what constitutes high stigma, we performed logistic regression with original, item-adjusted stigma scores dichotomized at 1.75, 2.00, and 2.25 to investigate how robust the results were to different cut-points for "high" stigma. Values around two were chosen as that value corresponds to responding "agree", on average, to each stigma item.

Analytic methods for specific aim two

Data from the 466 symptomatic patients with TB were used in the analysis for specific aim two. Patient delay was the primary outcome of interest. TB and AIDS stigma from both the *community perspective* and *patient perspective*, recorded at enrollment, were

the exposures of interest. Other covariates included demographic, TB knowledge, access to care, and clinical variables (Tables 4.4 – 4.6).

Outcome definition. Patient delay was defined as the number of days from the first TB related symptom to the first visit to a qualified provider for those symptoms. This could be a public or private hospital, private clinic, or TB center. All patients were enrolled shortly after diagnosis and asked about the length of time each symptom had been occurring and the date of the first visit to a qualified provider. If the date was not known, the length of time since that visit was recorded and subtracted from the study enrollment date to calculate the date of the first qualified provider visit. The date of first symptom was calculated by identifying the symptom each patient had experienced the longest and subtracted that length of time from the enrollment date.

Primary analysis. The delay distribution was normalized using the $\log_{10}$ transformation to satisfy linear regression assumptions. Stigma scores and log-transformed delay were modeled as continuous variables using multivariable linear regression (SAS 9.1, PROC GENMOD with identity link and normal distribution). Four regression models were built using each summed stigma score as the exposure. A sufficient set of confounders was identified with the aid of directed acyclic graphs and included in the multivariable regression model (Figure 4.3). These were age, sex, religion, education, income, number of children and adults in the household, availability of a friend for travel to the health provider, travel time to the first qualified provider, mode of travel, TB knowledge (cause, transmission, and HIV interaction), prior testing for AIDS, HIV status, and TB symptoms. *A priori* interactions between stigma and gender, HIV status, and TB symptoms were assessed individually by using interaction terms in the fully adjusted model. An interaction term with a p-value <0.20

was interpreted as evidence of heterogeneity. For covariates with more than two categories, a Type III test using the Wald Chi-square statistic was performed to simultaneously assess the contribution of each category's interaction with stigma. If evidence of heterogeneity was found for one stigma scale, the interaction term was included in all four models.

Figure 4.3. Directed acyclic graph for analyzing the association of TB and AIDS stigma with delay in seeking care for TB symptoms.
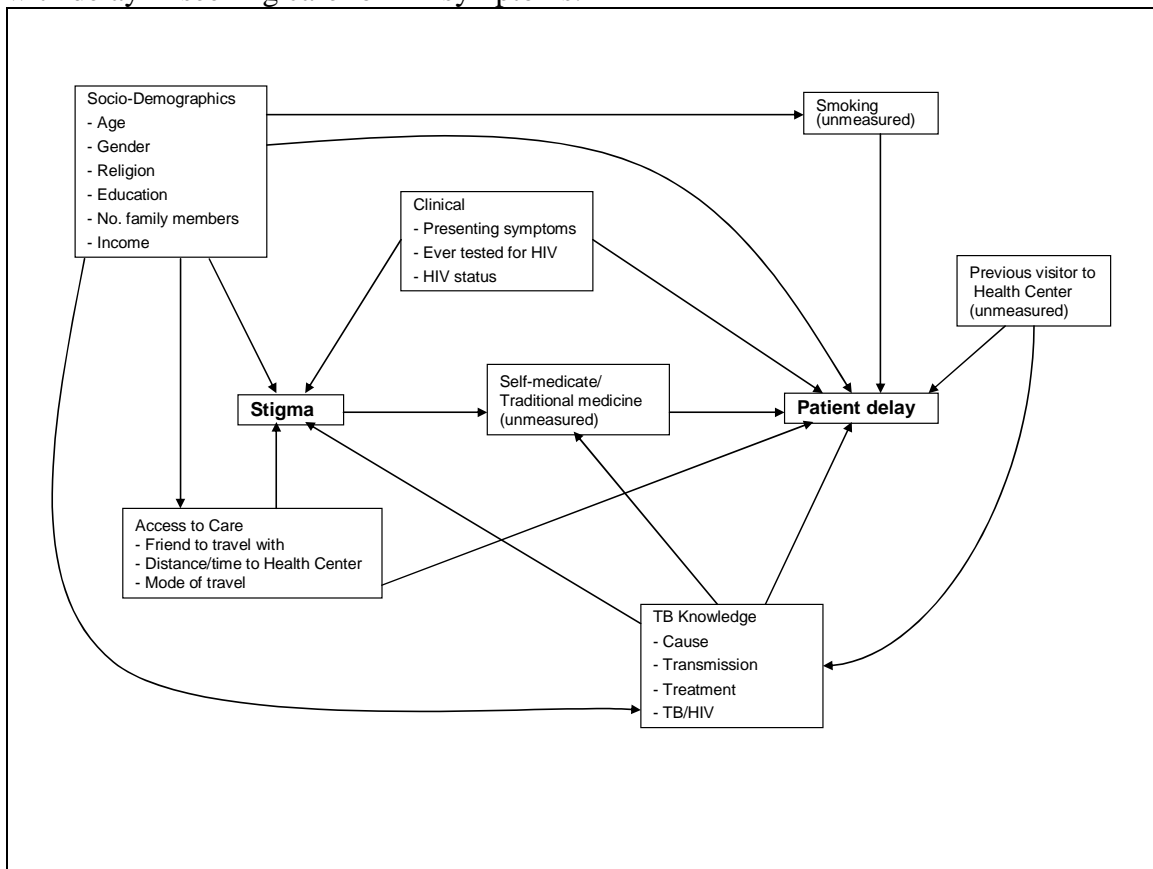
Sensitivity analysis. For many patients, the first TB symptom was not a cough. Because the WHO recommends that individuals with a cough for longer than three weeks be tested for TB (WHO 2004), the decision to not seek care in the absence of a cough may not be considered delay. Therefore, a sensitivity analysis was performed to assess the impact of including time spent with a non-cough symptom as part of the delay time. The primary

analysis was repeated with delay defined as the time from first cough to the first visit at a qualified provider.

Analytic methods for specific aim three

Data from the 466 symptomatic patients with TB were used in the analysis for specific aim three. Treatment adherence was the primary outcome of interest. TB and AIDS stigma from both the *community perspective* and *patient perspective*, recorded at enrollment and after approximately two months of treatment, were the exposures of interest. Other covariates included demographic, TB knowledge, and clinical variables (Tables 4.4 – 4.6).

Outcome definition. Two adherence outcomes were used in this study. As a treatment outcome, *default* was defined as missing more than two consecutive months of treatment. *Non-adherence* was defined as the proportion of days with a missed dose during the observed treatment period (proportion of missed doses) that were not attributed to drug side effects. Adherence information was documented every time a patient was seen by clinic staff. For each additional visit, documented information included the date, number of pills brought to the clinic, number of days a dose was missed, reason for missing doses, number of doses newly prescribed, and whether or not the patient had begun the continuation phase of treatment (usually after completing two months of treatment). Standard treatment outcomes were assigned to each patient at the end of treatment or when lost to follow up. These include cure, treatment completion, treatment failure, default, death, or transferred out.

Because there are changes in the treatment regimen and symptom between intensive and continuation phases of treatment, it was important to assign treatment outcomes and non-adherence to the appropriate phase. Eighty-four percent (n=405) of patients had a clinic visit

after beginning continuation phase treatment, indicating that treatment outcomes occurred during the continuation phase. For the 75 patients missing this information, any visit occurring after 55 days of treatment was considered to have occurred during the continuation phase. For all patients, the first clinic visit during the continuation phase of treatment contained information on adherence during the intensive phase.

Primary default analysis. Defaulters at any time during treatment were compared to those who completed treatment. Those who died, transferred out, or had their diagnosis changed to non-TB were excluded from this analysis. Default was further divided into default during the intensive phase of treatment and default during the continuation phase. Patients who died, transferred out, or had their diagnosis changed during the intensive phase were excluded, while patients experiencing these outcomes during the continuation phase were considered to have completed the intensive phase but were excluded from the continuation phase analysis.

Multivariable logistic regression (SAS 9.2, PROC GENMOD with logit link and binomial distribution) was used to assess the association between continuous stigma scores and default while controlling for measured confounders. Because data comes from a prospective cohort and default occurred in <10% of patients, the estimated odds ratios are interpreted as risk ratios. For each definition of default (total, intensive, and continuation), four regression models were fit using each stigma score measured at the start of treatment as the exposure of interest. Nine of the 25 defaulters (36%) during the continuation phase of treatment were missing follow-up stigma scores measured after two months of treatment. As a result an analysis of two-month stigma scores and continuation phase default was not performed.

A sufficient set of confounders was identified with the aid of directed acyclic graphs and included in the multivariable regression model (Figure 4.4). These included age, gender, religion, education, income, number of children and adults in the household, assignment to directly observed therapy, knowledge of TB transmission and the link between TB and HIV, presenting symptoms, and HIV status. Assignment of DOT is likely to be independent of stigma or, possibly, a result of the patient's stigma. In either case, it does not meet the criteria for a confounder. Covariates for knowledge of TB cure and cause were not included due to sparse data and problems with model convergence. Interactions between stigma scores and covariates were not assessed due to the small number of defaults in many covariate strata.

Figure 4.4. Directed acyclic graph for analyzing the effects of TB and AIDS stigma on adherence to TB treatment.
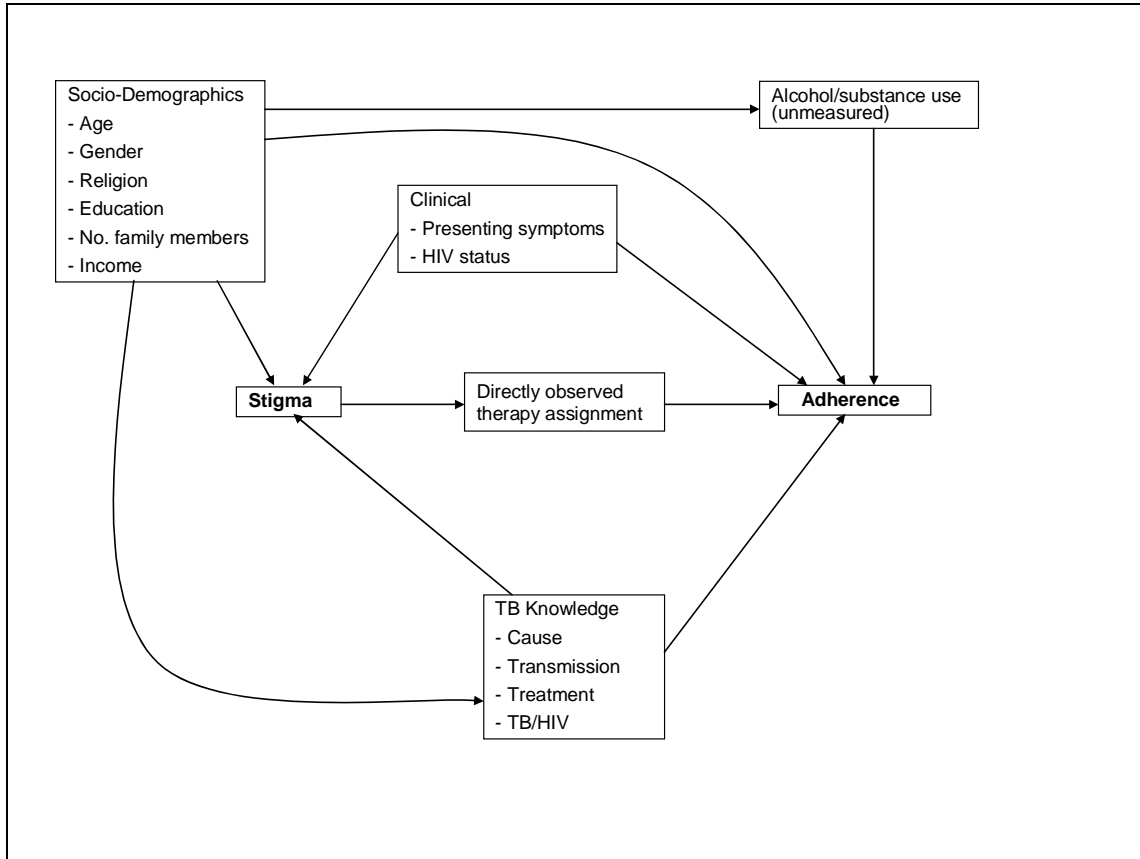
Primary non-adherence analysis. Non-adherence was analyzed as a repeated

measure. Each patient had one to three observations depending on the timing of stigma re-

assessment or change from intensive to continuation phase treatment. All patients, regardless

of treatment outcome, were included in the non-adherence analysis until they finished

treatment or were lost to follow-up.

Multivariable negative binomial regression (SAS 9.2, PROC GENMOD with log link

and negative binomial distribution) was used to assess the effect of stigma on the rate of non-

adherence while controlling for measured confounder. The negative binomial distribution

was chosen because the frequency distribution of predicted counts fit the observed data better

than those from the Poisson and zero-inflated Poisson distributions. Stigma scores, TB

knowledge and treatment phase were included as time-varying exposures and covariates, respectively. Generalized estimating equations with an exchangeable correlation matrix were specified to account for within subject correlations due to the repeated observations. Four regression models were fit using the continuous stigma scores, measured at the start of treatment and after two months of treatment treatment, as the exposure of interest.

A sufficient set of confounders was identified with the aid of directed acyclic graphs and included in the multivariable regression model (Figure 4.4). These covariates included age, gender, religion, education, income, number of children and adults in the household, knowledge of TB transmission and the link between TB and HIV, presenting symptoms, HIV status, and treatment phase. Assignment of DOT and knowledge of TB cure and cause were not included for the same reasons listed above in the analysis of treatment default. Interactions between stigma scores and gender, HIV status, symptoms, and treatment phase were assessed using interaction terms in separate models. A p-value <0.20 was interpreted as evidence of heterogeneity. For covariates with more than two categories, a Type III test using the Wald Chi-square statistic was performed to simultaneously assess the contribution of each category's interaction with stigma. If evidence of heterogeneity was found for one stigma score, the interaction term was included in all four models.

CHAPTER 5

DETERMINANTS OF TUBERCULOSIS STIGMA IN SOUTHERN

THAILAND: COMMUNITY AND PATIENT PERSPECTIVES

BACKGROUND

Tuberculosis (TB) remains one of the most important infectious diseases worldwide

with an estimated 9.2 million new cases and 1.7 million deaths in 2006 (WHO 2008). In

addition to the traditional focus on treatment and cure rates, attention has turned to a more

comprehensive approach towards disease control that addresses poverty and social factors, of

which stigma is one component (WHO 2006). Stigma was originally defined by Goffman as

"an undesirable or discrediting attribute that an individual possesses, thus reducing that

individual's status in the eyes of society" (Goffman 1963). The concept has more recently

been expanded to include the larger social process that involves "labeling, stereotyping,

separation, status loss, and discrimination" occurring together in the context of a power

differential (Link and Phelan 2001). This conceptualization incorporates the contribution of

both the community and the patient, with negative social consequences resulting from actual

experiences or anticipation of discriminating responses (Weiss and Ramakrishna 2006).

Individuals diagnosed with TB report fears of isolation and rejection such as losing

employment, becoming divorced or diminishing marriage prospects, not being allowed to

share meals, utensils or sleeping quarters with family members, and general avoidance or

gossip among community members (Liefooghe, Michiels et al. 1995; Long, Johansson et al. 2001; Eastwood and Hill 2004; Baral, Karki et al. 2007). Fear of these consequences may lead to delays in seeking care for TB symptoms and could affect adherence to treatment (Rubel and Garro 1992; Liefooghe, Michiels et al. 1995; Nair, George et al. 1997; Long, Johansson et al. 2001; Godfrey-Faussett and Ayles 2003; Baral, Karki et al. 2007).

Qualitative studies have found that stigma may be related to religion, socioeconomic status, level of education, and gender roles (Johansson, Long et al. 2000; Sengupta, Pungrassami et al. 2006) with women more often than men feeling that TB is stigmatizing (Long, Johansson et al. 2001; Eastwood and Hill 2004). Fear of, and negative attitudes towards, TB may arise from its contagious nature (Ngamvithayapong, Winkvist et al. 2000; Baral, Karki et al. 2007), incorrect knowledge of its cause, transmission, or treatment (Long, Johansson et al. 1999; Ngamvithayapong, Winkvist et al. 2000; Eastwood and Hill 2004; Sengupta, Pungrassami et al. 2006; Baral, Karki et al. 2007), or because of its association with marginalized groups (Johansson, Long et al. 1999; Ngamvithayapong, Winkvist et al. 2000; Eastwood and Hill 2004; Dimitrova, Balabanova et al. 2006; Sengupta, Pungrassami et al. 2006; Baral, Karki et al. 2007). As the epidemics of TB and HIV/AIDS have converged in many areas of the world, there is growing concern that AIDS stigma will compound existing TB stigma (Ngamvithayapong, Winkvist et al. 2000; Nnoaham, Pool et al. 2006). Focus groups with community members and patients with TB in southern Thailand identified the presence of symptoms similar to those of AIDS as a reason for stigmatizing attitudes towards TB (Sengupta, Pungrassami et al. 2006).

While these reports help identify possible determinants of stigma, quantitative studies are needed to assess the level of stigma in a population, assess the strength of association

between stigma and potential determinants, assess the effect of stigma on public health, and evaluate the effectiveness of interventions (Weiss and Ramakrishna 2006). Unfortunately, few quantitative studies have been performed (Macq, Solis et al. 2006). Two used brief scales that were not formally developed or not evaluated for internal consistency (Westaway 1989; Jaramillo 1999), while one study used a well developed TB-stigma scale with moderate internal consistency (Somma, Thomas et al. 2008).

We used formally developed and validated scales (Van Rie, Sengupta et al. 2008) to measure the level of TB stigma from both a *community perspective* (attitudes and actions of the community towards individuals with TB) and a *patient perspective* (feelings and experiences of patients with TB) and to evaluate the strength of association between stigma and its potential determinants among newly diagnosed TB patients and healthy community members.

METHODS

Study site and participants

Adults (>17 years old) newly diagnosed with TB between August 2005 and July 2006 at the regional TB center or seven hospital-based TB clinics in southern Thailand were eligible to participate. Patients were not enrolled if they had been receiving TB treatment for more than one month. Patients were referred for counseling and testing if their HIV status was unknown or if they had tested negative more than six months prior to enrollment. However, an HIV test was not required for participation.

Additionally, in April 2007, a convenience sample of healthy, adult community members were invited to participate while visiting friends or family members (admitted for reasons other than TB or AIDS) at one government and one private hospital from which TB

patients had also been enrolled. To rule out possible TB disease among community

participants, individuals were not eligible if they reported a cough for three weeks or longer.

HIV status was unknown but assumed negative as the adult prevalence of HIV in southern

Thailand is low (0.19% among blood donors and 0.59% among women at ante-natal

clinics)(RODPC 2007).

Data collection and stigma scores

Information on age, gender, religion, socioeconomic status, TB knowledge, TB

symptoms (patients only), HIV status (patients only), and knowing someone with TB

(community members only) were collected by trained interviewers using a standardized

questionnaire. Four stigma scales (Tables 5.1 and 5.2) were administered to all participants:

TB stigma from the *community perspective* (11 items) and *patient perspective* (12 items), and

AIDS stigma from the *community perspective* (11 items) and *patient perspective* (10 items).

Stigma items were scored on a Likert scale with four levels: strongly disagree (0),

disagree (1), agree (2), and strongly agree (3), where a higher response indicates higher

stigma. Responses were summed for each scale and summed scores were used in regression

analyses. Item-adjusted scores were created for comparison between scales by dividing the

summed scores by the number of items in the scale, creating an item-adjusted score ranging

from 0 to 3.

Analysis

Potential determinants of TB stigma were identified from the published literature and

substantive knowledge. Sufficient sets of confounders for each covariate-stigma relationship

were identified with the aid of directed acyclic graphs (Glymour and Greenland 2008).

These schematics provide a visual aid to help identify sets of adjustment variables sufficient

to control confounding by measured covariates. Using the directed acyclic graphs, we

identified no confounders of the relationship between age or religion and stigma, and the

following confounders for the remaining potential determinants: for gender, age and

religion; for income, age, religion and education; for education, religion and gender; for TB

knowledge, age, education, knowing someone with TB (community members only) and

income (TB patients only); for AIDS stigma, age, gender, religion, education, income,

TB/HIV knowledge, HIV status (TB patients only), and TB symptoms (TB patients only); for

knowing someone with TB, age and income; for HIV status, age, religion and income; and

for TB symptoms, gender and HIV status.

Continuous scores for community and patient perspectives of TB stigma were

modeled as separate outcomes using multivariable linear regression (SAS 9.1, PROC

GENMOD with identity link and normal distribution). Separate regression models were fit

for each covariate, first among patients with TB, then among community members.

Differences in mean stigma scores were estimated along with 95% confidence intervals.

Sensitivity analyses

We performed three sensitivity analyses. First, we assessed the impact of an

unmeasured confounder (knowing someone who died of TB) of the association between TB

knowledge variables and stigma scores among patients with TB. Two parameters were

needed to perform this analysis: the effect of the confounder on stigma and the difference in

the prevalence of knowing someone who died of TB between index and reference levels of

TB knowledge. Triangular probability distributions (Greenland and Lash 2008) for these parameters were centered at their observed value in the community sample, in which knowing someone who died of TB was ascertained. Monte Carlo simulations were used to adjust the estimated association between TB knowledge and stigma for the unmeasured confounder among patients with TB and to account for increased uncertainty due to specifying probability distributions for the missing parameters.

In the second sensitivity analysis, we assessed the impact of assuming even spacing between stigma item response options. We repeated the original analyses using item response scoring of 0,1,3,4 (a greater difference between agree and disagree response options), and 0, 2, 3, 5 (a greater difference between strongly disagree and disagree and strongly agree and agree response options).

Finally, as there is no consensus on what constitutes high stigma, we performed logistic regression with original item-adjusted stigma scores dichotomized at 1.75, 2.00, and 2.25 to investigate how robust the results were to different cut-points for "high" stigma. Values around two were chosen as that value corresponds to responding "agree", on average, to each stigma item.

RESULTS

Participant characteristics

Information was collected on 480 patients with TB and 300 healthy community members. Compared with community members, patients tended to be older, less educated, and more often male and Muslim (Table 5.3). Infection, smoking, or having a weak body were common beliefs about the cause of TB among all participants. Community members

also believed eating or drinking with a person who has TB is a cause, whereas patients

believed working hard can cause TB. Most participants stated that TB can be transmitted by

a cough or sneeze, but beliefs that transmission occurs through routes such as eating and

drinking with a patient were also common, especially among patients. Nearly all patients and

most community members knew TB is curable. High awareness of a link between TB and

HIV was present among all participants.

Most patients reported symptoms typically associated with TB. Upon diagnosis of

TB, 72 (15%) patients were co-infected with HIV and knew their serostatus. Of the 333

patients referred for HIV testing, 79% accepted, resulting in 21 newly identified infections

and an overall HIV prevalence of 20%.   Among community members, 89 (30%) knew at

least one person who suffered from TB and 38 of these indicated they knew someone who

had died from TB.

Stigma scale responses

On the TB stigma scales, 14 (2.9%) patients were excluded from the *community*

perspective scale analysis due to missing item responses, while 20 (4.2%) patients were

excluded from the *patient perspective* scale analysis due to missing item responses. All

community members had complete item responses. Internal consistency (Cronbach's

coefficient alpha) for each scale ranged from 0.79 to 0.88 (Table 5.2) and all scores were

approximately normally distributed with mean item-adjusted scores ranging from 1.65 to

1.86 (Figures 5.1 and 5.2). Community members reported higher stigma scores than patients

on both scales.

On the AIDS stigma scales, 19 (4.0%) patients had missing item responses on the *community perspective* scale, while 17 (3.5%) had missing item responses on the *patient perspective* scale. No item responses were missing from community members. Internal consistency (Cronbach's coefficient alpha) for each scale ranged from 0.83 to 0.91 (Table 5.2) and all scores were approximately normally distributed with mean item-adjusted scores ranging from 1.69 to 2.21. Scores for the *patient perspective* scale were higher than for the *community perspective* scale, and community members reported higher stigma than patients on both scales.

Factors associated with TB stigma

Mean differences (MD) in stigma scores and 95% confidence intervals (CI) for each potential determinant, by stigma scale and participant group, are shown in Table 5.4. Most differences were relatively small, estimated to be less than a one point change in the stigma score, and few characteristics were consistently associated with stigma across scales and participant groups. For example, while female community members had higher *patient perspective* stigma compared with male community members (MD=1.20; CI=0.13, 2.27), female patients reported lower *patient perspective* stigma compared with male patients (-0.80; -1.67, 0.07). There was no evidence that gender affected *community perspective* stigma. Similarly, the mean difference in stigma for Muslims versus Buddhists differed in direction between community members and patients.

Individuals with some or no primary education consistently reported higher stigma on both scales. The largest mean difference was among community members on the *community perspective* scale (1.61; 0.14, 3.08). There was no evidence that income was associated with

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stigma and little evidence that beliefs about the cause, transmission, and cure of TB affected stigma. Participants believing that TB is hereditary or curable consistently reported lower stigma, while those believing that TB could be transmitted sexually consistently had higher stigma. These estimates, however, were imprecise and included the null.

Higher TB stigma was reported for several factors relating to HIV/AIDS. Participants who believed that having TB could increase the chance of getting AIDS reported higher *patient perspective* stigma regardless of whether they were a community member (1.17; 0.12, 2.22) or a patient (2.16; 1.38, 2.94). Patients reporting that TB and AIDS symptoms appear similar had higher stigma, both on the *community perspective* (0.86; -0.12, 1.84) and *patient perspective* (0.86; -0.03, 1.75) scales. Participants expressing higher AIDS stigma consistently reported higher TB stigma, with a one point increase in AIDS stigma being associated with a 0.38 to 0.63 point increase in TB stigma. Patients with TB who were aware of their HIV co-infection prior to study enrollment had higher *community perspective* (0.66; -0.64, 1.96) and *patient perspective* (1.54; 0.37, 2.71) stigma.

Patients presenting with fever or extrapulmonary symptoms only had lower *community perspective* (-1.70; -3.18, -0.21) and *patient perspective* (-0.60; -1.92, 0.72) stigma. The experience of knowing someone who died of TB was associated with higher *community perspective* (2.59; 0.96, 4.22) and *patient perspective* (1.96; 0.36, 3.57) stigma compared with not knowing anyone with TB.

Sensitivity analyses

When accounting for possible unmeasured confounding due to knowing someone who died of TB, estimates of the effects of TB knowledge on TB stigma did not change

substantially. No substantive differences in results were found when different item scoring systems were used. Compared with the main analyses, results for dichotomized TB stigma scores were robust to different cut-points across both populations. However, eating or drinking with a patient as a route of transmission was consistently associated with increased stigma when stigma was dichotomized at 2.00. All associations were imprecise when stigma was dichotomized at 2.25, as few participants had high community (12%) or patient (11%) perspective stigma at this cut-point.

DISCUSSION

Using formally developed scales with good internal consistency, we quantified TB stigma from the *community perspective* (attitudes and actions of the community towards TB patients) and *patient perspective* (feelings and experiences of TB patients) in southern Thailand. TB stigma was observed among both healthy community members and patients with TB. Evaluated factors had minimal associations with stigma scores: most mean differences in stigma scores were <1.0 and only three were > 2.0. The largest, most precise, and consistent associations with TB stigma were those factors relating to the intersection of TB with HIV.

The belief that TB increases the chances of getting AIDS and the level of AIDS stigma were consistently and precisely associated with TB stigma. Knowing someone who died of TB had the largest difference in mean stigma score. While it is possible TB deaths are independent of HIV, they are many times associated with HIV co-infection. In northern Thailand, women whose TB/HIV co-infected husbands died from TB believed that TB was incurable (Ngamvithayapong, Winkvist et al. 2000). In a multi-country study, areas affected

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by HIV tended to have lower proportions of people who believed TB was curable (Somma, Thomas et al. 2008).

In a qualitative study in the same area of southern Thailand, religion, low TB knowledge, severe symptoms, and symptoms similar to AIDS were identified as reasons for stigmatizing attitudes towards TB (Sengupta, Pungrassami et al. 2006). Some of these qualitative observations were supported by our quantitative findings, but conclusions are difficult to make because many socio-demographic factors either showed inconsistent relationships across scales and/or participant groups, or estimates were very imprecise. Specifically, all estimates for perceived causes and transmission routes of TB were imprecise.

Our study underscores the importance of quantitative analyses to further inform the generalizability and magnitude of qualitative results. Our results also draw attention to the importance and complexity of assessing different perspectives in stigma research. While community members and patients with TB have knowledge of stigma from their respective groups, they also have perceptions about stigma in the others' group (Table 5.1). These cross-group perceptions are likely to play an important role in the impact of stigma, especially TB patients' perception of the community's stigma towards them. It remains to be seen which measure is more important for assessing the effects of stigma on health.

Only three other quantitative studies of TB stigma have been published (Westaway 1989; Jaramillo 1999; Somma, Thomas et al. 2008), and detailed comparisons between these studies warrant caution, as different scales, study populations, and potential determinants were used. Similar to our findings, lack of consistent associations between determinants and stigma among different populations was also observed by Somma and colleagues (Somma,

Thomas et al. 2008) in a study in Bangladesh, India, Malawi and Colombia. In that study, only marital status, financial problems, social distress, and seeking care at a private hospital were found to increase stigma in more than one study site.

Documenting the level of stigma and identifying determinants of stigma are important steps towards developing interventions to reduce stigma (Weiss and Ramakrishna 2006). In contrast to HIV/AIDS, little has been published on interventions for TB stigma. An evaluation of tuberculosis clubs to decrease stigma among patients undergoing treatment was performed in Ethiopia and Nicaragua (Demissie, Getahun et al. 2003; Macq, Solis et al. 2008). While these provide increased social support to patients, TB clubs do not address stigma in the community. Stigma in the community is perceived by individuals suffering from TB symptoms and may play an important role in whether or not individuals seek care (Rubel and Garro 1992; Long, Johansson et al. 2001; Baral, Karki et al. 2007).

It is often suggested that increasing knowledge and education can decrease stigma (Eastwood and Hill 2004; Hoa, Diwan et al. 2004). However, we found that TB knowledge itself appears to play a minor role in TB stigma. Furthermore, many people who understood the link between HIV and TB expressed high TB stigma. Thus, correcting misconceptions may inadvertently lead to higher stigma. In our study, factors related to HIV/AIDS had the strongest, most precise, and most consistent associations with TB stigma. This suggests that interventions aimed at decreasing TB stigma should also address the HIV/AIDS epidemic. This may include macro level factors such as reducing AIDS stigma in the community, decreasing mortality from AIDS, especially among TB patients, media and public education campaigns to raise awareness that not all TB patients are co-infected with HIV, and that TB is curable, even among those who are co-infected with HIV.

Some limitations of our study should be noted. First, the small number of responses for all causes and transmission routes of TB reduced the precision of estimates. Second, the convenience sample of community members recruited from area hospitals may not be representative of the general population from which the TB patients arise. It is possible that the level of stigma in the community may be higher than documented, as people who visit a hospitalized friend or family member may (temporarily) hold less stigmatizing attitudes towards people suffering from diseases such as TB.

TABLES AND FIGURES

Table 5.1. Relationship between stigma perspectives and study participants.

	Stigma from the community perspective	**Stigma from the patient perspective**
Community members	Item responses based on *membership in* community group	Item responses based on *perception of* patient group
Patients with TB	Item responses based on *membership in* and *perception of* community group	Item responses based on *membership in* patient group
Sample items*	– Some people are afraid of those with TB – Some people think that those with TB are disgusting – Some people prefer not to have those with TB living in their community – If a person has TB, some community members will behave differently towards that person for the rest of his or her life	– Some people who have TB feel alone – Some people who have TB are afraid to tell those outside their family that they have TB – Some people who have TB lose friends when they share with them they have TB – Some people who have TB feel hurt of how others react to knowing they have TB

* For the AIDS stigma scales, the word "TB" is be replaced with "AIDS".

Table 5.2. Stigma scale characteristics and score distributions.

	TB stigma		**AIDS stigma**	
	Community perspectives scale (11 items)	Patient perspectives scale (12 items)	Community perspectives scale (11 items)	Patient perspectives scale (10 items)
Patients with TB				
Cronbach's alpha	0.88	0.82	0.91	0.83
Mean summed score (SD)	18.43 (4.95)	19.85 (4.43)	18.58 (5.15)	19.74 (3.52)
Mean adjusted score (SD)	1.68 (0.45)	1.65 (0.37)	1.69 (0.47)	1.97 (0.35)
Community members				
Cronbach's alpha	0.85	0.79	0.85	0.87
Mean summed score (SD)	20.13 (4.87)	22.30 (4.74)	20.77 (5.09)	22.06 (4.27)
Mean adjusted score (SD)	1.83 (0.44)	1.86 (0.39)	1.89 (0.46)	2.21 (0.43)

Table 5.3. Distribution of participant characteristics, by participant group.

Continuous participant characteristics		Patients with TB	Community members
Age	Age in years (median, range)	37 (18 – 79)	34 (18 – 69)
Income	Thousand Baht per month (median, range)	10 (0 – 90)	10 (1 – 100)
Categorical participant characteristics		**N (%)**	**N (%)**
Gender	Male	317 (66.0)	146 (48.7)
	Female	163 (34.0)	154 (51.3)
Religion	Buddhist	319 (66.7)	244 (81.3)
	Muslim	159 (33.3)	56 (18.7)
Education	Less than or no primary school	160 (33.4)	61 (20.3)
	Completed primary school	191 (39.8)	103 (34.3)
	Completed secondary school	129 (26.9)	136 (45.3)
TB knowledge*	Infected from family/others	87 (18.1)	42 (14.0)
(Cause)	Work hard	71 (14.8)	3 (1.0)
	Smoking/drinking	162 (33.8)	158 (52.7)
	Heredity	20 (4.2)	25 (8.3)
	Weak body	82 (17.1)	27 (9.0)
	Eat or drink with patient	20 (4.2)	43 (14.3)
	Other	38 (7.9)	2 (0.7)
TB knowledge†	Eat/drink	291 (61.9)	109 (36.7)
(Transmission)	Touch	41 (8.7)	32 (10.8)
	Sex	46 (9.8)	16 (5.4)
	Cough/sneeze	396 (84.3)	224 (75.4)
	Other	64 (13.6)	50 (16.8)
TB knowledge	Curable	463 (96.5)	231 (77.0)
(Cure)	Not curable	17 (3.5)	69 (23.0)
TB knowledge†	TB increase AIDS	242 (50.4)	142 (47.3)
(TB/HIV)	AIDS increases TB	346 (72.1)	219 (73.0)
	AIDS/TB appear similar	339 (70.6)	186 (62.0)
Know TB patient	Did not know person with TB		211 (70.3)
	Knew person with TB (lived)		51 (17.0)
	Knew person with TB (died)		38 (12.7)
Symptoms‡	Cough	236 (49.2)	
	Hemoptysis	116 (24.2)	
	Weight loss	59 (12.3)	
	Fever and/or extrapulmonary only	55 (11.5)	
	No symptoms	14 (2.9)	
HIV status§	Negative	295 (61.5)	
	New positive	21 (4.4)	
	Known positive	73 (15.2)	
	Refused	91 (19.0)	

* Exclusive or † non-exclusive categories

‡ Cough and hemoptysis may include other symptoms; Weight loss excludes cough but may include other symptoms

§ Known positives had previously tested positive for HIV infection; New positives identified when diagnosed with TB

Table 5.4. Adjusted differences in mean, summed stigma scores for participant characteristics.

		Community perspectives stigma scale		Patient perspectives stigma scale	
		Patients with TB	Community members	Patients with TB	Community members
		MD* (95% CI)	MD* (95% CI)	MD* (95% CI)	MD* (95% CI)
Age	Age (per 10 year)	0.61 (0.29, 0.92)	0.66 (0.22, 1.11)	0.17 (-0.12, 0.45)	-0.20 (-0.64, 0.23)
Gender	Male	0.0	0.0	0.0	0.0
	Female	0.16 (-0.79, 1.11)	0.30 (-0.80, 1.39)	-0.80 (-1.67, 0.07)	1.20 (0.13, 2.27)
Religion	Buddhist	0.0	0.0	0.0	0.0
	Muslim	-1.37 (-2.32, -0.42)	0.56 (-0.85, 1.98)	0.04 (-0.83, 0.90)	0.33 (-1.04, 1.71)
Education	Completed secondary	0.0	0.0	0.0	0.0
	Completed primary	-0.41 (-1.53, 0.72)	0.21 (-1.03, 1.46)	0.54 (-0.46, 1.55)	0.96 (-0.24, 2.17)
	Some or no primary	0.78 (-0.39, 1.96)	1.61 (0.14, 3.08)	1.22 (0.17, 2.28)	0.49 (-0.94, 1.92)
Income	Baht/month (1,000 baht)	0.00 (-0.04, 0.03)	-0.01 (-0.06, 0.04)	-0.02 (-0.05, 0.02)	-0.03 (-0.08, 0.02)
TB Knowledge† (Cause)	Infection from others	0.0	0.0	0.0	0.0
	Eat/drink with patient	-1.46 (-3.87, 0.95)	1.13 (-0.86, 3.11)	-0.62 (-2.76, 1.52)	0.69 (-1.27, 2.65)
	Smoking/drinking	-0.66 (-1.97, 0.65)	0.03 (-1.57, 1.63)	0.42 (-0.77, 1.62)	0.43 (-1.15, 2.01)
	Work hard	-1.57 (-3.15, 0.01)	Too few	-0.17 (-1.61, 1.28)	Too few
	Heredity	-0.98 (-3.40, 1.44)	-1.44 (-3.78, 0.91)	-1.23 (-3.37, 0.92)	-0.36 (-2.68, 1.96)
	Weak body	-0.30 (-1.78, 1.17)	0.43 (-1.84, 2.69)	-0.36 (-1.71, 0.99)	1.72 (-0.52, 3.96)
TB Knowledge‡ (Transmission)	Cough/sneeze	0.08 (-1.09, 1.25)	-0.28 (-1.51, 0.95)	0.40 (-0.67, 1.47)	0.61 (-0.60, 1.83)
	Eat/drink	0.52 (-0.39, 1.43)	1.73 (0.62, 2.84)	0.44 (-0.39, 1.26)	0.76 (-0.35, 1.86)
	Touch	-0.14 (-1.73, 1.45)	-0.33 (-2.17, 1.51)	1.21 (-0.22, 2.64)	0.31 (-1.51, 2.12)
	Sex	1.06 (-0.44, 2.55)	1.94 (-0.47, 4.34)	0.92 (-0.46, 2.30)	1.33 (-1.04, 3.71)
TB Knowledge (Cure)	Not curable	0.0	0.0	0.0	0.0
	Curable	-1.41 (-3.84, 1.02)	-0.93 (-2.23, 0.37)	-0.91 (-3.17, 1.35)	-0.74 (-2.02, 0.55)
TB Knowledge‡ (TB/HIV)	TB increases AIDS	1.08 (0.19, 1.86)	0.55 (-0.52, 1.62)	2.16 (1.38, 2.94)	1.17 (0.12, 2.22)
	AIDS increases TB	0.42 (-0.59, 1.42)	0.86 (-0.35, 2.06)	0.85 (-0.07, 1.77)	1.04 (-0.15, 2.22)
	AIDS/TB appear similar	0.86 (-0.12, 1.84)	-0.55 (-1.66, 0.57)	0.86 (-0.03, 1.75)	-0.09 (-1.19, 1.00)
HIV/AIDS stigma (per unit increase)	Community perspective scale	0.60 (0.53, 0.66)	0.52 (0.43, 0.61)	0.45 (0.39, 0.52)	0.38 (0.28, 0.47)
	Patient perspective scale	0.63 (0.51, 0.74)	0.46 (0.34, 0.58)	0.60 (0.50, 0.70)	0.56 (0.46, 0.67)
Know TB patients	Did not know person with TB		0.0		0.0
	Knew person with TB (lived)		0.13 (-1.32, 1.57)		-0.54 (-1.96, 0.89)
	Knew person with TB (died)		2.59 (0.96, 4.22)		1.96 (0.36, 3.57)
Symptoms§	Cough	0.0		0.0	

	Hemoptysis	-0.52 (-1.64, 0.60)	-0.59 (-1.60, 0.42)
	Weight loss	-0.20 (-1.70, 1.30)	0.51 (-0.86, 1.88)
	Fever and/or extrapulmonary only	-1.70 (-3.18, -0.21)	-0.60 (-1.92, 0.72)
	No symptoms	1.67 (-0.98, 4.32)	-0.32 (-2.76, 2.12)
HIV status‖	Negative	0.0	0.0
	New positive	-0.59 (-2.74, 1.55)	-0.66 (-2.60, 1.29)
	Known positive	0.66 (-0.64, 1.96)	1.54 (0.37, 2.71)
	Unknown/Refused	-0.99 (-2.15, 0.18)	-0.04 (-1.09, 1.02)

* MD, mean difference in summed stigma scores; CI, confidence interval; 0.0 indicates referent level

† Exclusive or ‡ non-exclusive categories

§ Cough and hemoptysis may include other symptoms; Weight loss excludes cough but may include other symptoms

‖ Known positives had previously tested positive for HIV infection; New positives identified when diagnosed with TB

Figure 5.1. Kernel-smoothed, item-adjusted TB stigma score distributions (community perspective scale). Community members, solid line; TB patients, dashed line.
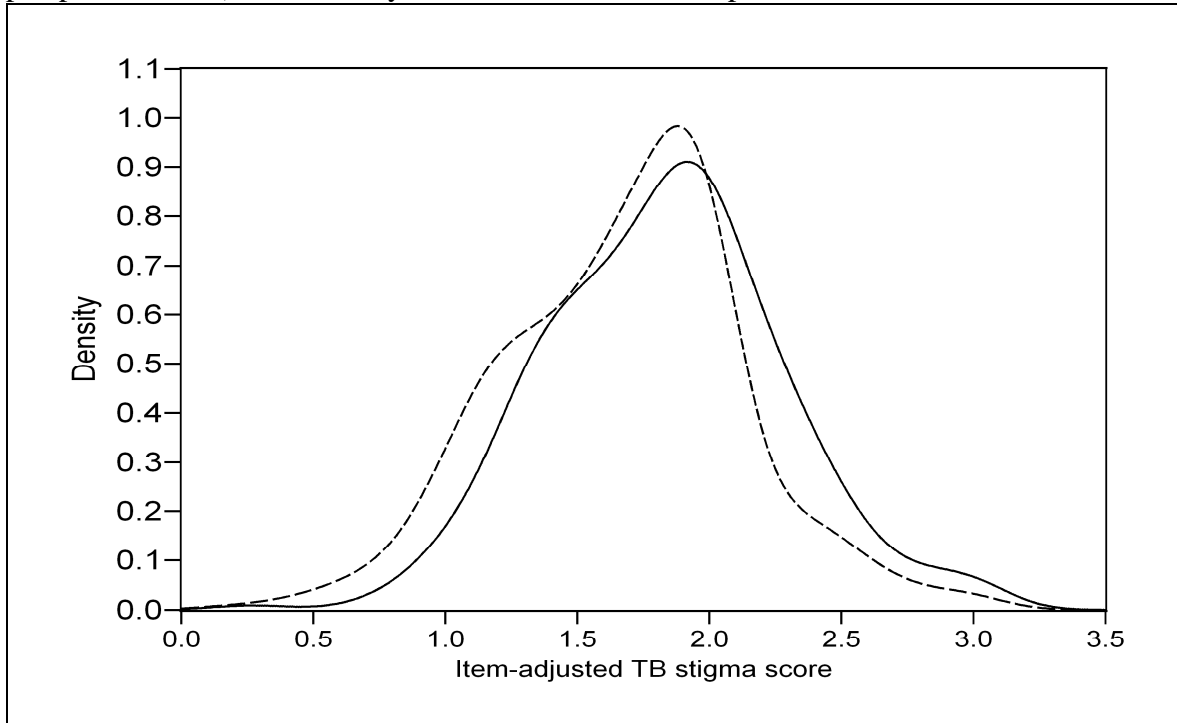
Figure 5.2. Kernel-smoothed, item-adjusted TB stigma score distributions (patient perspective scale). Community members, solid line; TB patients, dashed line.
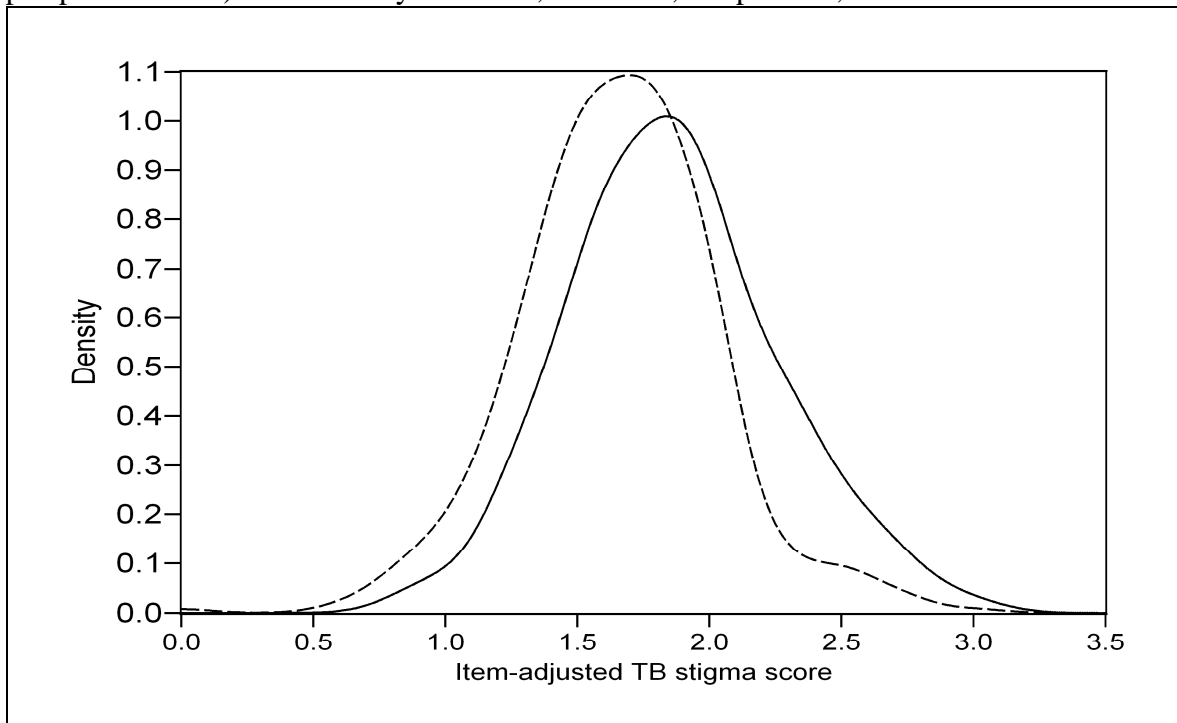
CHAPTER 6

TUBERCULOSIS AND AIDS STIGMA AMONG PATIENTS WHO DELAY

SEEKING CARE FOR TUBERCULOSIS SYMPTOMS

BACKGROUND

From its introduction in 1994, directly observed therapy (DOTS) has been the backbone
of tuberculosis (TB) control around the world. With its focus on passive case detection,
availability of diagnostic techniques, and directly observed therapy to minimize drug resistant
TB, DOTS has been criticized as a treatment guideline and biomedical strategy that does not
account for social factors related to TB control rather than a comprehensive control plan
(Lienhardt and Ogden 2004; Whalen 2006). Delay in presentation to a health facility is an
important concern of TB control as it contributes to delays in initiating treatment. This can result
in greater morbidity and mortality for the patient and increased transmission of *Mycobacterium
tuberculosis* in the community (Madebo and Lindtjorn 1999; Barker, Millard et al. 2006; Golub,
Bur et al. 2006; Lin, Chongsuvivatwong et al. 2008).

There is a large body of literature on factors associated with delay in seeking care for TB
symptoms. These can be broadly grouped into access to care, personal characteristics,
socioeconomic, clinical, TB knowledge or beliefs, and social support or psychosocial factors
(Storla, Yimer et al. 2008). One psychosocial factor of interest is health-related stigma, often
defined as a social process "characterized by exclusion, rejection, blame, or devaluation resulting

from experience or reasonable anticipation of an adverse social judgment" because of a particular health condition (Weiss and Ramakrishna 2006). Some studies have suggested that TB stigma could lead to delays in patients seeking appropriate medical care (Rubel and Garro 1992; Long, Johansson et al. 2001; Baral, Karki et al. 2007). Others note that AIDS stigma and fears of being labeled as an AIDS patient could deter potential TB patients from seeking care because of the belief that someone with TB also has AIDS (Ngamvithayapong, Winkvist et al. 2000; Godfrey-Faussett, Kaunda et al. 2002).

Six studies of delay among patients with TB or cough have included some measurement of stigma as a covariate. In five of these, stigma was not found to be associated with patient delay (Auer, Sarol et al. 2000; Godfrey-Faussett, Kaunda et al. 2002; Cambanis, Yassin et al. 2005; Yimer, Bjune et al. 2005; Cambanis, Ramsay et al. 2007). A multi-country study by the World Health Organization (WHO) in their eastern Mediterranean region reported that increased stigma was associated with decreased patient delay in Somalia (WHO/ROEM 2006). A seventh study specifically designed to assess the relationship between TB stigma and delay in seeking care for TB symptoms used a modified stigma scale initially developed for AIDS and cancer (Woith and Larson 2008). No studies, however, have been performed to assess the effect of both TB and AIDS stigma on TB patient delay using formally developed and culturally relevant scales.

Using formally developed stigma scales (Van Rie, Sengupta et al. 2008), this study sought to investigate whether higher TB or AIDS stigma is associated with longer delay in seeking care for TB symptoms in southern Thailand.

METHODS

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Study participants and data collection

Adults (>17 yrs) with newly diagnosed TB between August 2005 and July 2006 were enrolled from the regional TB center and seven hospital-based TB clinics in southern Thailand. Patients were not eligible if they had been receiving TB treatment for more than one month. Information on demographics, socioeconomic status, access to the first qualified health provider visited (private or public health clinic or hospital), TB knowledge, and TB symptoms were collected by trained interviewers using a standardized questionnaire. Patients were referred for counseling and testing if their HIV status was unknown or if they had tested negative more than six months prior to enrollment. However, an HIV test was not required for participation. Four stigma scales were administered to all participants: TB stigma from the community perspective (11 items) and patient perspective (12 items); and AIDS stigma from the community perspective (11 items) and patient perspective (10 items) (Van Rie, Sengupta et al. 2008). Items were scored using a Likert scale with four levels: strongly disagree (0), disagree (1), agree (2), and strongly agree (3), with higher responses indicating higher stigma. Responses were summed for each scale to create stigma scores to be used in analyses. Stigma scores were standardized by dividing the summed score by the number of items in the scale, resulting in a possible range of 0 to 3. These item-adjusted scores were used to compare scores between scales.

Patient delay, defined as the time between onset of TB symptoms and the first visit to a qualified provider, was the outcome of interest. Health services delay, defined as the time between first presentation to a provider and diagnosis of TB was not considered in this analysis because stigma would not be expected to affect clinical decisions or diagnostic processes. Upon enrollment in the study, patients were asked to recall the duration of their symptoms and when the first visit to a qualified provider occurred. Delay was calculated as the number of days

between these two points. Patients who were asymptomatic were excluded from the analysis. The delay distribution was normalized using the $\log_{10}$ transformation to satisfy regression assumptions.

Data analysis

Stigma scores and log-transformed delay were modeled as continuous variables using multivariable linear regression (SAS 9.1, PROC GENMOD with identity link and normal distribution). Four regression models were fit using each stigma score as the exposure of interest. Potential confounders were included in the model based on substantive knowledge and with the aid of directed acyclic graphs (Glymour and Greenland 2008; Greenland 2008). These covariates included age, sex, religion, education, income, number of children and adults in the household, availability of a friend for travel to the health provider, travel time to the first qualified provider, mode of travel, TB knowledge (cause, transmission, and HIV interaction), prior testing for AIDS, HIV status, and TB symptoms. We considered interactions between stigma and gender, HIV status, and TB symptoms. It has been suggested that stigma adversely affects women (Johansson, Long et al. 2000) and that AIDS factors may play an important role in both stigma and delay (Ngamvithayapong, Winkvist et al. 2000; Godfrey-Faussett, Kaunda et al. 2002). These interactions were assessed individually using interaction terms in the fully adjusted model. Interactions with $p \leq 0.20$ in at least one model were used in all four models. Regression results are presented as mean differences in log-transformed delay. Anti-log transformation of the parameter estimates requires bias-correction and was not undertaken. However, anti-log transformation of the upper (or lower) confidence limit provides an upper (or lower) bound for the relative increase (or decrease) in delay on the day scale, rather than the log-day scale, which aids in the interpretation of the results.

RESULTS

Participant characteristics

Fourteen asymptomatic patients (3%) were excluded from the analysis. An additional 34 (7%) patients were excluded due to improbable calculations of delay (32 with delay <0 days, two with delay >600 days). The final sample size for analysis was 432 patients. There was very little difference in exposure and covariate distributions among patients who were included and those excluded from the analysis, with the exception of mode of transportation (Table 6.1).

Nearly all patients (97%) knew that TB was curable. Patients primarily attributed their TB to smoking or drinking (34%), followed by infection from someone else (18%) or having a weak body (17%). While many reported non-infectious causes, they also reported that TB could be transmitted, either by eating or drinking with a patient or via a patient coughing or sneezing. Most patients were aware of the link between TB and HIV.

Most patients experienced cough, with or without hemoptysis (76%). Upon diagnosis of TB, 67 (17%) patients were co-infected with HIV and knew their serostatus. Of the 314 patients referred for HIV testing, 235 (75%) accepted and 19 new infections were identified for an overall HIV prevalence of 20%.

Stigma and delay

Stigma scores could not be calculated for 13 (3%) patients due to incomplete item responses on the TB stigma from the community perspective scale and 16 patients (4%) for each of the remaining scales. All stigma scores had an approximately normal distribution. Mean

item-adjusted scores ranged from 1.65 to 1.97 with the highest score for AIDS stigma from the patient perspective (Table 6.1).

Delay was highly skewed and ranged from 1 to 365 days (Figure 6.1). Median delay was 26 days with noticeable digit preference. Log_{10} transformation normalized the delay distribution. Within categories of covariates, median delay times ranged from 14 days among those who presented with fever and/or extrapulmonary disease only, to 30 days among those who were HIV co-infected and those who presented with hemoptysis. The median delay time among men was one week longer than among women (28 vs. 21.5 days).

Adjusted results for the association of stigma with delay are reported in Table 6.2 as the mean difference in log-transformed delay per unit increase in the summed stigma score. Results are reported for all TB patients and then stratified by gender and presenting symptoms. Among all patients with TB, stigma had no effect on delay with mean differences nearly equal to zero. Among men, a one unit increase in TB stigma from the community perspective was associated with a 0.012 (95% CI: -0.001, 0.025) increase in log-delay. Similar results were observed for TB stigma from the patent perspective. AIDS stigma had no effect on delay times among men. The opposite was observed among women, where those with higher stigma had a *decrease* in log-delay. AIDS stigma from the community perspective was also associated with a 0.015 (95% CI: -0.032, 0.002) *decrease* in log-delay among women.

When the effect of stigma on delay was stratified by presenting symptoms, there was no association between stigma and delay among patients presenting with cough. Patients with hemoptysis, however, had a 0.022 (95% CI: 0.001, 0.043) increase in log-delay per unit increase in TB stigma from the community perspective and a 0.035 (95% CI: 0.011, 0.060) increase for TB stigma from the patient perspective. AIDS stigma from the community perspective had a

slightly smaller association. Among patients with fever or extrapulmonary symptoms only, both

TB stigma scales had an inverse relationship with delay. This also occurred for AIDS stigma

from the community perspective where patients had a 0.034 (95% CI: -0.069, 0.002) *decrease* in

log-delay per unit increase in stigma.

Similar results were observed when delay was calculated as the time from first cough to

the first visit to a qualified provider (Table 6.2).

DISCUSSION

This is the first study to use formally developed TB and AIDS stigma scales to estimate

the association between stigma and delay in seeking care for TB symptoms in the era of the HIV

co-epidemic. Overall, we did not observe an association between TB or AIDS stigma and delay

in seeking health care among individuals who were diagnosed with active TB. However, the

estimates differed by gender, with men who reported higher TB stigma having longer delay

times, and women who reported higher TB stigma having shorter delays. Qualitative studies

have reported that TB stigma adversely affects women more than men, primarily because of their

sensitivity to social interactions (Johansson, Long et al. 2000). In the context of seeking care for

TB symptoms, our findings suggest women who report higher levels of TB stigma may seek care

more quickly in an effort to relieve their symptoms and minimize any social consequences due to

disease.

Among patients with hemoptysis, a symptom highly suggestive of TB, higher TB stigma

was associated with increased delay time, while among patients with fever or extrapulmonary

symptoms only, higher TB and AIDS stigma showed an inverse relationship with delay. It was

interesting to find that, among patients with atypical, non-cough symptoms, higher AIDS stigma

from the community perspective was associated with shorter delay times. These patients may

seek care in hopes that their symptoms are attributable to TB, rather than AIDS

(Ngamvithayapong, Winkvist et al. 2000).

The actual impact of stigma on increasing or decreasing the duration of delay may not be

large. The 95% CI limit furthest from the null was for TB stigma from the patient perspective

among those with fever or extrapulmonary disease. Anti-log transformation of this limit ($10^{-0.069}$

$= 0.85$) indicates that the lower bound for any change in delay per unit increase in stigma is a

15% decrease. Given the median delay of 26 days in our study population, this corresponds to a

maximum of a four day decrease in delay time for a one point increase in stigma. The impact of

stigma would likely be greater in populations where the baseline delay is much higher.

Similarly, changes in stigma by more than one point could have a greater impact on delay.

However, a study of possible determinants of TB stigma in the same population found that

modifiable, socio-economic, TB knowledge, and HIV-related factors would only change

summed stigma scores by a maximum of two points.

Only one other study aimed to assess the effect of TB stigma on delay in seeking care for

TB symptoms and did not find any association (Woith and Larson 2008). However, they

modified a stigma scale that had been developed for AIDS and cancer and found poor reliability

among one of the sub-scales. Additionally, measurement of delay had important limitations.

Recall error in delay time likely occurred because all patients had received at least three months

of treatment when enrolled and only crude delay categories of < 4 weeks to > 52 weeks by four-

week intervals were collected.

Other studies of delay included a measure of TB stigma as one of many predictor

variables. These included informal measures of stigma such as feeling ostracized (Auer, Sarol et

al. 2000), a single question about whether TB is stigmatizing or not (Cambanis, Yassin et al. 2005; Cambanis, Ramsay et al. 2007), or multi-item measures of stigma that were categorized for analysis (Godfrey-Faussett, Kaunda et al. 2002; Yimer, Bjune et al. 2005). Among these, only feeling ostracized was associated with increased delay (Auer, Sarol et al. 2000). A multi-country study of delay found that high stigma was associated with decreased delay in Somalia (WHO/ROEM 2006). The scale that was used may not have been a valid measure of stigma because it included questions on the economic cost of illness and biologic effect on female reproductive outcomes and breastfeeding. While some researchers suggest that poor TB knowledge can lead to higher stigma, poor knowledge should not be confused or mixed with stigma.

Some limitations of our study should be acknowledged. It should be noted that stigma was assessed only after patients presented at the TB clinics, concurrently with delay time calculation. The levels of stigma observed may not accurately capture the level of stigma near the time of symptoms onset if stigma changes over time. Additionally, selection bias may have occurred because we only enrolled patients who presented at TB clinics. We expect this bias to be minimal, however, because our findings are already close to the null, and the effect of stigma would have to be many times stronger among those who never presented. It is also likely that some recall error occurred. Two-thirds of the patients excluded (32/48) had a calculated delay time that was negative, indicating error in recalling either the duration of symptoms or when the first visit to a qualified provider occurred. It is unlikely that this affected our results as these patients did not differ appreciably from those with valid delay times. For these reasons, interpreting these results as associations is more appropriate than as causal estimates. Finally, information on smoking was not collected in this study. While smoking is thought to be a cause

of delay because smokers may mistakenly attribute their cough to smoking (Selvam, Wares et al. 2007; Slama, Chiang et al. 2007), we do not expect this to bias our findings because smoking is unlikely to be associated with TB or AIDS stigma.

TABLES AND FIGURES

Table 6.1. Distribution of patient characteristics, by inclusion status.

Continuous characteristics		Included (n=432)	Excluded (n=48)
TB stigma	Community perspective (mean, SD)	1.67 (0.45)	1.73 (0.41)
(Item-adjusted score)	Patient perspective (mean, SD)	1.65 (0.37)	1.70 (0.36)
AIDS stigma	Community perspective (mean, SD)	1.69 (0.47)	1.71 (0.47)
(Item-adjusted score)	Patient perspective (mean, SD)	1.97 (0.36)	2.00 (0.32)
Age	Age in years (median, range)	37 (18-79)	36 (18-73)
Income	Thousand Baht per month (median, range)	10 (0-90)	12 (0-52)
Household members	Children (<15 years old) (median, range)	1 (0-8)	1 (0-8)
	Adults (median, range)	3 (0-9)	3 (1-10)
Travel time to provider	Minutes to qualified provider (median, range)	20 (5-120)	25 (5-120)
Categorical characteristics		N (%)	N (%)
Gender	Male	284 (65.7)	33 (68.8)
	Female	148 (34.3)	15 (31.3)
Religion	Buddhist	286 (66.2)	33 (68.8)
	Muslim	144 (33.3)	15 (31.3)
Education	Less than primary school	143 (33.1)	17 (35.4)
	Completed primary	174 (40.3)	17 (35.4)
	Completed secondary	115 (26.6)	14 (29.2)
Friend to see	Yes	398 (92.1)	46 (95.8)
doctor with	No	34 (7.9)	2 (4.2)
Mode of transportation	Car/Motorcycle	338 (78.2)	35 (72.9)
	Bus	69 (16.0)	13 (27.1)
	Walk, Bicycle, Other	25 (5.8)	0 (0.0)
TB knowledge*	Infected from family/others	78 (18.1)	9 (18.8)
(Cause)	Work hard	64 (14.8)	7 (14.6)
	Smoking/drinking	146 (33.8)	16 (33.3)
	Heredity	18 (4.2)	2 (4.2)
	Weak body	75 (17.4)	7 (14.6)
	Eat or drink with patient	17 (3.9)	3 (6.3)
	Other	34 (7.9)	4 (8.3)
TB knowledge†	Eat/drink with patient	263 (60.9)	28 (58.3)
(Transmission)	Cough/sneeze	357 (82.6)	39 (81.3)
	Other (touch, sex, other)	113 (26.2)	15 (31.3)
TB knowledge	Yes	418 (96.8)	45 (93.8)
(Cure)	No	14 (3.2)	3 (6.3)
TB knowledge†	TB increases chance of AIDS	221 (51.2)	21 (43.8)
(TB/HIV)	AIDS increases chance of TB	310 (71.8)	36 (75.0)
	Symptoms appear similar	305 (70.6)	34 (70.8)
Ever tested for AIDS	Yes	184 (42.6)	24 (50.0)
	No	248 (57.4)	24 (50.0)
HIV status‡	Negative	266 (61.6)	29 (60.4)
	New positive	19 (4.4)	2 (4.2)
	Known positive	67 (15.5)	6 (12.5)
	Refused test	80 (18.5)	11 (22.9)
TB symptoms§	Cough	221 (51.2)	17 (35.4)
	Hemoptysis	105 (24.3)	11 (22.9)

Weight loss	55 (12.7)	4 (8.3)
Fever and/or extrapulmonary only	51 (11.8)	2 (4.2)
No symptoms	0 (0.0)	14 (29.2)

* Exclusive or † non-exclusive categories

‡ Known positives had previously tested positive for HIV infection; New positives identified when diagnosed with

§ Cough and hemoptysis may include other symptoms; Weight loss excludes cough but may include other symptoms

Table 6.2. Adjusted differences in mean, log-transformed delay times per one point increase in stigma score*.

Stigma scale	Stratification	Any symptom delay MD (95% CI)	Homog. p-value	Pulmonary delay[†] MD (95% CI)
TB stigma (Community perspective)	All patients	0.004 (-0.007, 0.014)		0.005 (-0.007, 0.017)
TB stigma (Patient perspective)	All patients	0.003 (-0.009, 0.015)		0.003 (-0.010, 0.017)
AIDS stigma (Community perspective)	All patients	-0.003 (-0.013, 0.007)		-0.004 (-0.015, 0.008)
AIDS stigma (Patient perspective)	All patients	0.002 (-0.013, 0.016)		0.002 (-0.015, 0.018)
TB stigma (Community perspectives)	Male	0.012 (-0.001, 0.025)	0.05	0.011 (-0.004, 0.026)
	Female	-0.009 (-0.026, 0.007)		-0.007 (-0.028, 0.014)
TB stigma (Patient perspective)	Male	0.011 (-0.004, 0.026)	0.12	0.010 (-0.007, 0.028)
	Female	-0.007 (-0.025, 0.010)		-0.007 (-0.028, 0.014)
AIDS stigma (Community perspective)	Male	0.004 (-0.009, 0.016)	0.08	0.002 (-0.012, 0.015)
	Female	-0.015 (-0.032, 0.002)		-0.015 (-0.035, 0.005)
AIDS stigma (Patient perspective)	Male	0.000 (-0.019, 0.018)	0.70	0.000 (-0.021, 0.020)
	Female	0.005 (-0.018, 0.029)		0.005 (-0.023, 0.032)
TB stigma (Community perspective)	Cough	-0.002 (-0.016, 0.012)	0.12	-0.003 (-0.017, 0.011)
	Hemoptysis	0.022 (0.001, 0.043)		0.024 (0.002, 0.045)
	Weight Loss	0.011 (-0.018, 0.039)		
	Fever or EPTB	-0.018 (-0.050, 0.014)		
TB stigma (Patient perspective)	Cough	-0.004 (-0.019, 0.011)	0.01	-0.005 (-0.021, 0.010)
	Hemoptysis	0.035 (0.011, 0.060)		0.028 (0.002, 0.053)
	Weight Loss	0.011 (-0.022, 0.044)		
	Fever or EPTB	-0.034 (-0.069, 0.002)		
AIDS stigma (Community perspective)	Cough	-0.008 (-0.022, 0.006)	0.15	-0.010 (-0.024, 0.004)
	Hemoptysis	0.015 (-0.004, 0.034)		0.010 (-0.010, 0.030)
	Weight Loss	-0.001 (-0.030, 0.027)		
	Fever or EPTB	-0.022 (-0.053, 0.009)		
AIDS stigma (Patient perspective)	Cough	-0.005 (-0.024, 0.014)	0.77	-0.003 (-0.022, 0.017)
	Hemoptysis	0.006 (-0.022, 0.035)		0.012 (-0.018, 0.042)
	Weight Loss	0.015 (-0.026, 0.056)		
	Fever or EPTB	0.014 (-0.037, 0.064)		

*Mean difference in $\log_{10}$ transformed days and 95% confidence interval; Homog. p-value, p-value homogeneity test
of stratum-specific effects.
†Pulmonary delay calculated as the time from first cough to the first visit to a qualified provider

Figure 6.1. Kernel-smoothed distribution of untransformed delay time.
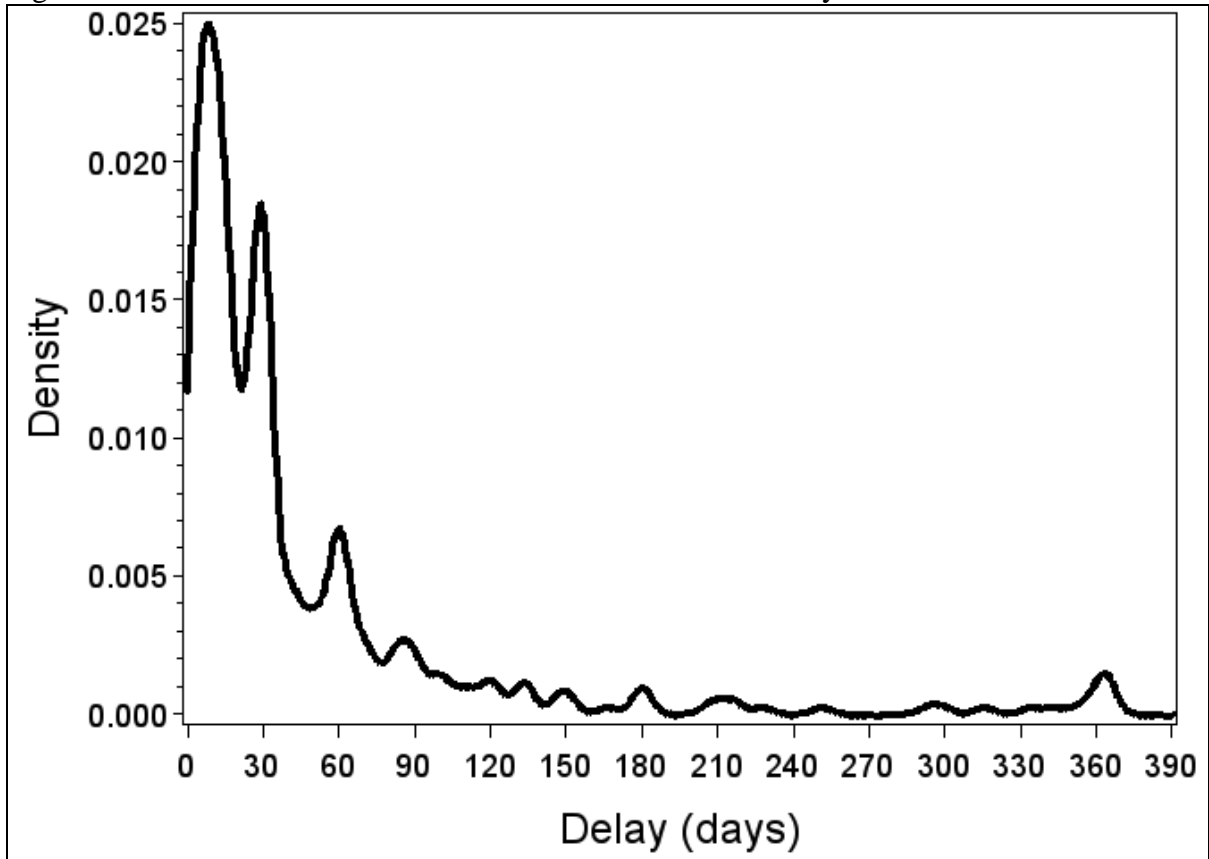
CHAPTER 7

TUBERCULOSIS TREATMENT DEFAULT AND NON-ADHERENCE DUE

TO TUBERCULOSIS AND AIDS STIGMA

BACKGROUND

Adherence to tuberculosis therapy is important because non-adherence, and not just

default, can lead to prolonged infectiousness, treatment failure, disease relapse, drug

resistance, or death (Chaulk and Kazandjian 1998; Gelmanova, Keshavjee et al. 2007). In a

review of qualitative studies, Munro et al. (Munro, Lewin et al. 2007) identified eight major

factors affecting adherence to TB treatment: organization of treatment and care;

interpretation of illness and wellness; financial burden; knowledge, attitudes, and beliefs

about treatment; law and immigration; personal characteristics; drug side effects; and family,

community, and household influence. These factors have been generally supported through

quantitative studies of adherence and default (Connolly, Davies et al. 1999; Santha, Garg et

al. 2002; Cayla, Caminero et al. 2004; Lertmaharit, Kamol-Ratankul et al. 2005; Mishra,

Hansen et al. 2005; Gelmanova, Keshavjee et al. 2007; Shargie and Lindtjorn 2007; Hasker,

Khodjikhanov et al. 2008).

Health-related stigma, defined as a social process "characterized by exclusion,

rejection, blame, or devaluation resulting from experience or reasonable anticipation of an

adverse social judgment" because of a particular health condition (Weiss and Ramakrishna

2006), may also reduce treatment adherence among patients with TB. In an effort to conceal their disease from others, patients may hide their treatment or try to avoid being seen at the clinic, resulting in poor adherence (Liefooghe, Michiels et al. 1995; Nair, George et al. 1997). Fear of losing their job may also prevent patients from asking for financial support or time off to complete treatment, further hindering adherence (Johansson, Diwan et al. 1996). Stigma and fear of isolation may affect adherence primarily among women, whereas poor adherence among men is often individually and financially motivated (Johansson, Long et al. 1999). Difficulty coping with a simultaneous AIDS diagnosis or fear that others would suspect an AIDS diagnosis could also lead to poor adherence among TB patients (Ngamvithayapong, Winkvist et al. 2000).

Only two studies have investigated the association between TB stigma and treatment adherence, neither of which used a formally developed measure of stigma validated in the study population. Comolet et al. found that defaulters were more likely to believe that TB was a shameful disease (Comolet, Rakotomalala et al. 1998), while Woith and Larson reported that high levels of financial insecurity were associated with lower adherence, whereas higher levels of shame were associated with better adherence (Woith and Larson 2008).

The purpose of this study was to estimate the effect of TB and AIDS stigma on adherence to TB treatment among TB patients in southern Thailand using formally developed and validated stigma scales.

METHODS

Study participants, data collection, and definitions

Adults in southern Thailand with newly diagnosed TB were enrolled from a regional TB center and seven TB clinics and followed prospectively through treatment. Patients were eligible if they had been receiving TB treatment for less than one month. Upon enrollment, information on demographics, socioeconomic status, TB knowledge, and TB symptoms were collected using a standardized questionnaire. Patients were referred for counseling and testing if their HIV status was unknown or if they had tested negative more than six months prior to enrollment, but an HIV test was not required for participation. Stigma was measured using two TB stigma scales and two AIDS stigma scales previously developed in southern Thailand (Van Rie, Sengupta et al. 2008). Items were scored using a Likert scale with four levels: strongly disagree (0), disagree (1), agree (2), and strongly agree (3). Responses were summed for each scale to create stigma scores, with higher responses indicating higher stigma. After two months of treatment, participants were re-administered the TB knowledge questions and stigma scales.

Adherence information was documented every time a patient was seen by clinic staff and included the number of pills brought back to the clinic, number of days a dose was missed, reason for missing doses, number of doses newly prescribed, and whether the patient was receiving the intensive or continuation phase treatment regimen. Standard treatment outcomes of cure, treatment completion, treatment failure, death, default, or transferred out (WHO 2003) were assigned to each patient as appropriate.

Two adherence outcomes were used in this study: default and non-adherence. Default was defined as two or more consecutive months without treatment (WHO 2003). Non-adherence was defined as the proportion of days on treatment with a missed dose that

were not attributable to adverse drug side effects. If no doses were missed and all prescriptions were collected on time, non-adherence was zero.

In Thailand, standard treatment for new TB cases involves two months of isoniazid, rifampicin, pyrazinamide, and ethambutol taken daily (2HRZE; intensive phase) followed by four moths of isoniazid and rifampicin taken daily (4HR; continuation phase). Directly observe therapy (DOT) is recommended for all patients, either at the clinic or by a family or community member, but is not required. This decision is made jointly by clinic staff and the patient, and depends on the patient's access to the clinic and availability of family or community members to perform observation.

Dichotomous analysis of default

Multivariable logistic regression (SAS 9.2, PROC GENMOD with logit link and binomial distribution) was used to assess the risk of baseline stigma on subsequent default while controlling for measured confounders. Defaulters during the entire course of treatment, during the intensive phase, and during the continuation phase were compared with those who completed each specific period. Patients who died, transferred out, or had their diagnosis changed to non-TB during the period of interest were excluded from that analysis. For each default analysis, four regression models were built using continuous stigma scores measured at the start of treatment as the exposure of interest.

Confounders were included in the model based on substantive knowledge and with the aid of directed acyclic graphs (Glymour and Greenland 2008; Greenland 2008). Covariates included age, gender, religion, education, income, number of children and adults in the household, knowledge of TB transmission and the link between TB and HIV,

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presenting symptoms, and HIV status. Assignment of DOT was likely independent of stigma or, possibly, a result of the patient's stigma. In either case, it does not meet the criteria for a confounder. Covariates for knowledge of TB cure and cause were not included due to sparse data and problems with model convergence. Interactions between stigma scores and covariates were not assessed due to the small number of defaults in many covariate strata.

Longitudinal analysis of non-adherence

Non-adherence was analyzed as a repeated observation when there was a change from intensive to continuation phase treatment or re-assessment of stigma, resulting in one to three observations per patient. All patients, regardless of treatment outcome, were included in the analysis until they completed treatment or were lost to follow-up.

Multivariable negative binomial regression (SAS 9.2, PROC GENMOD with log link and negative binomial distribution) was used to assess the effect of stigma on the rate of non-adherence while controlling for measured confounders. TB knowledge and treatment phase were included as time-varying covariates. Generalized estimating equations with an exchangeable correlation matrix were specified to account for within subject correlations due to the repeated observations. Four regression models were built using time-varying, continuous stigma scores as the exposure of interest.

Confounders were included in the model based on substantive knowledge and with the aid of directed acyclic graphs (Glymour and Greenland 2008; Greenland 2008). These covariates included age, gender, religion, education, income, number of children and adults in the household, knowledge of TB transmission and the link between TB and HIV, presenting symptoms, HIV status, and treatment phase. Assignment of DOT and knowledge

of TB cure and cause were not included for the same reasons listed above in the analysis of treatment default. Interactions between stigma scores and gender, HIV status, symptoms, and treatment phase were assessed using interaction terms in separate models.   A p-value <0.20 was interpreted as evidence of heterogeneity. For covariates with more than two categories, a Type III test using the Wald Chi-square statistic was performed to simultaneously assess the contribution of each category's interaction with stigma. If evidence of heterogeneity was found for one stigma score, the interaction term was included in all four models.

RESULTS

Patient characteristics

A total of 480 patients were enrolled and followed prospectively, of whom 390 (81.3%) completed treatment, 45 (9.4%) defaulted, and 28 (5.8%) died. Twenty (44.4%) defaults and 12 (43%) deaths occurred during the intensive phase of treatment. The median time to treatment completion was 182 days, while the median time to default and death was 64 and 88 days, respectively. Sixty-one percent (295/480) of patients did not miss any doses during the entire course of treatment or until lost to follow-up. Among those missing at least one dose (n=181), the median number of days with a missed dose was four and median non-adherence was 2.2% (Figure 7.1). Only 6 (3%) had 20% or greater non-adherence. Four patients were missing adherence data. Fourteen (3%) asymptomatic patients were excluded from the analyses.

In bivariate analysis, defaulting increased as the rate of non-adherence increased (Mantel-Hanzel chi-square test, p=0.12) (Table 7.1). However, 63% (27/41) of defaulters had perfect adherence up to the time of default.

For each stigma scale measured at baseline, between 14 and 20 (3-4%) patients had incomplete item responses and stigma scores could not be calculated. Missing stigma scores did not differ between treatment completers and defaulters. Compared with those who completed treatment, defaulters were more often male, not assigned to DOT, co-infected with HIV or refused to be tested, and believed that TB was caused by smoking or drinking (Tables 7.2 and 7.3). Fewer defaulters believed that TB could be transmitted via cough or sneeze, and they presented with hemoptysis less often.

Of the 441 patients completing intensive phase treatment, 423 (96%) completed a second stigma and TB knowledge assessment (Table 7.4). Median stigma scores did not change more than one point between the first and second assessment. After two months of treatment, a lower proportion of defaulters believed that TB was caused by infection from someone else, and the majority still believed that smoking or drinking was the cause of TB. In contrast, a larger proportion of treatment completers believed that TB was caused by infection. Among all patients, the proportion that recognized the link between TB and AIDS increased.

Dichotomous analysis of default

Results from the analysis comparing defaulters to those who completed treatment are shown in Table 7.5. There was little evidence that stigma measured at start of treatment had any effect on default during the entire course of treatment. When patients defaulting during

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the intensive phase were compared to those completing the intensive phase, higher stigma

scores from the community perspective for both TB and AIDS decreased the risk of default

(adjusted OR: 0.93, 95% CI: 0.83, 1.03; adjusted OR: 0.91, 95% CI: 0.82, 1.01). Stigma

scores from the patient perspective scales had no effect on the risk of default during intensive

phase treatment. In contrast, patients reporting higher TB stigma from the patient

perspective at enrollment had an increased risk of default during the continuation phase of

treatment (adjusted OR: 1.10, 95% CI: 0.98, 1.24). Stigma scores from the community

perspective scales did not have an affect on the risk of default during the continuation phase

of treatment. Of the 25 defaulters completing the intensive phase, 9 (36%) were missing a

second stigma score. Therefore we did not estimate the effect of stigma measured after two

months of treatment on default during the continuation phase.

Longitudinal analysis of non-adherence

In multivariable analysis of the time-varying effect of stigma on non-adherence,

stigma was not found to affect the overall rate of non-adherence (Table 7.6). When results

were stratified by HIV status, stigma had little to no effect on non-adherence among patients

who were HIV negative. Among patients co-infected with HIV, those reporting higher TB

stigma from the community and patient perspectives had 1.08 (95% CI: 1.00, 1.17) and 1.10

(95% CI: 1.01, 1.20) times the rate of non-adherence compared to those with a one point

lower stigma score, respectively. In contrast, among patients who refused the HIV test, those

reporting higher TB stigma from both scales had higher rates of adherence (adjusted RR:

0.93, 95% CI: 0.86, 1.00). AIDS stigma showed no effect on non-adherence with the

exception of AIDS stigma from the patient perspective among patients who refused the HIV test (adjusted OR: 0.89, 95% CI: 0.82, 0.96).

When results were stratified by presenting symptoms, there was little to no effect of stigma among patients presenting with cough. Among patients presenting with hemoptysis, those with higher TB stigma from the community perspective had 1.13 (95% CI: 1.05, 1.21) times the rate of non-adherence. In fact, higher TB stigma from the patient perspective scale and from both AIDS stigma scales was associated with an increased rate of non-adherence among patients presenting with either hemoptysis or non-cough symptoms (adjusted RRs of 1.05 to 1.08).

DISCUSSION

Among patients with TB in southern Thailand, TB and AIDS stigma had a minimal effect on default and adherence when measured using formally developed stigma scales. However, the observed null effects are likely due to differential effects within specific sub-groups. Higher stigma from the community perspective scales for both TB and AIDS decreased the risk of default during the intensive phase of treatment, when patients are still symptomatic and identifiable in the community. In contrast, higher stigma from both patient perspective scales increased the risk of default during the continuation phase of treatment, when patients may be more concerned about their personal experiences, rather than community perceptions. This finding is similar to results from a retrospective study where defaulters were more likely to feel that TB was a shameful disease (crude OR of 2.97) (Comolet, Rakotomalala et al. 1998).

Similar to default, we did not find an overall effect of stigma on the rate of non-adherence. HIV status and presenting symptoms, however, did modify the effect of stigma. TB and AIDS stigma had little to no effect on adherence among HIV negative patients. Higher TB stigma from both the community and patient perspective scales, however, increased the rate of non-adherence among patients co-infected with HIV. In contrast, among those who refused an HIV test, higher TB stigma and AIDS stigma from the patient perspective improved adherence. Surprisingly, AIDS stigma also had no effect among patients who were HIV co-infected. This could occur because HIV status is a hidden, rather than visible, attribute. As long as a patient does not disclose his or her status, others in the community will not know, and therefore any existing stigma may not have an adverse effect. Nevertheless, it has been reported that HIV status itself is associated with default and non-adherence (Connolly, Davies et al. 1999; Naing, D'Este et al. 2001). Our findings are similar to that observed among TB patients in Russia, where higher feelings of shame (one aspect of our patient perspective scale) were associated with improved adherence (Woith and Larson 2008). The Russian study, however, only considered adherence during the continuation phase of treatment and did not report on the HIV status of participants.

We also found that presenting symptoms modified the effect of stigma on non-adherence. Among patients with hemoptysis, both TB-and AIDS-stigma, especially TB stigma from the community perspective, increased the rate of non-adherence. This was also true among patients presenting without a cough, where higher TB stigma from the patient perspective and AIDS stigma increased the rates of non-adherence. Unlike HIV status, TB symptoms are a visible attribute. And because severe or atypical symptoms could suggest HIV infection, existing AIDS stigma could exert an adverse effect on those patients.

When results from both the default and non-adherence analyses are considered, several important points emerge. First, stigma appears to have a minimal effect on adherence. The largest effects of stigma that we observed were to increase default or non-adherence by 10%. Given that default and non-adherence were low in our study population, this translates into an increase that may not be clinically relevant. Nevertheless, any level of poor adherence increases the risk of drug resistant TB. Second, stigma has a negative effect on adherence among specific sub-groups, including patients who are co-infected with HIV and those presenting with hemoptysis or atypical symptoms. Third, there were instances of higher stigma improving adherence, rather than being a barrier to it. Both TB and AIDS stigma from the community perspective decreased the risk of default during the intensive phase, while TB stigma and AIDS stigma from the patient perspective decreased the rate of non-adherence among those with unknown HIV status. This suggests that awareness of cultural norms and fear of social consequences can motivate health behavior. Finally, our study suggests that important, differential effects exist within specific sub-groups which could go unobserved if they are collapsed across the entire study population. The effect of stigma on adherence is complex, with the potential to be a barrier or motivator depending on the sub-group of the population. Future studies should take this into account to properly identify the effects of stigma, while interventions should be targeted to the groups that would benefit from stigma reduction.

Some potential limitations should be addressed. First, data on alcohol and substance abuse, travel time to the clinic, and quality of care were not collected. While these factors are suspected to influence adherence (Santha, Garg et al. 2002; Gelmanova, Keshavjee et al. 2007; Shargie and Lindtjorn 2007), we would not expect these factors to affect stigma and

therefore they would not confound the observed associations. Some misclassification of treatment phase could have occurred for the 75 (16%) patients who did not have specific information on when intensive phase treatment was completed. Such misclassification, however, is expected to be independent of stigma, default, and non-adherence. Nevertheless, the differential effects observed for intensive phase default and continuation phase default may be exaggerated. There was also the potential for misclassification of adherence. While steps were taken to correctly record doses that were and were not ingested, there is the possibility that patients disposed of their prescriptions rather than bringing them to the clinic visit. Our findings could be biased if such practices occurred differentially among patients with higher stigma.

TABLES AND FIGURES

Table 7.1. Crude association between non-adherence and default.

Non-adherence	All patients*	Completers	Defaulters	COR	(95% CI)[†]
0%	261	235	26		Referent
≤5%	120	113	7	0.56	(0.24, 1.33)
≤10%	25	21	4	1.72	(0.55, 5.40)
≤20%	10	8	2	2.20	(0.46, 11.21)
>20%	4	2	2	9.04	(1.22, 66.88)

*excludes 28 deaths, 12 transfers, 5 with changed diagnosis to non-TB, 14 with no symptoms, and one with missing adherence data

[†]OR, odds ratio; CI, confidence interval; Mantel-Hanzel Chi-square test for correlation across ordinal levels: x^2=2.70; d.f.=1; exact p-value=0.12

Table 7.2. Baseline participant characteristics (continuous), by treatment outcome.

		Completed (N=390)	Default (N=45)	Others (N=45)*
		Median (Range)	**Median (Range)**	**Median (Range)**
TB Stigma	Community perspectives (11 items)	19 (2 – 33)	19 (7 – 33)	20 (10 – 26)
	Patient perspectives (12 items)	19 (0 – 36)	20 (9 – 30)	22 (14 – 33)
AIDS Stigma	Community perspectives (11 items)	20 (5 – 33)	18 (7 – 30)	21 (9 – 32)
	Patient perspectives (10 items)	20 (3 – 30)	20 (10 – 29)	20 (11 – 28)
Age	Age in years	36.5 (18 – 79)	34 (21 – 63)	39 (25 – 67)
Income	Thousand Baht per month	10 (0 – 90)	10 (2 – 50)	9 (1 – 80)
Household Members	Children (<15 years old)	1 (0 – 8)	1 (0 – 8)	1 (0 – 3)

*Includes 28 deaths, 12 who transferred out, and 5 with changed diagnosis to non-TB.

Table 7.3. Baseline participant characteristics (categorical), by treatment outcome.

		Completed	Default	Others*
		N (%)	N (%)	N (%)
Gender	Male	244 (62.6)	37 (82.2)	36 (80.0)
	Female	146 (37.4)	8 (17.8)	9 (20.0)
Religion	Buddhist	261 (66.9)	28 (62.2)	30 (66.7)
	Muslim	129 (33.1)	15 (33.3)	15 (33.3)
Education	Less than primary school	126 (32.3)	15 (33.3)	19 (42.2)
	Completed primary	154 (39.5)	21 (46.7)	16 (35.6)
	Completed secondary	110 (28.2)	9 (20.0)	10 (22.2)
Directly Observed Therapy	None	212 (54.4)	36 (80.0)	18 (40.0)
	Health care worker	77 (19.7)	1 (2.2)	7 (15.6)
	Family member	101 (25.9)	8 (17.8)	20 (44.4)
TB knowledge: (Cure)	No	13 (3.3)	3 (6.7)	1 (2.2)
	Yes	377 (96.7)	42 (93.3)	44 (97.8)
TB knowledge: (Cause)	Infected from family/others	72 (18.5)	10 (22.2)	5 (11.1)
	Work hard	58 (14.9)	5 (11.1)	8 (17.8)
	Smoking/drinking	125 (32.1)	19 (42.2)	18 (40.0)
	Heredity	18 (4.6)	2 (4.4)	0 (0.0)
	Weak body	72 (18.5)	6 (13.3)	4 (8.9)
	Eat/drink with patient	18 (4.6)	1 (2.2)	1 (2.2)
	Other	27 (6.9)	2 (4.4)	9 (20.0)
TB knowledge: (Transmission)	Eat/Drink	241 (61.8)	29 (64.4)	21 (46.7)
	Cough/Sneeze	331 (84.9)	31 (68.9)	34 (75.6)
	Other (touch, sex, other)	105 (26.9)	16 (35.6)	7 (15.6)
TB knowledge: (TB/HIV)	TB increases chance of AIDS	191 (49.0)	25 (55.6)	26 (57.8)
	AIDS increases chance of TB	288 (73.8)	33 (73.3)	25 (55.6)
	Symptoms appear similar	280 (71.8)	34 (75.6)	25 (55.6)
HIV Status	Negative	268 (68.7)	17 (37.8)	10 (22.2)
	Positive	60 (15.1)	14 (31.1)	20 (44.5)
	Refused test	62 (15.9)	14 (31.1)	15 (33.3)
Symptoms	Cough	190 (48.7)	22 (48.9)	24 (53.3)
	Hemoptysis	100 (25.6)	8 (17.8)	8 (17.8)
	Non-cough	89 (22.8)	12 (26.7)	13 (28.9)
	No symptoms	11 (2.8)	3 (6.7)	0 (0.0)

*Includes 28 deaths, 12 who transferred out, and 5 with changed diagnosis to non-TB.

Table 7.4. Second assessment of stigma and TB knowledge among patients completing intensive phase therapy, by treatment outcome (N=423).

Stigma		Complete (N=385) Median (Range)	Default (N=16) Median (Range)	Others (N=22)* Median (Range)
TB Stigma	Community perspectives (11 items)	19 (0 – 30)	18 (12 – 22)	19 (8 – 28)
	Patient perspectives (12 items)	20 (3 – 35)	19 (13 – 24)	21 (3 – 34)
AIDS Stigma	Community perspectives (11 items)	20 (5 – 33)	18 (11 – 23)	20 (7 – 33)
	Patient perspectives (10 items)	20 (0 – 30)	19 (17 – 29)	20 (6 – 30)
TB knowledge		N (%)	N (%)	N (%)
Cure	No	1 (0.3)	0 (0.0)	0 (0.0)
	Yes	384 (99.7)	16 (100.0)	22 (100.0)
Cause	Infected from family/others	106 (27.5)	2 (12.5)	5 (22.7)
	Work hard	45 (11.7)	0 (0.0)	2 (9.1)
	Smoking/drinking	103 (26.8)	8 (50.0)	9 (40.9)
	Heredity	16 (4.2)	1 (6.3)	0 (0.0)
	Weak body	69 (17.9)	2 (12.5)	3 (13.6)
	Eat/drink with patient	36 (9.4)	2 (12.5)	1 (4.6)
	Other	10 (2.6)	1 (6.25)	2 (9.1)
Transmission	Eat/Drink	239 (62.1)	11 (68.8)	11 (50.0)
	Cough/Sneeze	340 (88.3)	12 (75.0)	14 (63.6)
	Other (touch, sex, other)	91 (23.6)	1 (6.3)	6 (27.3)
TB/HIV	TB increases chance of AIDS	243 (63.1)	11 (68.8)	17 (77.3)
	AIDS increases chance of TB	347 (90.1)	14 (87.5)	21 (95.5)
	Symptoms appear similar	294 (76.4)	15 (93.8)	19 (86.4)

*Includes 14 deaths and 8 who transferred out

Table 7.5. Odds ratios for the effect of baseline TB and AIDS stigma on treatment default*.

Default at any time during treatment	Events	COR (95% CI)	Events	AOR (95% CI)
TB stigma (Community perspectives)	40	0.99 (0.93, 1.06)	38	0.98 (0.91, 1.05)
TB stigma (Patient perspectives)	38	1.08 (1.01, 1.17)	37	1.05 (0.97, 1.15)
AIDS stigma (Community perspectives)	41	0.98 (0.93, 1.05)	39	0.97 (0.91, 1.04)
AIDS stigma (Patient perspectives)	41	1.00 (0.92, 1.10)	39	1.01 (0.91, 1.11)
Default during intensive phase treatment	**Events**	**COR (95% CI)**	**Events**	**AOR (95% CI)**
TB stigma (Community perspectives)	19	0.96 (0.88, 1.06)	18	0.93 (0.83, 1.03)
TB stigma (Patient perspectives)	16	1.04 (0.93, 1.16)	16	1.00 (0.88, 1.14)
AIDS stigma (Community perspectives)	19	0.94 (0.87, 1.03)	18	0.91 (0.82, 1.01)
AIDS stigma (Patient perspectives)	18	0.96 (0.85, 1.10)	17	0.97 (0.84, 1.12)
Default during continuation phase treatment	**Events**	**COR (95% CI)**	**Events**	**AOR (95% CI)**
TB stigma (Community perspectives)	21	1.02 (0.94, 1.11)	20	1.02 (0.92, 1.12)
TB stigma (Patient perspectives)	22	1.11 (1.01, 1.22)	21	1.10 (0.98, 1.24)
AIDS stigma (Community perspectives)	22	1.02 (0.94, 1.11)	21	1.02 (0.93, 1.12)
AIDS stigma (Patient perspectives)	23	1.03 (0.92, 1.16)	22	1.06 (0.93, 1.21)

* Events, number who defaulted; COR, crude odds ratio; AOR, adjusted odds ratio (see Methods section); CI, confidence interval

Table 7.6. Rate ratios for the effect of stigma on non-adherence to TB treatment*.

Stigma scale	Stratification	CRR (95% CI)	ARR (95% CI)	Homog. p-value
TB stigma (community perspective)	All patients	1.01 (0.96, 1.07)	0.99 (0.95, 1.03)	
TB stigma (patient perspective)	All patients	1.04 (0.99, 1.09)	1.02 (0.97, 1.07)	
AIDS stigma (community perspective)	All patients	1.02 (0.97, 1.07)	1.01 (0.97, 1.05)	
AIDS stigma (patient perspective)	All patients	1.02 (0.97, 1.08)	1.01 (0.96, 1.06)	
TB stigma (community perspective)	HIV negative	1.00 (0.95, 1.06)	0.99 (0.93, 1.05)	0.01
	HIV positive	1.11 (0.99, 1.25)	1.08 (1.00, 1.17)	
	Refused test	0.94 (0.87, 1.02)	0.93 (0.87, 1.00)	
TB stigma (patient perspective)	HIV negative	1.04 (0.98, 1.11)	1.02 (0.95, 1.09)	0.01
	HIV positive	1.09 (0.96, 1.23)	1.10 (1.01, 1.20)	
	Refused test	0.95 (0.88, 1.04)	0.93 (0.86, 1.00)	
AIDS stigma (community perspective)	HIV negative	1.03 (0.96, 1.11)	1.01 (0.95, 1.07)	0.60
	HIV positive	1.00 (0.94, 1.05)	1.04 (0.98, 1.10)	
	Refused test	0.99 (0.91, 1.09)	0.99 (0.90, 1.08)	
AIDS stigma (patient perspective)	HIV negative	1.05 (0.97, 1.13)	1.04 (0.96, 1.12)	0.03
	HIV positive	0.93 (0.84, 1.02)	0.95 (0.86, 1.06)	
	Refused test	0.89 (0.83, 0.97)	0.89 (0.82, 0.96)	
TB stigma (community perspective)	Cough	0.97 (0.92, 1.03)	0.96 (0.90, 1.02)	<0.01
	Hemoptysis	1.15 (1.07, 1.23)	1.13 (1.05, 1.21)	
	Non-cough	0.96 (0.89, 1.04)	0.97 (0.91, 1.04)	
TB stigma (patient perspective)	Cough	0.99 (0.92, 1.07)	0.99 (0.92, 1.07)	0.25
	Hemoptysis	1.11 (1.00, 1.24)	1.08 (0.98, 1.18)	
	Non-cough	1.10 (1.04, 1.16)	1.08 (1.01, 1.15)	
AIDS stigma (community perspective)	Cough	0.98 (0.93, 1.03)	0.96 (0.91, 1.00)	<0.01
	Hemoptysis	1.10 (0.99, 1.22)	1.08 (0.99, 1.18)	
	Non-cough	1.02 (0.96, 1.09)	1.07 (1.01, 1.14)	
AIDS stigma (patient perspective)	Cough	0.98 (0.92, 1.04)	0.98 (0.92, 1.05)	0.24
	Hemoptysis	1.09 (0.96, 1.24)	1.06 (0.94, 1.20)	
	Non-cough	1.05 (0.98, 1.12)	1.05 (0.99, 1.12)	

*CRR, crude rate ratio; ARR, adjusted rate ratio (see Methods section); CI, confidence interval; Homog. p-value, p-value homogeneity test of stratum-specific effects.

Figure 7.1. Distribution of non-adherence during treatment*.
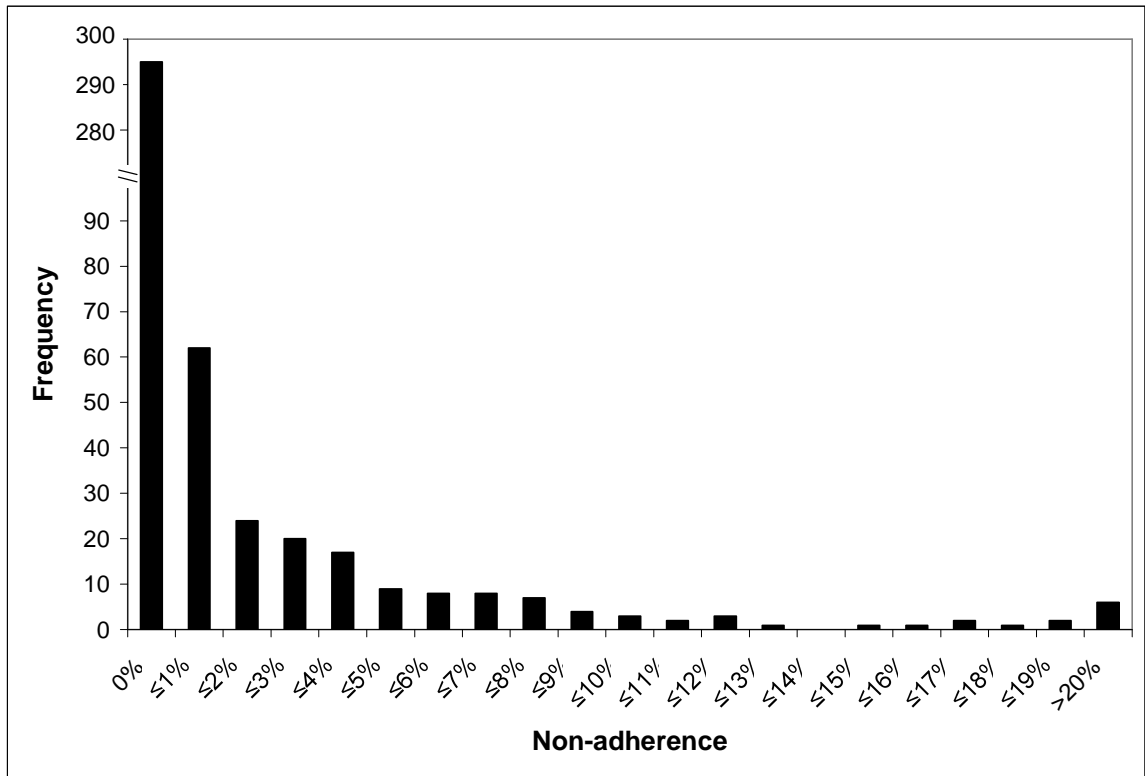
*6 patients had non-adherence ≥20%; 4 had missing adherence data.

CHAPTER 8

DISCUSSION AND FUTURE DIRECTIONS

OVERVIEW

Health-related stigma has received increasing attention as an important factor in public health. It is now understood to be a complex social process that involves attitudes, practices, and actions on the part of healthy community members towards affect or potentially affect individuals, as well as the perceptions, experiences, and internalization of the community's beliefs on the part of the affected individual. A complex research agenda for health-related stigma includes documenting the burden of stigma, comparing stigma in different settings, identifying determinants and effects of stigma, and evaluating changes in stigma over time and in response to interventions. While TB stigma has historically been reported, it remains unclear what impact it has on TB control, including seeking care for symptoms, adherence, and ultimately ongoing transmission. There is also concern that stigma related to HIV/AIDS may compound existing TB stigma and adversely affect TB control.

Numerous measures of HIV/AIDS stigma have been developed, but this has not been true for TB, making it difficult to quantify the presence, determinants, and effects of stigma on TB control. Some measures have been published recently that are well-developed, and they indicate relatively low levels of stigma in the study populations and offer conflicting results about why stigma exists. There are even fewer studies that have quantified the

association between TB stigma and delay in seeking care for symptoms or adherence to treatment. All of them suffer from methodologic limitations related to measurement of stigma, variation in the study population, definition of delay, and definition of adherence. Specifically, few used any formal measure of stigma.

The current study performed in southern Thailand has contributed to the growing literature of TB and AIDS stigma. The developed scales measure nearly identical community and patient perspectives of both TB and AIDS stigma, thus reliably capturing the complex nature of stigma for these overlapping diseases. And the findings from this study are some of the first to quantitatively evaluate the presence of stigma, its possible determinants, and the effect it has on seeking care for TB symptoms and adherence to TB treatment.

STUDY FINDINGS

We found high levels of both TB and AIDS stigma in southern Thailand. Mean, item-adjusted scores, which can range from zero to three, were observed to range from 1.65 for TB stigma from the *patient perspective* among TB patients to 2.21 for AIDS stigma from the *patient perspective* among healthy community members. A score of one corresponds to a response of "disagree", a score of two corresponds to a response of "agree", and a score of three corresponds with "strongly agree". Few factors were identified that could be determinants of higher TB stigma. Knowledge about the cause, transmission, or curability of TB were not consistently associated with higher stigma. However, among both community members and patients with TB, beliefs about the link between TB and AIDS and higher AIDS stigma consistently resulted in small increases in TB stigma. And among community

members, those who knew someone who died of TB had summed stigma scores that were two points higher, the largest difference observed.

While high levels of TB and AIDS stigma were reported, patients with TB had relatively short times from symptom onset to first health provider visit (median of 26 days) and very good adherence to treatment: 61% had perfect adherence, only 3% missed ≥20% of their days on treatment, and 9% defaulted. In the analysis of stigma on delay times in seeking care for TB symptoms, the upper bound for changes in delay time was 15%, or approximately four days relative to the median time, per unit increase in stigma score. In the analysis of stigma on adherence to treatment, observed effects ranged from an 11% *decrease* to 13% *increase* in the risk of default and non-adherence among sub-groups. As with the delay analysis, these are small absolute effects given the baseline level of default and adherence, although any form of incomplete treatment can contribute to the development of drug resistance. Many of the analyses showed stigma to have a null effect on either delay or adherence. Given that differences in socio-demographic, TB knowledge, and clinical factors only resulted in one to two point changes in stigma scores, it can be concluded that stigma has a minimal impact on TB control in southern Thailand. This is not to suggest, however, that stigma may not play an important role in TB control in other areas with higher rates of HIV co-infection, longer delay times, or poorer adherence.

Nevertheless, some important points should not be overlooked. First, in both the delay and adherence analyses, TB stigma tended to have larger effects than AIDS stigma. Second, in each of the analyses, there were sub-groups within the study population in which the effect of stigma was to decrease the delay time (women, presenting with non-cough symptoms) and improve adherence (patients with TB who refused an HIV test). While this

does not suggest that experiences of stigma are not detrimental to individuals, it does demonstrate how awareness of cultural norms and fear of social consequences can motivate health behavior. It also suggests that stigma may exert its negative effect within specific sub-groups of a population and not necessarily across the entire population, where opposite effects within sub-groups may combine to a null overall effect.

The strengths of these studies should be acknowledged. This is the first study to use formally developed stigma scales to assess the determinants and effects of stigma on TB control. As a result, we are confident that stigma was reliably measured. Previous studies developed stigma scales primarily to measure stigma or used crude measures of stigma in larger studies of TB services research. This study used the formally developed scales to both measure the level of stigma and to identify its possible determinants and effects. Furthermore, this is the first study to investigate the effect of AIDS stigma on TB control, rather than just TB stigma. As the epidemics of TB and HIV continue to converge, it may be important to distinguish between these overlapping stigmas.

Previous studies on TB treatment adherence were primarily restricted to retrospective studies of treatment defaulters and completers. Our adherence study was prospective and collected data on regular adherence, not just default. As a result, we were able to analyze less severe forms of non-adherence and were less likely to suffer from selection and recall bias introduced when defaulters and completers have to be traced and interviewed.

The limitations to our study should also be mentioned. Many of the estimated results had poor precision. This occurred in the analysis of determinants of TB stigma in which many categories within the "knowledge of TB cause" domain had small numbers of respondents. Similarly, the delay and adherence studies stratified results by gender, HIV

status, and presenting symptoms. Our original analyses of precision, power and sample size did not account for these sub-group analyses. Nevertheless, point and interval estimates of the estimates were small, and increased precision would likely not have changed any of the conclusions.

The delay analysis suffered from two major limitations. First, it selected only patients who successfully presented to a TB clinic. Patients with cough symptoms due to another disease and those who never sought care for their symptoms were not captured by the study. It is reasonable to assume that stigma could affect their health-seeking behavior. There was also the potential for recall bias because patients were asked to recall their duration of symptoms and when their first visit to a qualified doctor occurred. The longer the duration of symptoms and the longer the duration between first presentation to a clinic and enrollment in the study, the more these measurements are prone to error. Delay time was calculated directly from these self reports, and therefore misspecification of delay time could have occurred in some cases.

The adherence analysis had the potential for misclassification of adherence. While steps were taken to correctly record doses that were and were not ingested, there is the possibility that patients disposed of their prescriptions rather than bringing them to the clinic visit. Our findings could be biased if such practices occurred differentially among patients with higher stigma.

FUTURE DIRECTIONS

Measurement

Health-stigma continues to be a difficult concept to measure because it is a complex social process. It necessarily involves interaction, whether directly or indirectly, between those who are healthy and those who are infected or appear to be infected. Two important issues emerge for future research.

Sub-group effects. Results from these studies suggest that stigma could be both a motivation and a barrier to accessing health care and controlling disease. At a population level, the presence of these effects may average out to show a null effect. Thus, exploration of interactions between stigma and other covariates of interest is important in understanding the effect of stigma. Qualitative reports have suggested that women are more adversely affected by the social consequences of stigma. As a result we considered interactions between stigma and gender. In the analysis of stigma and delay in seeking care for symptoms, the effect of higher stigma was to increase delay time among men, while decreasing delay time among women. The difference in effects was small, but the opposite direction of the effects suggests that future research should be performed giving attention to these groups, rather than averaging across them. It is likely that other important sub-groups exist, and future studies should involve sufficient sample sizes to explore these sub-groups.

Unit of measurement. The complex and social nature of stigma raises the question of whether it should be measured at the individual level or at a community or systems level. Currently, no aggregate measure of community stigma exists. All scales have been developed and analyzed within individual units. But conceptualizing stigma as a social process implies that individuals deciding to seek care for symptoms do so within the context of a stigmatizing (or non-stigmatizing) community. It is unknown whether asking patients about their perceived or experienced stigma provides valid information about whether or not

the community they live in is a stigmatizing community. This has important implications for intervention. Typically, if patients report stigmatizing attitudes, and these attitudes are deemed to negatively affect access to health care or health behavior, then interventions are suggested to educate the community about the disease. Yet the actual level of stigma in the community, and whether or not it affects a patient's access to care, have not been assessed.

Multi-level analyses (or hierarchical models) may prove useful in this context. Community levels of stigma could be measured by aggregating community perspective stigma responses from community surveys or through a structural measurement that does not involve respondents, such as quantifying relevant policies or media in the community. Theoretically, if this could be measured in a number of well-defined communities, while simultaneously enrolling patients who present at health facilities within the selected communities, multilevel models could be used to estimate the effect of community level stigma on individual outcomes.

Interventions

The results of these studies have implications for stigma interventions. First, stigma appeared to have opposite effects among different sub-groups. This suggests that for some individuals, the presence of stigma may act as a motivator. While the presence of high stigma is a concern, our findings suggest that there may be some instances where stigma reduction is not necessary to improve health. A second, and related implication, is that of targeting sub-groups for stigma intervention. Discussions about stigma interventions have tended to focus on the general population or the entire patient population. However, our results found that stigma could have a negative, null, or positive effect on health behavior

depending on the sub-group under study. Therefore, future interventions should identify sub-groups that would most benefit from stigma reduction. Not only will this improve the overall effectiveness of the intervention, but will also conserve resources.

Interventions should also consider stigma from other, related health conditions in addition to the one under study. In our study, we found that both TB and AIDS stigma had an effect on TB control. In some contexts, such as areas with high rates of HIV infection, reductions in AIDS stigma may lead to reductions in TB stigma, while simultaneously improving TB control.

APPENDIX: SENSITIVITY ANALYSIS TABLES FOR SPECIFIC AIM ONE

Table A1. Specified distributions for the two bias parameters needed to perform a sensitivity analysis of an unmeasured confounder (knowing someone with TB who died) on the association between TB knowledge and TB stigma among patients with TB*.

		Distribution of the unmeasured confounder within categories of knowledge			
TB knowledge	**Knowledge category**	**Observed frequency of knowing someone with TB who died, within knowledge category (p)**	**Observed frequency of knowing someone with TB who died, within referent knowledge category (q)†**	**Rounded value of the difference in frequency of knowing someone with TB who died, between knowledge categories (p-q)**	**Lower/Upper bound of the difference in frequency [(p-q)±0.15]**
Cause	Eat/drink with patient	0.05	0.12	-0.05	-0.20, 0.10
	Smoking/drinking	0.13	0.12	0.00	-0.15, 0.15
	Work hard	0.00	0.12	-0.10	-0.25, 0.05
	Heredity	0.36	0.12	0.25	0.10, 0.40
	Weak body	0.07	0.12	-0.05	-0.20, 0.10
Transmission	Cough/sneeze	0.12	0.14	0.00	-0.15, 0.15
	Eat/drink	0.17	0.10	0.05	-0.10, 0.20
	Touch	0.38	0.10	0.30	0.15, 0.45
	Sex	0.19	0.12	0.05	-0.10, 0.20
Curable	Yes	0.12	0.16	-0.05	-0.20, 0.10
TB/HIV	TB increases AIDS	0.14	0.11	0.00	-0.15, 0.15
	AIDS increases TB	0.12	0.14	0.00	-0.15, 0.15
	AIDS/TB appear similar	0.12	0.14	0.00	-0.15, 0.15
		Effect of the unmeasured confounder on TB stigma			
	Stigma	**Observed mean difference (std error) for knowing someone with TB who died**		**Rounded mean difference for knowing someone with TB who died (w)**	**Lower/Upper bound of the mean difference (w ± 2.00)**
TB stigma (community perspective)		2.59 (0.83)		2.50	0.50, 4.50
TB stigma (patient perspective)		1.96 (0.82)		2.00	0.00, 4.00

* Observed valued obtained from community member data.

† Referent category for TB cause is infection from family/others; All others are dichotomous yes/no

Table A2. Sensitivity analysis of an unmeasured confounder for TB knowledge and TB stigma from the community perspective among patients with TB*.

		Community perspective stigma scale					Patient perspective stigma scale				
		L95UL	LSAE	SAE	USAE	U95UL	L95UL	LSAE	SAE	USAE	U95UL
TB Knowledge†	Infection from others			0.00					0.00		
(Cause)	Eat/drink with patient	-3.73	-1.91	-1.31	-0.56	1.09	-2.64	-1.02	-0.53	0.18	1.69
	Smoking/drinking	-2.01	-1.34	-0.66	0.02	0.72	-0.83	-0.18	0.42	1.02	1.65
	Work hard	-2.94	-1.80	-1.31	-0.45	0.34	-1.49	-0.37	0.01	0.83	1.52
	Heredity	-4.12	-2.78	-1.61	-1.03	0.83	-3.90	-2.83	-1.73	-1.23	0.42
	Weak body	-1.66	-0.75	-0.18	0.60	1.33	-1.66	-0.76	-0.28	0.44	1.10
TB Knowledge‡	Cough/sneeze	-1.14	-0.60	0.07	0.76	1.31	-0.72	-0.20	0.41	1.00	1.50
(Transmission)	Eat/drink	-0.58	-0.38	0.39	0.97	1.35	-0.54	-0.36	0.34	0.84	1.21
	Touch	-2.57	-2.17	-0.89	-0.22	0.81	-0.92	-0.59	0.62	1.21	2.07
	Sex	-0.62	0.16	0.93	1.51	2.45	-0.58	0.12	0.81	1.32	2.23
TB Knowledge	Not curable			0.00					0.00		
(Cure)	Curable	-3.74	-1.86	-1.26	-0.51	1.20	-3.10	-1.31	-0.81	-0.11	1.51
TB Knowledge‡	TB increases AIDS	0.15	0.41	1.08	1.76	2.04	1.32	1.56	2.17	2.76	2.97
(TB/HIV)	AIDS increases TB	-0.62	-0.26	0.42	1.10	1.46	-0.07	0.25	0.86	1.45	1.80
	AIDS/TB appear similar	-0.19	0.19	0.86	1.54	1.87	-0.05	0.26	0.87	1.46	1.79

* SAE, sensitivity analysis estimate of the mean difference in summed stigma score; LSAE/USAE, lower and upper sensitivity analysis estimates given the minimum and maximum bias parameters from the triangular distribution; L95UL/U95UL, lower and upper 95% uncertainty limits obtained by sampling from the distribution of updated mean differences.

† Exclusive or ‡ non-exclusive categories.

Table A3. Sensitivity analysis of adjusted differences in mean, summed stigma scores for participant characteristics with stigma item responses coded as 0, 1, 3, 4.

| | | Community perspectives stigma scale | | Patient perspectives stigma scale | |
| | | Patients with TB | Community | Patients with TB | Community |
		MD* (95% CI)	MD* (95% CI)	MD* (95% CI)	MD* (95% CI)
Age	Age (per 10 year)	1.14 (0.62, 1.66)	1.07 (0.39, 1.76)	0.35 (-0.13, 0.83)	-0.29 (-0.94, 0.36)
Gender	Male	0.0	0.0	0.0	0.0
	Female	0.20 (-1.36, 1.76)	0.54 (-1.14, 2.23)	-1.37 (-2.80, 0.06)	1.83 (0.23, 3.42)
Religion	Buddhist	0.0	0.0	0.0	0.0
	Muslim	-2.32 (-3.89, -0.76)	0.69 (-1.49, 2.87)	0.28 (-1.15, 1.71)	0.27 (-1.77, 2.32)
Education	Completed secondary	0.0	0.0	0.0	0.0
	Completed primary	-0.68 (-2.53, 1.17)	0.15 (-1.77, 2.06)	1.04 (-0.61, 2.70)	1.47 (-0.33, 3.26)
	Some or no primary	1.48 (-0.45, 3.41)	2.41 (0.14, 4.67)	2.26 (0.53, 4.00)	0.88 (-1.25, 3.00)
Income	Baht/month (1,000 baht)	0.00 (-0.06, 0.06)	-0.01 (-0.09, 0.07)	-0.03 (-0.08, 0.03)	-0.05 (-0.12, 0.02)
TB Knowledge†	Infection from others	0.0	0.0	0.0	0.0
(Cause)	Eat/drink with patient	-2.61 (-6.57, 1.35)	1.15 (-1.92, 4.22)	-1.27 (-4.79, 2.25)	0.33 (-2.59, 3.25)
	Smoking/drinking	-0.99 (-3.14, 1.16)	-0.39 (-2.86, 2.09)	0.78 (-1.19, 2.75)	0.31 (-2.04, 2.66)
	Work hard	-2.42 (-5.02, 0.18)	Too few	-0.21 (-2.59, 2.17)	Too few
	Heredity	-1.94 (-5.91, 2.04)	-2.79 (-6.42, 0.83)	-2.01 (-5.55, 1.52)	-0.97 (-4.42, 2.48)
	Weak body	-0.46 (-2.88, 1.96)	0.61 (-2.89, 4.11)	-0.64 (-2.86, 1.58)	2.37 (-0.97, 5.70)
TB Knowledge‡	Cough/sneeze	0.43 (-1.48, 2.35)	-0.27 (-2.18, 1.63)	0.95 (-0.81, 2.72)	1.24 (-0.56, 3.05)
(Transmission)	Eat/drink	0.96 (-0.53, 2.45)	2.71 (1.00, 4.42)	0.93 (-0.43, 2.28)	0.81 (-0.84, 2.46)
	Touch	-0.54 (-3.15, 2.07)	-0.24 (-3.08, 2.60)	1.91 (-0.45, 4.27)	0.56 (-2.14, 3.26)
	Sex	1.82 (-0.64, 4.28)	3.45 (-0.26, 7.15)	1.58 (-0.70, 3.85)	2.64 (-0.89, 6.16)
TB Knowledge	Not curable	0.0	0.0	0.0	0.0
(Cure)	Curable	-2.43 (-6.41, 1.56)	-1.46 (-3.47, 0.55)	-1.59 (-5.32, 2.14)	-1.24 (-3.15, 0.67)
TB Knowledge‡	TB increases AIDS	1.85 (0.41, 3.30)	1.19 (-0.47, 2.84)	3.80 (2.52, 5.08)	2.20 (0.65, 3.75)
(TB/HIV)	AIDS increases TB	0.59 (-1.06, 2.24)	1.81 (-0.05, 3.67)	1.52 (0.01, 3.04)	1.83 (0.06, 3.59)
	AIDS/TB appear similar	0.97 (-0.64, 2.58)	-1.08 (-2.80, 0.63)	1.35 (-0.11, 2.82)	-0.27 (-1.90, 1.37)
HIV/AIDS stigma	Community perspective scale	0.59 (0.52, 0.65)	0.53 (0.44, 0.63)	0.43 (0.36, 0.50)	0.35 (0.26, 0.45)
(per unit increase)	Patient perspective scale	0.67 (0.54, 0.79)	0.49 (0.35, 0.63)	0.62 (0.51, 0.73)	0.57 (0.45, 0.70)
Know TB patients	Did not know person with TB		0.0		0.0
	Knew person with TB (lived)		-0.05 (-2.29, 2.18)		-1.33 (-3.45, 0.79)
	Knew person with TB (died)		3.67 (1.15, 6.19)		2.68 (0.29, 5.07)

Symptoms§	Cough	0.0	0.0
	Hemoptysis	-0.83 (-2.67, 1.02)	-1.07 (-2.73, 0.59)
	Weight loss	-0.50 (-2.98, 1.97)	0.96 (-1.29, 3.22)
	Fever and/or extrapulmonary only	-2.37 (-4.82, 0.08)	-1.26 (-3.44, 0.92)
	No symptoms	3.43 (-0.94, 7.81)	-0.22 (-4.24, 3.80)
HIV status‖	Negative	0.0	0.0
	New positive	1.16 (-0.97, 3.30)	2.84 (0.91, 4.77)
	Known positive	-0.86 (-4.38, 2.67)	-0.81 (-4.01, 2.39)
	Refused	-1.30 (-3.21, 0.62)	-0.04 (-1.79, 1.70)

* MD, mean difference in summed stigma scores; CI, confidence interval; 0.0 indicates referent level

† Exclusive or ‡ non-exclusive categories

§ Cough and hemoptysis may include other symptoms; Weight loss excludes cough but may include other symptoms

‖ Known positives had previously tested positive for HIV infection; New positives identified when diagnosed with TB

Table A4. Sensitivity analysis of adjusted differences in mean, summed stigma scores for participant characteristics with stigma item responses coded as 0, 2, 3, 5.

		Community perspectives stigma scale		Patient perspectives stigma scale	
		Patients with TB	Community	Patients with TB	Community
		MD* (95% CI)	MD* (95% CI)	MD* (95% CI)	MD* (95% CI)
Age	Age (per 10 year)	0.68 (0.24, 1.13)	0.92 (0.25, 1.59)	0.15 (-0.26, 0.55)	-0.32 (-1.00, 0.37)
Gender	Male	0.0	0.0	0.0	0.0
	Female	0.28 (-1.06, 1.62)	0.35 (-1.30, 2.00)	-1.03 (-2.24, 0.19)	1.78 (0.11, 3.46)
Religion	Buddhist	0.0	0.0	0.0	0.0
	Muslim	-1.78 (-3.12, -0.44)	1.00 (-1.11, 3.12)	-0.17 (-1.38, 1.04)	0.73 (-1.42, 2.87)
Education	Completed secondary	0.0	0.0	0.0	0.0
	Completed primary	-0.54 (-2.12, 1.04)	0.50 (-1.37, 2.36)	0.59 (-0.83, 2.00)	1.41 (-0.47, 3.30)
	Some or no primary	0.88 (-0.77, 2.53)	2.41 (0.21, 4.62)	1.40 (-0.08, 2.89)	0.60 (-1.64, 2.83)
Income	Baht/month (1,000 baht)	-0.01 (-0.07, 0.04)	-0.03 (-0.10, 0.05)	-0.03 (-0.07, 0.02)	-0.05 (-0.12, 0.03)
TB Knowledge† (Cause)	Infection from others	0.0	0.0	0.0	0.0
	Eat/drink with patient	-1.78 (-5.18, 1.62)	2.23 (-0.76, 5.21)	-0.59 (-3.60, 2.42)	1.74 (-1.34, 4.82)
	Smoking/drinking	-1.00 (-2.84, 0.84)	0.47 (-1.93, 2.87)	0.50 (-1.19, 2.18)	0.98 (-1.50, 3.45)
	Work hard	-2.28 (-4.51, -0.05)	Too few	-0.29 (-2.32, 1.75)	Too few
	Heredity	-1.01 (-4.43, 2.40)	-1.52 (-5.04, 2.01)	-1.66 (-4.68, 1.36)	-0.11 (-3.75, 3.53)
	Weak body	-0.45 (-2.52, 1.63)	0.67 (-2.74, 4.07)	-0.44 (-2.34, 1.46)	2.80 (-0.71, 6.31)
TB Knowledge‡ (Transmission)	Cough/sneeze	-0.19 (-1.84, 1.45)	-0.57 (-2.42, 1.29)	0.24 (-1.26, 1.75)	0.60 (-1.31, 2.50)
	Eat/drink	0.60 (-0.68, 1.89)	2.48 (0.81, 4.15)	0.39 (-0.78, 1.55)	1.46 (-0.27, 3.19)
	Touch	0.13 (-2.12, 2.37)	-0.76 (-3.52, 2.01)	1.73 (-0.28, 3.75)	0.36 (-2.48, 3.20)
	Sex	1.35 (-0.76, 3.47)	2.36 (-1.25, 5.98)	1.19 (-0.76, 3.13)	1.36 (-2.36, 5.08)
TB Knowledge (Cure)	Not curable	0.0	0.0	0.0	0.0
	Curable	-1.80 (-5.23, 1.62)	-1.33 (-3.29, 0.63)	-1.13 (-4.32, 2.05)	-0.97 (-2.98, 1.05)
TB Knowledge‡ (TB/HIV)	TB increases AIDS	1.37 (0.13, 2.62)	0.46 (-1.15, 2.07)	2.67 (1.56, 3.78)	1.30 (-0.35, 2.95)
	AIDS increases TB	0.65 (-0.76, 2.07)	0.76 (-1.05, 2.58)	1.02 (-0.28, 2.32)	1.28 (-0.58, 3.14)
	AIDS/TB appear similar	1.62 (0.24, 2.99)	-0.55 (-2.23, 1.12)	1.23 (-0.03, 2.48)	-0.01 (-1.73, 1.71)
HIV/AIDS stigma (per unit increase)	Community perspective scale	0.59 (0.52, 0.65)	0.51 (0.42, 0.60)	0.47 (0.41, 0.54)	0.41 (0.31, 0.50)
	Patient perspective scale	0.55 (0.45, 0.65)	0.42 (0.32, 0.52)	0.55 (0.47, 0.64)	0.55 (0.46, 0.64)
Know TB patients	Did not know person with TB		0.0		0.0
	Knew person with TB (lived)		0.43 (-1.75, 2.60)		-0.29 (-2.52, 1.94)
	Knew person with TB (died)		4.08 (1.64, 6.53)		3.21 (0.70, 5.72)

Symptoms§	Cough	0.0	0.0
	Hemoptysis	-0.74 (-2.31, 0.83)	-0.70 (-2.12, 0.71)
	Weight loss	-0.09 (-2.19, 2.01)	0.56 (-1.36, 2.49)
	Fever and/or extrapulmonary only	-2.72 (-4.80, -0.64)	-0.54 (-2.40, 1.32)
	No symptoms	1.58 (-2.12, 5.29)	-0.75 (-4.19, 2.69)
HIV status‖	Negative	0.0	0.0
	New positive	0.81 (-1.02, 2.64)	1.79 (0.14, 3.44)
	Known positive	-0.92 (-3.95, 2.10)	-1.17 (-3.90, 1.57)
	Refused test	-1.67 (-3.31, -0.02)	-0.06 (-1.55, 1.43)

* MD, mean difference in summed stigma scores; CI, confidence interval; 0.0 indicates referent level

† Exclusive or ‡ non-exclusive categories

§ Cough and hemoptysis may include other symptoms; Weight loss excludes cough but may include other symptoms

‖ Known positives had previously tested positive for HIV infection; New positives identified when diagnosed with TB

Table A5. Sensitivity analysis of adjusted odds ratios for patient characteristics and high stigma (item-adjusted scores ≥1.75).

| | | Community perspectives stigma scale | | Patient perspectives stigma scale | |
| | | Patients with TB | Community members | Patients with TB | Community members |
		OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)
Age	Age (per 10 year)	1.41 (1.23, 1.62)	1.24 (1.02, 1.50)	1.09 (0.95, 1.24)	0.91 (0.75, 1.10)
Gender	Male	1.0	1.0	1.0	1.0
	Female	1.29 (0.86, 1.93)	1.30 (0.81, 2.07)	0.90 (0.61, 1.34)	1.62 (1.00, 2.63)
Religion	Buddhist	1.0	1.0	1.0	1.0
	Muslim	0.58 (0.39, 0.86)	1.30 (0.72, 2.37)	1.03 (0.70, 1.53)	1.23 (0.66, 2.29)
Education	Completed secondary	1.0	1.0	1.0	1.0
	Completed primary	0.95 (0.59, 1.51)	0.96 (0.57, 1.62)	1.23 (0.77, 1.97)	1.40 (0.82, 2.41)
	Some or no primary	1.70 (1.04, 2.77)	1.59 (0.84, 3.01)	1.60 (0.98, 2.60)	1.38 (0.72, 2.65)
Income	Baht/month (1,000 baht)	1.00 (0.98, 1.01)	0.99 (0.97, 1.02)	0.99 (0.97, 1.00)	0.99 (0.97, 1.01)
TB Knowledge† (Cause)	Infection from others	1.0	1.0	1.0	1.0
	Eat/drink with patient	0.88 (0.31, 2.50)	1.26 (0.52, 3.03)	0.72 (0.26, 2.00)	0.43 (0.17, 1.05)
	Smoking/drinking	1.01 (0.58, 1.77)	1.01 (0.50, 2.05)	1.44 (0.82, 2.50)	0.99 (0.47, 2.08)
	Work hard	0.63 (0.32, 1.25)	Too few	1.00 (0.51, 1.95)	Too few
	Heredity	1.01 (0.35, 2.88)	0.56 (0.20, 1.60)	0.89 (0.32, 2.46)	0.59 (0.20, 1.73)
	Weak body	1.36 (0.73, 2.57)	2.20 (0.76, 6.32)	1.04 (0.55, 1.95)	1.10 (0.37, 3.21)
TB Knowledge‡ (Transmission)	Cough/sneeze	1.02 (0.62, 1.67)	0.85 (0.50, 1.46)	1.02 (0.62, 1.67)	1.07 (0.61, 1.85)
	Eat/drink	1.31 (0.88, 1.93)	2.49 (1.49, 4.16)	1.07 (0.73, 1.56)	1.04 (0.63, 1.72)
	Touch	0.73 (0.37, 1.45)	1.01 (0.45, 2.25)	2.32 (1.17, 4.63)	0.65 (0.28, 1.48)
	Sex	1.55 (0.82, 2.93)	2.64 (0.81, 8.62)	1.73 (0.91, 3.29)	1.59 (0.48, 5.24)
TB Knowledge (Cure)	Not curable	1.0	1.0	1.0	1.0
	Curable	0.58 (0.21, 1.61)	0.78 (0.44, 1.38)	0.73 (0.26, 2.07)	0.50 (0.27, 0.95)
TB Knowledge‡ (TB/HIV)	TB increases AIDS	1.50 (1.03, 2.19)	1.32 (0.82, 2.10)	2.59 (1.76, 3.79)	2.20 (1.34, 3.62)
	AIDS increases TB	0.94 (0.61, 1.44)	2.07 (1.22, 3.51)	1.40 (0.91, 2.16)	1.85 (1.08, 3.17)
	AIDS/TB appear similar	1.07 (0.71, 1.63)	0.73 (0.45, 1.19)	1.37 (0.90, 2.08)	1.06 (0.64, 1.75)
HIV/AIDS stigma (per unit increase)	Community perspective scale	1.29 (1.21, 1.37)	1.31 (1.22, 1.41)	1.19 (1.13, 1.25)	1.14 (1.08, 1.21)
	Patient perspective scale	1.21 (1.13, 1.30)	1.23 (1.14, 1.32)	1.25 (1.16, 1.34)	1.23 (1.14, 1.32)
Know TB patients	Did not know person with TB		1.0		1.0
	Knew person with TB (lived)		1.39 (0.74, 2.63)		0.73 (0.39, 1.36)
	Knew person with TB (died)		1.81 (0.86, 3.80)		2.23 (0.97, 5.15)

Symptoms§	Cough	1.0	1.0
	Hemoptysis	0.81 (0.51, 1.29)	1.04 (0.65, 1.66)
	Weight loss	0.85 (0.46, 1.57)	1.18 (0.62, 2.23)
	Fever and/or extrapulmonary only	0.65 (0.35, 1.21)	0.61 (0.32, 1.15)
	No symptoms	2.68 (0.81, 8.84)	1.33 (0.43, 4.10)
HIV status‖	Negative	1.0	1.0
	New positive	1.15 (0.46, 2.89)	0.54 (0.20, 1.45)
	Known positive	1.32 (0.76, 2.29)	1.69 (0.98, 2.92)
	Unknown/Refused	1.15 (0.70, 1.91)	1.10 (0.67, 1.80)

* OR, odds ratio; CI, confidence interval; 1.0 indicates referent level

† Exclusive or ‡ non-exclusive categories

§ Cough and hemoptysis may include other symptoms; Weight loss excludes cough but may include other symptoms

‖ Known positives had previously tested positive for HIV infection; New positives identified when diagnosed with TB

Table A6. Sensitivity analysis of adjusted odds ratios for patient characteristics and high stigma (item-adjusted scores ≥2.00).

| | | Community perspectives stigma scale | | Patient perspectives stigma scale | |
| | | Patients with TB | Community members | Patients with TB | Community members |
		OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)
Age	Age (per 10 year)	1.29 (1.12, 1.49)	1.27 (1.05, 1.54)	1.20 (1.02, 1.41)	0.98 (0.81, 1.19)
Gender	Male	1.0	1.0	1.0	1.0
	Female	0.90 (0.57, 1.43)	1.13 (0.70, 1.82)	0.86 (0.51, 1.44)	1.61 (1.00, 2.60)
Religion	Buddhist	1.0	1.0	1.0	1.0
	Muslim	0.45 (0.28, 0.73)	1.31 (0.73, 2.35)	0.98 (0.60, 1.62)	1.19 (0.66, 2.16)
Education	Completed secondary	1.0	1.0	1.0	1.0
	Completed primary	0.88 (0.52, 1.49)	1.03 (0.60, 1.76)	1.26 (0.67, 2.38)	1.54 (0.90, 2.63)
	Some or no primary	1.17 (0.68, 2.02)	1.51 (0.82, 2.81)	1.90 (1.01, 3.58)	1.43 (0.76, 2.68)
Income	Baht/month (1,000 baht)	0.99 (0.98, 1.01)	0.99 (0.97, 1.02)	0.99 (0.97, 1.02)	1.00 (0.97, 1.02)
TB Knowledge† (Cause)	Infection from others	1.0	1.0	1.0	1.0
	Eat/drink with patient	0.95 (0.28, 3.29)	1.84 (0.74, 4.55)	0.57 (0.12, 2.77)	0.78 (0.31, 1.97)
	Smoking/drinking	1.46 (0.76, 2.80)	1.07 (0.51, 2.26)	1.25 (0.60, 2.58)	0.92 (0.44, 1.92)
	Work hard	1.30 (0.60, 2.82)	Too few	1.20 (0.51, 2.82)	Too few
	Heredity	0.77 (0.20, 3.02)	0.46 (0.15, 1.46)	0.27 (0.03, 2.22)	0.71 (0.24, 2.10)
	Weak body	1.62 (0.80, 3.32)	1.43 (0.50, 4.07)	1.23 (0.54, 2.81)	1.84 (0.67, 5.05)
TB Knowledge‡ (Transmission)	Cough/sneeze	0.97 (0.56, 1.69)	0.88 (0.51, 1.52)	1.07 (0.57, 2.00)	1.35 (0.77, 2.37)
	Eat/drink	1.59 (1.02, 2.49)	2.02 (1.23, 3.32)	1.33 (0.81, 2.18)	1.74 (1.06, 2.86)
	Touch	1.01 (0.48, 2.14)	0.89 (0.39, 2.03)	1.85 (0.88, 3.88)	1.42 (0.63, 3.18)
	Sex	1.74 (0.89, 3.40)	1.38 (0.48, 3.96)	1.89 (0.93, 3.87)	1.68 (0.59, 4.78)
TB Knowledge (Cure)	Not curable	1.0	1.0	1.0	1.0
	Curable	0.73 (0.25, 2.18)	0.83 (0.46, 1.48)	0.87 (0.24, 3.18)	0.73 (0.41, 1.28)
TB Knowledge‡ (TB/HIV)	TB increases AIDS	1.45 (0.95, 2.21)	1.07 (0.67, 1.73)	2.87 (1.72, 4.79)	1.83 (1.13, 2.96)
	AIDS increases TB	1.01 (0.63, 1.63)	1.31 (0.76, 2.27)	1.40 (0.80, 2.45)	1.77 (1.01, 3.11)
	AIDS/TB appear similar	1.49 (0.92, 2.42)	0.74 (0.45, 1.21)	1.95 (1.08, 3.53)	0.96 (0.59, 1.58)
HIV/AIDS stigma (per unit increase)	Community perspective scale	1.29 (1.20, 1.38)	1.30 (1.21, 1.40)	1.26 (1.17, 1.35)	1.24 (1.16, 1.33)
	Patient perspective scale	1.27 (1.18, 1.37)	1.29 (1.19, 1.38)	1.39 (1.26, 1.52)	1.33 (1.23, 1.44)
Know TB patients	Did not know person with TB		1.0		1.0
	Knew person with TB (lived)		1.23 (0.66, 2.32)		0.83 (0.43, 1.59)
	Knew person with TB (died)		2.47 (1.21, 5.03)		2.22 (1.10, 4.46)

Symptoms§	Cough	1.0		1.0	
	Hemoptysis	0.68	(0.40, 1.17)	0.63	(0.33, 1.20)
	Weight loss	1.19	(0.61, 2.35)	1.28	(0.61, 2.69)
	Fever and/or extrapulmonary only	0.46	(0.20, 1.03)	0.74	(0.32, 1.70)
	No symptoms	2.43	(0.82, 7.27)	1.09	(0.28, 4.20)
HIV status‖	Negative	1.0		1.0	
	New positive	0.69	(0.22, 2.18)	0.30	(0.04, 2.33)
	Known positive	1.08	(0.58, 2.01)	2.24	(1.17, 4.28)
	Unknown/Refused	0.66	(0.37, 1.19)	1.90	(1.06, 3.41)

* OR, odds ratio; CI, confidence interval; 1.0 indicates referent level

† Exclusive or ‡ non-exclusive categories

§ Cough and hemoptysis may include other symptoms; Weight loss excludes cough but may include other symptoms

‖ Known positives had previously tested positive for HIV infection; New positives identified when diagnosed with TB

Table A7. Sensitivity analysis of adjusted odds ratios for patient characteristics and high stigma (item-adjusted scores ≥2.25).

| | | Community perspectives stigma scale | | Patient perspectives stigma scale | |
| | | Patients with TB | Community members | Patients with TB | Community members |
		OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)
Age	Age (per 10 year)	1.06 (0.85, 1.33)	1.09 (0.85, 1.39)	0.96 (0.72, 1.28)	0.95 (0.75, 1.21)
Gender	Male	1.0	1.0	1.0	1.0
	Female	1.32 (0.67, 2.60)	1.16 (0.63, 2.15)	0.97 (0.42, 2.28)	1.32 (0.73, 2.37)
Religion	Buddhist	1.0	1.0	1.0	1.0
	Muslim	0.46 (0.21, 1.03)	1.25 (0.59, 2.62)	0.76 (0.31, 1.84)	1.56 (0.78, 3.10)
Education	Completed secondary	1.0	1.0	1.0	1.0
	Completed primary	0.66 (0.29, 1.53)	1.22 (0.60, 2.45)	0.91 (0.33, 2.55)	2.06 (1.06, 4.00)
	Some or no primary	1.13 (0.51, 2.48)	1.53 (0.70, 3.35)	1.26 (0.46, 3.46)	1.42 (0.64, 3.19)
Income	Baht/month (1,000 baht)	0.97 (0.93, 1.00)	0.99 (0.96, 1.02)	1.00 (0.97, 1.03)	0.98 (0.95, 1.02)
TB Knowledge† (Cause)	Infection from others	1.0	1.0	1.0	1.0
	Eat/drink with patient	0.43 (0.05, 3.66)	2.11 (0.67, 6.64)	0.72 (0.08, 6.39)	1.36 (0.42, 4.44)
	Smoking/drinking	0.70 (0.29, 1.72)	1.12 (0.42, 3.01)	0.68 (0.22, 2.09)	1.40 (0.53, 3.70)
	Work hard	0.89 (0.31, 2.53)	Too few	0.79 (0.20, 3.09)	Too few
	Heredity	Too few	0.52 (0.11, 2.44)	Too few	0.61 (0.13, 2.81)
	Weak body	0.78 (0.29, 2.11)	0.43 (0.07, 2.41)	1.08 (0.33, 3.51)	1.27 (0.33, 4.85)
TB Knowledge‡ (Transmission)	Cough/sneeze	0.65 (0.30, 1.39)	0.68 (0.34, 1.32)	0.69 (0.27, 1.80)	1.23 (0.61, 2.47)
	Eat/drink	0.95 (0.49, 1.84)	1.46 (0.78, 2.74)	1.45 (0.61, 3.42)	1.95 (1.07, 3.56)
	Touch	1.14 (0.38, 3.46)	0.69 (0.23, 2.06)	1.24 (0.35, 4.48)	1.58 (0.61, 4.06)
	Sex	1.21 (0.44, 3.32)	1.69 (0.50, 5.68)	1.65 (0.53, 5.14)	1.42 (0.42, 4.77)
TB Knowledge (Cure)	Not curable	1.0	1.0		
	Curable	0.42 (0.11, 1.57)	0.63 (0.31, 1.29)	Too few	Too few
TB Knowledge‡ (TB/HIV)	TB increases AIDS	1.72 (0.88, 3.35)	0.73 (0.39, 1.36)	3.40 (1.34, 8.67)	1.21 (0.67, 2.17)
	AIDS increases TB	5.37 (1.61, 17.91)	0.88 (0.45, 1.73)	1.58 (0.57, 4.37)	1.09 (0.56, 2.11)
	AIDS/TB appear similar	5.61 (1.69, 18.59)	0.72 (0.39, 1.34)	3.23 (0.94, 11.02)	1.14 (0.62, 2.11)
HIV/AIDS stigma (per unit increase)	Community perspective scale	1.56 (1.37, 1.78)	1.30 (1.20, 1.41)	1.48 (1.30, 1.68)	1.28 (1.18, 1.39)
	Patient perspective scale	1.61 (1.40, 1.84)	1.21 (1.12, 1.32)	1.51 (1.32, 1.73)	1.51 (1.35, 1.69)
Know TB patients	Did not know person with TB		1.0		1.0
	Knew person with TB (lived)		1.25 (0.55, 2.84)		1.20 (0.55, 2.63)
	Knew person with TB (died)		2.37 (1.06, 5.27)		1.71 (0.76, 3.85)

Symptoms§	Cough	1.0		1.0	
	Hemoptysis	0.79	(0.35, 1.81)	0.81	(0.28, 2.39)
	Weight loss	1.67	(0.66, 4.24)	1.88	(0.60, 5.94)
	Fever and/or extrapulmonary only	0.16	(0.02, 1.23)	1.02	(0.27, 3.80)
	No symptoms	0.77	(0.09, 6.27)		
HIV status‖	Negative	1.0		1.0	
	New positive	1.09	(0.24, 5.01)	0.95	(0.12, 7.66)
	Known positive	1.07	(0.43, 2.63)	1.15	(0.36, 3.64)
	Refused test	0.43	(0.14, 1.26)	1.72	(0.67, 4.44)

* OR, odds ratio; CI, confidence interval; 1.0 indicates referent level
† Exclusive or ‡ non-exclusive categories
§ Cough and hemoptysis may include other symptoms; Weight loss excludes cough but may include other symptoms
‖ Known positives had previously tested positive for HIV infection; New positives identified when diagnosed with TB

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