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Adherence Issues of Isoniazid Therapy Among Children

by

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DISSERTATION

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AHDERENCE TO TREATMENT OF LATENT TUBERCULOSIS INFECTION IN

CHILDREN

Shiow-Huey Chang, MS, RN, CNS

ABSTRACT

An estimated 8.7 million individuals worldwide are infected with the bacillus *mycobacterium tuberculosis*, with 1.4 million deaths from tuberculosis (TB) in 2011. A 9-month course of isoniazid therapy is a standard regimen to treat children with latent tuberculosis infection (LTBI) and to prevent development of active tuberculosis later in life. Given evidence from past studies, the predictors for adherence to therapy are not fully understood in affected populations, particularly in children. The aim of this dissertation was to expand knowledge on medication adherence among children with LTBI by examining factors contributing to adherence. Three key findings from this study include: 1) TB has different meanings to different cultural groups based on social context; 2) successful completion of isoniazid therapy in children was influenced by age, ethnicity, and symptoms of adverse reactions; and 3) isoniazid hepatotoxicity in children less than 21 years of age may be more common than previously thought and may be diagnosed by monitoring symptoms, physical examination, and serum transaminase levels. Treatment of LTBI is a critical step to eliminate TB in children. To promote adherence to the treatment in children, clinicians need to facilitate parental and family involvement in the treatment decision, have high awareness of symptoms of adverse reactions, and consider cultural variation in the development of interventions aimed at improving adherence to the treatment.

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CHAPTER I

INTRODUCTION

An estimated 8.7 million individuals worldwide are infected with the bacillus *mycobacterium tuberculosis*, with 1.4 million deaths from tuberculosis (TB) in 2011(World Health Organization, 2012). A 9-month course of isoniazid therapy is a standard regimen to treat children with latent tuberculosis infection and to prevent development of active tuberculosis later in life (American Thoracic Society, 2000). Without 9- to 10-month adherence to isoniazid, therapeutic efficacy may not be achieved (Comstock, 1999). This long regimen presents a risk for nonadherence that can result in an individual's progression to active TB or later development of drug-resistant TB, which can be more difficult to treat (Centers for Disease Control and Prevention, 2010).

Piaget's Child Development Theory

Pediatric adherence behavior can be influenced by a child's developmental stage. Piaget's Child Development Theory specifies four developmental stages: the sensorimotor, preoperational, concrete operational, and formal operational (Piaget & Inhelder, 1966). At the sensorimotor stage, from birth to age two, children focus on themselves and have not developed the ability of perceiving the world from others' viewpoints. Children experience and learn the world through their five senses and movement. At the preoperational stage, age two to seven, children's egocentrism grows strong and then weakens. At this stage, a child lacks the ability for logical thinking. In the concrete operational stage, age seven to eleven, children are able to think logically and not egocentrically. In the formal operational stage, ages eleven to sixteen, children

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develop abstract reasoning (see Table 1). This theoretical perspective supports the need

for studies of medication adherence that include factors such as the child's developmental

stage as well as age, and whether the child's cognitive ability is mature enough for

understanding the reasoning, meaning, and consequences of taking or not taking a

medicine.

Table 1.   Piaget's Four Developmental Stages

Four Stages	Developmental Outcomes
Preoperational stage 2 – 7 years old	Lacks logical thinking capability Egocentrism increasing and then decreasing
Concrete operational stage 7 – 11 years old	Logical thinking Not egocentric
Formal operational stage 11 – 16 years old	Develops abstract reasoning

Pediatric Medication Adherence

There is empirical evidence that a child's developmental age impacts his or her

medication adherence. By age seven, children can share approximately 20% of

responsibility for their medications; by age 11, the percentage is 50% and by age 15, it is

75% (Orrell-Valente, Jarlsberg, Hill, & Cabana, 2008). Studies on adherence to other

pediatric medical regimens that demand long-term self management, such as asthma

medications, provide examples similar to isoniazid therapy. In one study of children ages

7 to 17, children over the age of 11 had higher correlations between asthma control and

all clinical variables compared to their parents (Guyatt, Juniper, Griffith, Feeny, & Ferrie,

1997). After reaching 11 years of age, children can better provide their own health

information than their parents can provide as a proxy informant. In a study of asthmatic children, ages nine to 15, children perceived parental reminders as annoying but helpful for adherence, and felt that use of rewards could best reinforce their adherence (Penza-Clyve, Mansell, & McQuaid, 2004). Lack of parental involvement in medication routines and difficulty remembering doses has been associated with poor adherence for children on psychotropic medication (Dean, Wragg, Draper, & McDermott, 2011). For younger children, mothers or caregivers assume the major responsibility for implementing the medical regimen (La Greca, 2003). However, sharing decision-making in managing medical issues helps children manage their illness (Butz, Walker, Pulsifer, & Winkelstein, 2007). To what degree parental involvement and children's decision sharing in a medication regimen promotes optimal adherence is unclear.

Parental Beliefs or Concerns about Child Medications

Adherence to medication regimen among young children is influenced in part by their parents' perception of the medication's efficacy and side effects. Researchers investigated the relationship between parental beliefs and medication adherence among asthmatic children, ages three to 7, and found that the more parents are concerned about medication, the less adherent their child is (Conn, Halterman, Lynch, & Cabana, 2007). When parents with children between 2 and 16 years of age consider a medication as necessary for the children, the child is more likely to report being adherent (Conn et al., 2007). Other researchers examined the perceptions and concerns of parents of children (mean age 7.1) with chronic asthma and found that children are more likely to miss more doses of medications if parents are concerned about an inhaled therapy compared to children of parents who are not concerned (Chan & DeBruyne, 2000).

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Parents' beliefs impact children's adherence, but also affect the outcome of illness. In a study of uncontrolled asthma in 8-year-old children, researchers found that parents' beliefs about medication uses and side effects were related to uncontrolled asthma (Koster et al., 2011). Nearly all of parents who believed medications were necessary for their child with Attention Deficit Hyperactive Disorder would use medication, whereas only half used medication for their child if the parent did not accept the treatment (DosReis et al., 2009). Focus group data from parents with asthmatic children, between 2 and 12 years of age, revealed that parents decided deliberately whether ongoing use of inhaled corticosteroids would be useful for their child and based this decision on their perceptions about illness and medication (Klok, Brand, Bomhof-Roordink, Duiverman, & Kaptein, 2011).

Despite these studies focused on young children, whether the influence of parental beliefs and concerns on children's medication adherence is greater on young children or older children remains inconclusive. The usage of terms "young" or "older" children in most of these studies does not appear to be based on any theoretical underpinnings such as age of independent thinking or consequences of decision making.

For young children, a parent or caregiver typically assumes the major responsibility for implementing the medical regimen (La Greca, 2003). Studies have shown that adherence to medication regimen among young children can be determined by their parent's perception of the medication's efficacy and side effects (Chan & DeBruyne, 2000; Conn et al., 2007; DosReis et al., 2009; Klok et al., 2011; Koster et al., 2011). This evidence supports the need to examine the adherence issues in children in the broader context of their parents' perceptions. The Children's Health Belief Model (CHBM) tested

in children ranging in age from 8 to 14 has successfully shown that a combination of parent's perceived severity of illness and perceived benefit of taking medicines, illness concerns, and perceived vulnerability together explain 60% of the variance in children's expected medication use (Bush & Iannotti, 1988, 1990).

Children's Health Belief Model

The Children's Health Belief Model (CHBM) in Figure 1 was developed for the prediction of medication use among preadolescent children in Black, White, and Hispanic populations (Bush & Iannotti, 1990). The CHBM was tested for its utility in explaining preadolescent children's expectations in taking medicines to treat common illness. The CHBM is comprised of three overarching factors: modifying, readiness, and behavior. These factors are related to expected medication use, which predicts actual medicine use.

Modifying factors in the model consist of four domains: 1) demographics that include age, socioeconomic status, and sex; 2) cognitive/affective that includes health locus of control, self-esteem, health risk-taking, medication knowledge, and medication autonomy; 3) the enabling domain that includes doctor visits and illness frequency; and 4) the environmental domain that includes caretaker's motivation for child, perceived child's illness threat, perceived benefit of medications, and expected child's medication use.

Figure 1. Children's Health Belief Model (Bush & Iannotti, 1988, 1990)

Modifying Factors

Readiness Factors

Behavior Factors

Demographic

Age

SES

Sex

Cognitive/Affective

Health locus of control

Self-esteem

Health risk-taking

Med knowledge

Med autonomy

Enabling

MD visits

Illness frequency

Environmental

Caretaker's

Motivations for child

Perceived child's illness threat

Perceived benefit of medicines

Expected child's med use

Motivations

Illness concern

Illness attribution

Perceived illness threat

Perceived vulnerability

Perceived severity

Perceived benefit of medicines

Perceived med benefit

Perceived nonmed benefit

Expected med use

Med use

Factors in the demographic domain positively or negatively influence cognitive/affective, enabling, and environmental domains, which then affect readiness. Readiness factors involve six indirect pathways, including motivation (i.e., illness concern, illness attribution), perceived illness threat (i.e., perceived vulnerability, perceived severity), perceived benefit of medicine (i.e., perceived medicine benefit, perceived non-medicine benefit), and behavior factors (i.e., expected medication use). In the CHBM, *expected* medication use is hypothesized to lead to *actual* medication use (Bush & Iannotti, 1990).

The CHBM purports that a caretaker's beliefs have a strong influence on the child's medication for children between 8.0 to 14.7 years of age, with a mean age of about 10.7 years (Bush & Iannotti, 1990). Researchers tested the CHBM variables and found that under the environment domain, a caretaker's perceptions could affect the child's readiness factors (motivations, perceived benefits, and illness threats), and expected medication use (Bush & Iannotti, 1988, 1990). They also found relationships among perceived severity of illness and perceived benefit of taking medicines, illness concern, and perceived vulnerability that together explained 63% of the adjusted variance in children's expected medication use (Bush & Iannotti, 1990). In the CHBM, children who had an internal Health Locus of Control in the cognitive/affective domain were less likely to be concerned when they experienced a common health problem, perceiving the problem as less severe, or a readiness factor. The demographic modifying factors for the children included: a higher social economic status, older, higher self-esteem, and more knowledge about medicines (Bush & Iannotti, 1988). The CHBM distinguished the influence of parental beliefs about medication use (environmental domain) from the

child's own cognitive correlates (cognitive/affective domain). The concept of stigma associated with the particular health problem has not been addressed in the CHBM model.

Implications of the Children's Health Belief Model

The CHBM can guide research to better understand adherence issues with isoniazid therapy for children and their parents for two reasons. First, the abovementioned factors (i.e., perceived severity of TB and perceived medication benefits of isoniazid, illness concerns, and perceived vulnerability) together can explain most of children's medication use behavior, which is the specific outcome relevant to the population of interest for this research. Results from studies that test the CHBM indicate that caretakers' health beliefs influence children's behavior; however, this theory does not address long-term behavior change or how to maintain adherence behavior, particularly in the face of social stigma related to a disease or communicable infection.

Time is not included as a concept in this model. Although the CHBM has been tested on diverse populations (i.e., Black, White, Hispanic), it has not been tested on immigrant populations, non-English speakers, or children younger than 8 years of age. Among these populations, it can be theoretically assumed that the influences from caretakers may be even more prominent. Given its accessibility and specificity, the CHBM was proposed to guide this dissertation research to expand knowledge about medication adherence among young children with LTBI.

Therefore, this model is adopted as a theoretical framework (Figure 2) to organize the evidence on predictors of completion of isoniazid therapy in 26 studies listed in Appendix 1. A summary of the literature on predictors of completion of isoniazid

therapy is presented using the following categories: modifying (Appendix 2), enabling

(Appendix 3), and environmental factors (Appendix 4). The CHBM illustrates predictors

that impact medication adherence for patients for all ages. The 26 existing studies suggest

that adherence to isoniazid therapy is affected by demographic, psychological,

physiologic, and environmental factors to various degrees. For pediatric populations, the

literature suggests that the surrounding environment (i.e., family, school, and the public

health infrastructure of accessible care and treatment) is key to minority children's'

adherence to medication. Yet the concept of social stigma in relation to children's

adherence is not widely discussed in the literature.

This dissertation study was conducted in Santa Clara County, where TB is a

public health issue in the community. In 2011, there were 181 TB cases reported (Santa

Clara County Public Health Department, 2012a). While rates of TB have slightly

decreased to 10 cases per 100,000 (n=181) in 2011 from 10.7 per 100,000 (n=193) in

2010. The rates were still higher than the case rate of 5.8 per 100,000 in California for

2011 and 6.0 per 100,000 in 2010 (California Department of Public Health, 2009; Santa

Clara County Public Health Department, 2012b).

Figure 2. Conceptual Framework of Predictors of Adherence to Treatment of Latent Tuberculosis Infection for Children

Modifying Factors
Behavior Factors

Child
Demographics

Age

Gender

Language

Ethnicity

Country of birth

Health risks

Enabling Factors

Regimen Monitoring

- Length and type of regimen (INH or RIF)

- Interruptions in treatment

- Side effects and symptoms

TB Intervention

- Received positive self-reinforcement

- Source case investigation

- PHNs who saw the client during treatment

- Directly Observed Therapy

Environmental Factors

TB risks

Parental perceptions of TB risks and INH therapy

Cultural background

Home and family environment

Access to care

Med Use/ Medication adherence
Appointments kept

Pill count

Verification of refills with pharmacies

Urine color test

Medication Event Monitoring System (recording frequency and dates of medications taken)

Parents' self-report

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Research Questions

The aim of this dissertation was to expand knowledge on medication adherence among children with LTBI by examining factors contributing to adherence. The specific goals of this study were to: 1) determine adherence to isoniazid therapy among children less than 21 years old, in which adherence is measured by 9-month completion rates: and 2) describe predictors of medication adherence. Given evidence from past studies, the relationships between potential predictors and adherence are not fully established in affected populations. Therefore, a correlational research design was proposed to address the gap in knowledge about adherence to isoniazid therapy among children. The purpose of a correlational research design was to describe and predict relationships among multiple, independent variables through assessing strength and direction of associations among independent variables and to help predict outcomes (Creswell, 2008). A retrospective review of medical records was chosen to answer the research questions for this study because of the large sample size required for meaningful analyses.

Summary

TB is a widespread global disease affecting family and social relationships and resulting in adverse health and economic consequences. Individuals with TB and their family members experience prejudice and negative attitudes including shame, blame and judgment. Individuals with TB who are most likely to feel shame are more likely to default on their TB treatment. The first paper in Chapter 2 is a systematic literature review that describes the cultural variations in knowledge, attitudes, and health responses in relation to TB and its stigma. Global perspectives are discussed from this review of 83

published papers on this topic. A total of 41 studies used quantitative methods, 32 used qualitative methods, and 10 used mixed methods. Study participants included individuals with TB, family members, and the general public.

Studies have shown treatment completion to be associated with shorter rifampin regimens, socio-demographic characteristics, family involvement, access to medical care, and behavioral or public health intervention. However, limited data are available about predictors of failure to complete treatment for LTBI in children. The second paper in Chapter 3 of this dissertation confirms the previously identified predictors of treatment non-completion for LTBI in pediatric populations.

Isoniazid hepatotoxicity, a major concern with isoniazid therapy, results in symptomatic or asymptomatic elevation of serum transaminase. Children with isoniazid-induced hepatic failure have undergone liver transplant and or have died due to inability to receive timely transplantation. Data are sparse about the clinical characteristics of children with hepatotoxicity associated with isoniazid treatment for LTBI. The paper in Chapter 4 evaluates the prevalence of hepatotoxicity, changes of serum transaminases, and demographic and clinical characteristics of children receiving isoniazid therapy.

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Chapter II

Global cultural variation in knowledge, attitudes and health responses

to tuberculosis stigma

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Shiow-Huey Chang, Janine Cataldo

Running head: Cultural attitudes toward TB

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Key Words: gender, HIV/AIDS, review, TB

SUMMARY

BACKGROUND: Stigma related to tuberculosis (TB) has been associated with lack of compliance to treatment. Individuals' perceptions of stigma differ by societal context. Limited data are available on cultural variation of TB stigma worldwide, particularly in countries with a high burden of TB. The purpose of this review is to describe cultural variation in knowledge, attitudes and health responses in relation to TB stigma.

METHODS: A review of international descriptive studies

RESULTS: A total of 1268 studies were identified from searches of PubMed/Medline, Web of Science, Cochrane, PsycINFO, and CINAHL databases. There were 83 studies from 35 countries that met inclusion criteria for English, peer-reviewed, original, and non-interventional studies. These studies described stigma resulting from misperceptions of the causes of TB, association with human immunodeficiency virus (HIV) infection, and negative attitudes. Decisions about disclosing illness and choices between traditional healers and public or private providers were influenced by this stigma. Gender influenced perceptions and management of TB. Public health responses contributed to TB stigma.

CONCLUSION: Findings from this review confirm cultural variation with respect to TB and potential for stigma. Cultural variation needs to be considered in the development of interventions aimed at reducing stigma and improving adherence to treatment.

INTRODUCTION

An estimated 8.7 million individuals worldwide are currently infected with bacillus *Mycobacterium tuberculosis*, with 1.4 million deaths from tuberculosis (TB) in 2011.[1] TB is a widespread global disease affecting family and social relationships[2] and resulting in adverse health and economic consequences.[3] Individuals with TB, and their family members, experience prejudice and negative attitudes including shame, blame and judgment.[4-9]

Social determinants of health are conditions in the environment in which people live that affect health functioning, and quality of life outcomes and risks.[10] Stigma is a social determinant that is created and maintained by institutional and community norms and interpersonal attitudes.[11] TB stigma is a personal experience characterized by exclusion, rejection, blame or devaluation that results from anticipation of an adverse judgment related to a TB diagnosis. TB stigma has been identified as a barrier to the directly observed therapy (DOT) program, particularly by patients who fear that nurses seen at their homes will cause the community to assume that a person is infected with TB.[12, 13] Given the impact that stigma has on health behavior and patient outcomes, it is important to understand the experience of TB stigma across geographic regions within a socio-cultural context. Multi-country studies that compared TB stigma suggest intra- and inter-country differences.[14-16] The aim of this review was to describe the cultural variation in knowledge, attitudes and health responses in relation to TB stigma.

METHODS

For this review, PubMed/Medline, Web of Science, Cochrane, PsycINFO and CINAHL databases were searched in January 2012. The search terms were 1) "tuberculosis" AND "tuberculosis/psychology" and 2) "prejudice" OR "stereotyping" OR "social perception" OR "social stigma" OR "social isolation" OR "health knowledge, attitudes, practice."

After deleting duplicates, this search yielded 1268 articles (Figure 1). Qualitative data analysis software (Nvivo version 9; QSR International Pty Ltd, Burlington MA) was used to retrieve data relevant to the study aims. The articles were screened by two authors; inclusion criteria were English language, peer-reviewed, and original research using qualitative, quantitative, or mixed methods. Exclusion criteria were intervention studies, review articles, dissertations, commentaries, letters and guidelines.

A qualitative meta-synthesis 'using the Signal and Noise' technique was conducted; a narrative interpretive method of systematic review, a technique that is intuitive and value based. This method can be used with both qualitative and quantitative studies and is based on themes, and results, without forcing the combination of data into one variable. As an alternative to evaluating the quality of studies, a 'signal score' is used to assess the relevance of publications. The process does not eliminate research simply because it lacks a certain level of evidence or has methodological weaknesses. According to Higginson et al., 'There may be some articles in which the design is suspect (high "noise" level) but the findings appear important (strong "signal").[17] The signal score (possible points 0-3) was based on study relevance. A total of 83 relevant studies were identified: 41 quantitative, 32 qualitative and 10 mixed methods (Table 1). Studies were

arranged in the order of six World Health Organization (WHO) regions: African, Eastern Mediterranean, European, the Americas, Southeast Asia, and Western Pacific (Table 2) Key findings were tabulated according to three themes related to TB: knowledge, attitudes, and health responses.

RESULTS

Results are presented for 35 countries including 17 of the 22 high countries (77%) identified by the WHO as having the highest TB prevalence in the world[1] (Table 2).

Knowledge of TB, Causal Factors, and Labels

Beliefs about causes of TB affect how individuals perceive their infection and treatment options. Across countries and cultures there was a wide range of causal attributes for TB (Table 3). TB is believed to be an infectious lung disease among Vietnamese in the United States;[2] caused by germs in Vietnam,[18] and Rwanda;[19] a respiratory infection in Russia;[20] and transmitted by air in Tanzania,[21] India,[22] and Malaysia.[23] In Ethiopia[6, 24, 25] and Kenya,[26] exposure to cold air is believed to cause TB. In Kenya,[26] Malawi,[27] South Africa[28, 29] and Uganda,[30] smoking is believed to be the cause of TB. Nutrition is implicated in Haiti,[14] Rwanda[19] and Peru,[31] and living conditions in Morocco.[32]

In many countries providers avoid using TB as a label and instead have names like "chebuonit", "kifua kikuu," in Kenya,[26] "weak lung" disease[33] in the Philippines, and "lay category bird" in Ethiopia.[34] In Rwanda,[19] Uganda,[30] and Ethiopia,[35] TB is believed to be caused by the super natural and is referred to as "evil eye."[4]

Scientifically unfounded beliefs regarding TB transmission predict prejudice in Colombia.[36] Mistaking TB for food-borne illness has resulted in bans on sharing utensils

in Uganda[30] and Peru[31] and among Mexican Americans in the United States.[37] Mistaking TB for a sexual illness has promulgated misinformed beliefs about sexual contact in Malawi[27] and India.[38] In Kenya,[26] Uganda[30] and Vietnam[18] TB is believed to be a hereditary condition. In Pakistan, TB is blamed for infertility and diminished marriageability[39] for women.[40] TB is attributed to hard labor in Kenya,[26] Rwanda,[19] South Africa[41] and Vietnam.[18] Mental health issues attributed to TB have included worry, stress, and trauma, in Pakistan,[39] India,[42] Vietnam[18] and Turkey,[43] and suicidal ideation in India.[44]

Association with HIV/AIDS

The belief of association of TB with HIV/AIDS is common in Ethiopia,[24, 35] Kenya,[45] Malawi[16] and Haiti[14] (Table 4). Signs of TB are considered to be signs of HIV/AIDS in Rwanda[19] and Zambia.[5] TB patients co-infected with HIV report feeling even more stigmatized than patients without co-infection in Ethiopia[46] and Thailand.[47] African TB patients living in the United Kingdom often refuse HIV testing, fearing stigmatization if results are positive.[48]

Attitudes toward TB

Contracting TB is experienced as embarrassing and shameful in Congo,[49] Zambia,[5] United States[15] and Malaysia[23] (Table 5). This "dirty" disease is believed to affect poor people, TB patients feel "less respected" by others or inferior in Ethiopia[4] and Vietnam,[7] with women in Bangladesh feeling shameful and rejected by others.[50] Discrimination and negative attitudes from others have been reported in South Africa,[41]

Indonesia[8] and Nepal.[51] Fear of infection has been reported in Ghana,[52-54] South Africa,[55] Zambia,[5] Colombia[56] and North Carolina in the United States.[57] Coughing in front of other people is extremely stigmatizing in Bangladesh[58] and India.[59] Greater stigma is experienced by Thai patients with TB if they have more symptoms,[60] and more stigma is associated with physical frailty in Ghana.[54] Weight loss in patients with a history of smoking or drinking experience greater stigma in Nigeria.[61] In Brazil, TB is perceived as difficult and isolating, changing a person's perception of themselves.[62]

Different societies have different levels of acceptance of patients with TB. People with TB are socially unacceptable in Ethiopia[24] and Pakistan[9] but socially acceptable in Malaysia[23] and the United Kingdom.[63] Social isolation, shunning or avoiding patients with TB has been reported in Congo,[49] Ethiopia,[24, 35] South Africa,[55, 64] Pakistan[40] and Croatia[65] and among Samoans[66] and African Americans in the United States.[67] Women fear isolation in India[38] and in Vietnam.[68] Loneliness is reported by Turkish patients.[43] Loss, sadness and dissatisfaction are common among patients with TB in Brazil.[62] Marriage prospects are affected as a result of TB in Ghana,[52] Pakistan,[40] India[69] and China.[70] Ethnic identity is negatively associated with TB among Haitians in the United States.[14] Adults who were tested for TB in Ecuador reported feeling stigmatized by just receiving the TB test.[3]

Treatment and Health responses to TB

Multiple factors related to stigma include knowledge, and social attitudes toward TB, preferences for treatment, time or costs constraints, convenience or confidentiality of TB treatment can influence treatment seeking behavior (Table 6). Patients with TB often

consult traditional healers in Gambia,[71] South Africa,[28] Uganda,[30] Thailand,[72] Malaysia[73] and the Philippines.[74] Traditional herbal medicine is used by Samoans in the United States.[66] Patients in Kenya[45] and Rwanda[19] who believe TB is caused by supernatural forces believe they can only be cured by traditional healers.

TB patients choose between self-treatment and private or public doctors. Patients prefer using self-medication first before formal treatment in Kenya,[26, 45] Tanzania[21] and China.[70] Self-medication is affected by the concept of "weak lung" in the Philippines where TB is thought to be like other lung diseases and normally treated by self-medication.[33] In Vietnam, self-medicating is preferred before turning to other providers, particularly for women.[68] When self-medication fails, patients with TB seek less qualified health care providers because of availability and cost concerns in China.[70] Patients seek private providers first in India[27, 42] and Bangladesh,[27] but public health services are sought first in Malawi.[27] Patients discontinue medication after symptoms are relieved in Pakistan.[39]

Age and gender differences in health responses

For TB patients, age and gender have a role in health-seeking behaviors for general health problems or minor illness that may not require advanced diagnosis or treatment. For example, young individuals in India generally seek care from private providers, whereas older individuals generally prefer government facilities.[75] Older patients are reluctant to cause financial burden on their children; the elderly are more likely to delay care than young people and choose care from village providers over the option of a public hospital due to cost concerns.[70]

Men and women report feeling different levels of stigmatization and experience different social and economic consequences of TB (Table 7). Four factors were discussed in the literature related to gender differences: 1) financial dependence of women on men to obtain treatment in Pakistan,[40] 2) low priority of women's health in Peru,[76] 3) social isolation of women in Bangladesh[27] and Vietnam,[68] and 4) decreased marital prospects in Malawi,[16] Pakistan[40] and India.[16, 38] In Vietnam, women worried more than men about social consequences of the disease,[12] and women perceived more TB stigma than men in Kosovo[13] and India.[77] However, one study reported a contradictory finding that In India, TB affects marital prospects for men rather than women.[78]

In general, men and women manage TB differently. Women in Gambia use healers more because of their stronger traditional beliefs, time restrictions, and confidentiality of care.[71] Men in Thailand who experience more TB stigma report increased time of treatment delay, whereas women report decreased time of treatment delay.[79] In Vietnam, men delayed treatment until the serious disease stage of TB and then sought public providers, while Vietnamese women self-medicated and then sought private services.[68]

Stigma related to public health responses

Public health responses can be associated with stigmatization of TB in African countries (Table 8). A strong possibility exists that stigma can arise from negative attitudes of health professionals toward patients with TB due to fear of infection. Healthcare workers may avoid, blame, and place restrictive practices leading to TB stigmatization in the communities of Ghana[53, 80] and South Africa.[81] Because of the

associated stigma with public health services for TB, patients chose to seek out private providers in Ethiopia.[34]

Disclosing TB diagnosis and stigma

Disclosure can affect how patients seek support for diagnosis and treatment of TB (Table 9). In Nicaragua, among community members and health personnel, responses to disclosure ranged from attitudes of patients deserving support to withholding support due to fear of infection and the belief that patients with TB are unlucky.[82] To avoid stigmatization, patients avoid disclosure of a TB diagnosis in South Africa,[83] Nicaragua,[82] India,[77, 78] the Philippines,[74] and Croatia.[65] However, disclosure is reported to bring encouragement or support in Malawi[84] or fear and discrimination in in Tanzania.[85] Patients experience stigma as a result of disclosure of TB status in Nigeria[61] and reactions to disclosure in India included worry and suicidal thoughts.[44]

DISCUSSION

This review of 83 studies suggests that TB has different meanings for different ethnic and cultural groups based on socio-cultural context. Cultural variation exists across 35 countries with respect to knowledge of TB related to causes and transmission routes, as well as attitudes and health responses. Age and gender affect how individuals perceive and manage TB, and public health responses contribute to TB stigma. The findings strongly suggest that TB stigma has a significant impact on women and the poor and less-educated, across countries. This is a critical finding, given that these are the marginalized members of society who are often at higher risk for health disparities. TB stigma may

ensure that women and the poor and less-educated are even more marginalized.

This review shows a cross-country and culture association of HIV with AIDS (Table 4). Visible signs or symptoms of TB are often believed to be a result of HIV/AIDS.[5] Patients co-infected with TB and HIV are more likely to have perceived stigma compared to patients who are not co-infected with HIV.[46] TB is most commonly associated with HIV/AIDS in countries with a high prevalence of HIV/AIDS, as in Africa where HIV/AIDS is the leading cause of death,[1] and in other parts of world, such as Haiti and Thailand. In Malawi, India and Bangladesh, women appear to suffer most from TB stigma because of their vulnerable situation in marital relationships. Stigma manifests itself where there is a societal power imbalance in not only class, race, and gender but also sexuality.[86] The implications of these findings can be far reaching for the provision of culturally sensitive TB treatment.

Due to the scope of this review, the causal relationship between stigma and public health responses was unable to be determined. The associations between stigma and public health responses need to be confirmed in future research.

Potential limitations of the present review include the fact that only English language articles for analysis was used. The search was limited by using words relevant to stigma without using "meaning," or "health and ethnology," which might have resulted in the inclusion of studies of broader understanding of the meaning of TB among different cultural groups.

CONCLUSION

As in other medical conditions, TB stigma maybe critical for treatment seeking and treatment adherence.[87] Further research is needed to elucidate the associations between TB stigma and health outcomes. It may be that interventions designed to improve treatment rates or adherence rates should include consideration of the individual patient's cultural and social context and the role that stigmatization may have in health seeking behaviors. TB stigma needs to be studied in a socio-cultural context and associations with affect knowledge, attitudes and health responses needs to be further explored. A successful stigma intervention may need to be sensitive to the cultural context of patients with TB and their families and communities.

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Table 1. Listing of 35 countries in 6 World Health Organization (WHO) regions

represented in the 83 studies surveyed in the present study

WHO region	Country	Study number	Number studies per country	High TB burden country
African Region	Congo	1	1	X
	Ethiopia	2	8	X
	Gambia	3	1	
	Ghana	4	4	
	Kenya	5	2	X
	Malawi	6	1	
	Nigeria	7	1	X
	Rwanda	8	1	
	South Africa	9	7	X
	Tanzania	10	2	X
	Uganda	11	1	X
	Zambia	12	1	
Eastern Mediterranean Region	Morocco	13	1	
	Pakistan	14	3	X
European Region	Croatia	15	1	
	Kosovo	16	1	
	Russia	17	1	X
	Turkey	18	1	
	United Kingdom	19	2	
Region of the Americas	Brazil	20	1	X
	Colombia	21	2	
	Ecuador	22	1	
	Haiti	23	1	
	Nicaragua	24	1	
	Peru	25	2	
	United States	26	8	
Southeast Asia Region	Bangladesh	27	4	X
	India	28	11	X
	Indonesia	29	1	X
	Nepal	30	1	
	Thailand	31	4	X
Western Pacific Region	China	32	1	X
	Malaysia	33	2	
	Philippines	34	1	X
	Vietnam	35	5	X

Table 2. Methodologies used in the 83 studies analyzed in the present study

Type of study	Number of studies	Methods	Study participants
Quantitative	41	Survey, cross-sectional study and structured questionnaire (interview)	Patients with tuberculosis (TB), their relatives, individuals suspected of having TB, community members, health care workers, university students, housewives, professionals, male and female parents/caretakers of children and adolescents, heads of household, school heads, opinion leaders, religious leaders, caregivers, educators, farmers, employers and nongovernmental organization representatives
Qualitative	32	Focus group discussion, in-depth interview, semi-structured questionnaire, key informant interview and ethnographic study (structured interview)	
Mixed methods	10	Combination of interview and focus group; cultural epidemiology, semi-structured Explanatory Model Interview Catalogue	

Table 3. Knowledge of TB and Causal Factors by Country (in alphabetical order)

Country	Selected Findings
Ethiopia	Caused by cold[24] or cold air[6, 25] or "evil eye"[4] or "evil spirit."[35] Perceive TB as "lay category bird," an illness caused by the cold or blowing wind.[34] Local model sees causal factors unrelated to *tubercle bacillus*.[88]
Haiti	Stigma is associated with poverty and malnutrition.[14]
India	Caused by germs and worry.[42] Sexual experience as the cause of TB.[38] Airborne transmission mode.[22]
Kenya	Smoking, alcohol, hard work, exposure to cold and sharing with TB patients; TB is hereditary.[26]
Malawi	Men emphasize smoking and drinking alcohol as causes of TB, and women report sexual causes associated with HIV/AIDS.[27]
Malaysia	Caused by germs, transmitted by air.[23]
Morocco	Causes related to living conditions. Popular understandings of TB etiology and transmission differ from biomedical view.[32]
Pakistan	Contaminated food as source of infection and emotional trauma/stress as causative agent.[39] TB leads to infertility and reduced chances of getting married following infection.[39] Pregnancy enhances the risk for relapse and decreases women's marriage prospects.[40]
Peru	Transmitted by sharing eating utensils and is prevented by nutrition.[31]
Philippines	"Weak lungs" associated with TB is broad and covers a variety of symptom states inclusive of TB. Some equate "weak lungs" with TB, many others think that weak lungs may develop into TB over time.[33]
Russia	Consider TB as per other respiratory infections.[20]
Rwanda	Causes of cough-related illness include biomedical (germs, internal body dysfunction and worms), environmental (seasonal changes and dust), cultural (inheritance), socioeconomic (hard work, malnutrition and tobacco) and supernatural (witchcraft).[19]
South Africa	Result of breaking cultural rules that demand abstinence from sex after the death of a family member and after a woman has a spontaneous abortion.[28] "Western" type TB caused by environmental pollution, smoking or alcohol excess.[28] Caused by smoking.[29]
Tanzania	Transmitted through air.[21]
Turkey	''Unhappiness and stress'' as the major cause of illness in patients with

	TB.[43]
Uganda	TB etiologies: sharing utensils, heavy labor, smoking, bewitchment and hereditary transmission.[30]
United States	Transmitted through air and widespread misperceptions about TB transmission (kissing, sharing clothing or eating utensils or exchanging body fluids) among Mexican Americans.[37] Hard manual labor, smoking, alcohol consumption and poor nutrition as risk factors among Vietnamese.[2]
Vietnam	Caused by germs. Traditional beliefs of four TBs: (1) 'Lao truyen' (hereditary TB), handed down from older generations via 'family blood'; (2) 'Lao luc' (physical TB), caused by hard work; (3) 'Lao tam' (mental TB), caused by too much worrying; (4) 'Lao phoi' (lung TB), dangerous and caused by TB germs, transmitted through the respiratory system.[18]

Table 4. Association with HIV/AIDS by Country (in alphabetical order)

Country	Selected Findings
Ethiopia	Those who had heard about HIV/AIDS considered an association between HIV/AIDS and TB.[35] Associated with HIV/AIDS.[24] HIV patients with coinfection of TB and HIV more stigmatized than those without coinfection.[46]
Haiti	Stigma associated with HIV coinfection.[14]
Kenya	Perceived link between TB and HIV.[45]
Malawi	Association with HIV/AIDS linked to TB stigma.[16]
Rwanda	TB symptoms mistaken for AIDS.[19]
Thailand	Co-infection with HIV is associated with greater TB stigma.[47]
United Kingdom	HIV disease worsens TB stigma. Patients decline HIV testing fearing stigmatization and poor illness outcome if positive (among Africans).[48]
Zambia	Association between TB and HIV.[5] Visible signs of TB a trigger for TB-HIV stigma.[5]

Table 5. Attitudes toward TB by Country (in alphabetical order)

Country	Selected Findings
Brazil	"Living with tuberculosis is suffering"—isolates people and changes an individual's perception of himself/herself and difficult treatment; presentation of TB is expressed as loss, sadness, and dissatisfaction.[62]
China	Social stigma associated with TB influences marriage prospects and impedes important social interactions within the community.[70]
Colombia	Cough, contagion, illness and fear.[56] Fear and compassion are associated with evocations among patients and their relatives, contagion among lay people and isolation among health care personnel.[56] Scientifically unfounded beliefs about TB transmission predict prejudice.[36]
Congo	Likens to a person (creature) invading people. Respond by isolation, shame and contempt of individuals with TB and uncertainty of who is infected with TB.[49]
Croatia	Report feeling uncomfortable near a TB patient and would avoid any contact.[65]
Ecuador	Link TB to multiple adverse health, economic, psychologic and social consequences, including stigma and feeling stigmatized just by being tested for TB.[3]
Ethiopia	Patients are not accepted in the community and fear physical contact with patients.[24] Individuals suspected of having TB consider themselves inferior.[4] Women and illiterate individuals have greater prejudice toward individuals with TB than men and literate individuals.[6] Stigmatization and social isolation of patients with TB.[24] Ostracism toward patients with TB.[35]
Ghana	Fear of infection.[52-54] Fear of infection, physical frailty, association with HIV/AIDS, perceived causes and spread of TB, outdated societal beliefs and practices regarding TB, public health practice and discourse, health staff's own fear of TB, self-stigmatization by those with TB, judgment, blaming and shaming of those with TB and past experiences with TB.[54] Those with TB considered not marriageable.[52] Health care workers fear infection when interacting with those with TB; shunned, avoided, and advocated the segregation of patients TB at home and in hospitals.[53]
India	Isolating TB patients from family, avoiding food sharing, quitting job, prohibiting marriage, shunning from social functions.[69]
Indonesia	TB patients face joblessness and negative attitudes from neighbors and relatives.[8]

Malaysia	TB patients are socially acceptable, but contracting TB is embarrassing.[23]
Nepal	Existences of patients' self-discrimination and discrimination from general public.[51]
Nicaragua	Contradictory feelings and attitudes: feelings of affection and supportive attitudes toward those with TB, as opposed to fear of being infected; consider those with TB to be unlucky, as opposed to mistrust of those with TB considered to be negligent.[82]
Nigeria	Stigma determined by age, low socioeconomic status, education below secondary level, history of weight loss, previous smoking and history of alcohol consumption.[61]
Pakistan	Community rejects those with TB.[9] Stigmatization and social isolation of those with TB and their families.[40]
South Africa	Fear of infection; not keen to associate with individuals with TB.[55] Isolation for TB sufferers and the harm TB sufferers do to others.[64] Stigma attached to TB patients by others and which differentiate TB patients from "normal" people.[41]
Thailand	TB disease severity and knowledge, individual's religion—associated with stigmatizing behaviors/attitudes and/or social support. TB patients with more severe symptoms experience greater stigma.[60]
Turkey	Three difficulties in their lives owing to TB: financial problems, loneliness and hospitalization.[43]
United Kingdom	Do not feel threatened by TB and believe TB is not infectious to their family or friends. Consider TB to be acceptable to family and friends.[63]
United States	Having TB adversely impacts work, family and community activities and relationships among Vietnamese in New York.[2] African-American patients felt family and friends avoided or shunned them, causing them to isolate themselves and became secretive about their illness.[67] Fear and aversion toward persons with TB among North Carolinians.[57] Belief of extreme contagiousness of TB leads to social stigma and isolation among Samoans.[66] TB more socially acceptable to Whites and Latinos compared to Blacks. Social stigma with TB—TB is dirty and an embarrassment.[15] TB stigma among Haitians in South Florida involve Haitian identity as a negatively stereotyped minority community within the larger society.[14]
Vietnam	Dirty disease affects poor people; TB patients feel less respected by others.[7] Women's fear of social isolation.[68]
Zambia	Judgment, blame, shame and fear of contagion.[5]

Table 6. Health responses toward TB by Country (in alphabetical order)

Country	Selected Findings
Bangladesh	Private doctors preferred.[27]
China	Only seek health care after they fail to treat themselves[70]; older people than younger less likely to seek care or more likely seek care from less-qualified village level health care providers.[70]
Ethiopia	Both private and public clinics manage patients according to the "lay category bird."[34] Therapeutic preference depends on using ethnobotanical remedies and their expected emetic effects.[88]
Gambia	Consult traditional healers and pharmacies first; women use these healers more because of stronger traditional beliefs, time constraints and increased confidentiality.[71]
Ghana	Sociophysical distance and participatory restrictions on those suffering from the disease.[52]
India	Private doctors preferred.[27] First source allopathic treatment, and shift to municipal and nongovernment organization health services when private treatment becomes unaffordable.[42] Whereas younger patients access care from private providers, older patients prefer government facilities.[75]
Kenya	TB patients treat themselves and consult with the traditional health sector.[26] Visit diviners, others alternate between self-treatment, hospital treatment and herbalists.[45] Sociostructural and superstructural forces in beliefs and perceptions on treatment and disease-causing factors affect treatment-seeking.[45]
Malawi	Public health services preferred.[27]
Malaysia	Seek modem medicine for cure; other forms of treatment (traditional medicine) sought if modem medicine fails to cure the disease.[73]
Pakistan	Owing to fear, patients deny the diagnosis and reject treatment.[40] Discontinue medications following relief of symptoms.[39]
Philippines	Faith in biomedicine is strong. Concept of "weak lungs" affects self-treatment practices and over-the-counter TB medications.[33]
Russia	Illness identity is associated with delay.[20] Internalized shame is associated with increased medication adherence, whereas financial insecurity is associated with decreased adherence.[20]
Rwanda	Home care, health facility and the traditional healer are three health-seeking endpoints.[19] Use of herbal treatment for chronic cough.[19]

	Believe TB is due to witchcraft and can only be treated traditionally.[19]
South Africa	If resulted from breaking culture rules, TB can only be treated by traditional healers, which delays presentation to hospitals.[28]
Tanzania	Self-medication preferred, health care facility consultation least preferred option.[21]
Thailand	TB patients with high stigma more likely to have taken antibiotics before TB treatment and to have first visited a traditional healer or private provider.[72]
Uganda	Care combined from traditional healers and biomedical system.[30]
United States	For Samoans in Hawaii, biomedical treatment is necessary; traditional herbal medicine is seen as adjunct to biomedical treatment.[66] Biomedical treatment is necessary, many believe in the effectiveness of traditional and popular treatments among Filipinos in California and Hawaii.[74]
Vietnam	Men neglect symptoms until the disease reaches a serious stage and then go directly to public health services.[68] Women seek out private services and practice self-medication before seeking care at public services.[68]

Table 7.   Gender Differences in Health Responses by Country (in alphabetical order)

<u>Country</u>   <u>Selected Findings</u>

Bangladesh   Exaggerated concerns about risk of spread despite treatment, contribute
              to social isolation of women.[27] Women faced with adverse consequences
              more often than men; coughing up sputum in public by women is
              culturally frowned upon, resulting in enormous suffering.[58] Men less
              likely to disclose condition, stay away from work, report spouse refused
              sex because of TB; women report feeling shamed or embarrassed, think
              less of themselves and feel others refuse to visit or avoid them.[50]

India   Women experience more stigma than men.[77] Marital problems
              anticipated more for women;[75] anticipation of support or attention is
              more definite for men.[75, 78] Marital problems more for males.[78] Men
              worry about impact of TB on income and job; women concerned about
              less chance of marriage.[16] Perceived stigma is higher for men; change of
              behavior of community, ashamed to cough in front of others.[59]

Kosovo   Women more stigmatized than men.[13]

Malawi   Women more concerned about impact on martial prospects.[16]

Pakistan   Both males and females face social and economic problems; females
              affected more in marriage.[40] Women economically depend on husbands
              and family-in-law and need their cooperation to use treatment.[40]

Peru   Women's health inherently lower priority than men's health.[76] Women
              experienced adverse psychosocial and economic consequences of TB
              diagnosis more than men.[76]

Thailand   Men with greater TB stigma have small _increase_ in delay times, whereas
              women have small _decrease_ in delay times.[79]

Vietnam   Men perceived to get TB more often than women because exposed more
              to risk factors during both work and leisure time.[18] Women contribute to
              delay of care, owing to fear of social isolation from family or
              community; men contribute to fear of individual costs of diagnosis and
              treatment.[68] Men worry about economic problems, whereas women
              worry about social consequences of the disease.[12] Insufficient knowledge
              and individual cost of treatment are main obstacles to compliance among
              men, whereas sensitivity to interaction with health staff and stigma in
              society are main obstacles among women.[89]

HIV/AIDS = human immunodeficiency virus infection/acquired immunodeficiency
syndrome; TB = tuberculosis

Table 8. Stigma related to public health responses by Country (in alphabetical order)

<u>Country</u>   <u>Selected Findings</u>

Ethiopia   Stigma associated with TB and public health services make many patients approach private clinics, causing further delay.[46]

Ghana   Healthcare system manifested stigma toward TB patients. Healthcare workers' fear of infection avoided the patients and blamed them for spreading infection. Posting to TB units/wards is as a punishment.[60]

Activities of health professionals may expose patients with TB to stigmatization in the community: isolation and exclusionary practices; behaviors of health professionals toward patients with TB; public health discourse; food safety and hygiene practices and prohibition of full burial rites to those having died from TB.[85]

South   Positive attitudes toward support and treatment for TB patients at
Africa   clinics and negative attitudes toward temporary disability grants, provision of information at work or school, and treatment at the TB hospital.[86]

Table 9. Disclosing TB diagnosis and stigma by country (in alphabetical order)

Country	Selected Findings
Croatia	Respondents with high education hide TB, compared to those with less education.[70]
India	Reaction to the disclosure of TB is worry and suicidal thoughts.[90] Immense stigma observed with patients hiding their disease from friends and neighbors.[16] Concealment of disease, owing to fear of losing social status, marital problems and hurtful behavior by the community.[83]
Malawi	Disclosure brings encouragement and empowerment.[89]
Nicaragua	Hiding the condition leads to a loss of confidence and depression.[87]
Nigeria	Stigma experience determined by disclosure of status to friends and colleagues.[14]
Pakistan	Owing to fear, patients often deny the diagnosis and reject treatment.[50]
Philippines	Do not seek attention or attempt to hide their illness to avoid social stigma and isolation, leading some to deny their illness.[79]
South Africa	Report hiding TB status, owing to fear of what others might say.[88]
Tanzania	Some openly speak about their illness to others, and friends and family respond in a considerate and sympathetic manner or become less friendly; the remaining openly display fear and try to discriminate against a patient even after starting medication.[93]
Thailand	Patients who conceal their TB are less accepted and tolerated and therefore more stigmatized than those who reveal their TB diagnosis.[66]

HIV/AIDS = human immunodeficiency virus infection/acquired immunodeficiency syndrome; TB = tuberculosis

Figure 1. Flow diagram for meta-synthesis review of cultural variation regarding

tuberculosis stigma

1339 studies identified from database search: *PubMed/Medline (n = 953) *Web of Science (n = 286) *Cochrane (n = 43) *PsycINFO (n = 24) *CINAHL (n = 33)

↓

1268 studies after duplicates removed		1148 excluded studies were non-English studies, dissertations, intervention studies, review articles, commentaries, letters and guidelines.

↓

120 studies screened

↓

120 full-text studies assessed for eligibility		37 full-text excluded studies were not related to attitudes, beliefs, or responses in relation to TB stigma

↓

83 studies included in data synthesis

↓

83 studies were from
35 countries* in 6 World Health Organization
regions for global tuberculosis reporting:
12 countries in African Region (n = 30 studies)
  2 in Eastern Mediterranean Region (n = 4 studies)
  5 in European Region (n = 6 studies)
  7 in Region of the Americas (n = 16 studies)
  5 in Southeast Asia Region (n = 21 studies)
  4 in Western Pacific Region (n = 9 studies)

*Some studies were conducted in more than one country.

Chapter III

Failure to Complete Isoniazid Therapy in Children

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Running head: Latent Tuberculosis Infection in Children

ABSTRACT

Rationale: A 9-month course of isoniazid is the standard regimen to treat latent tuberculosis infection (LTBI) in children to prevent progression of active TB disease. The completion rate of isoniazid therapy in children remains suboptimal.

Objectives: To describe the completion rate of isoniazid therapy among children under 21 years of age, and factors associated with failure to complete treatment for LTBI.

Methods: Retrospective review of medical records in children less than 21 years of age referred for isoniazid therapy between 2005 to 2011 at two California county sites: the public health department and a clinic for LTBI.

Measures and Main Results: There were 1,931 eligible patients referred for isoniazid therapy initiation. Of the 1,626 patients who initiated treatment, 78% completed their 9-month therapy; 80% of 1,308 children under 15 years of age and 69% of 307 children between 15-21 years of age completed treatment. Using bootstrap analysis, noncompletion rates of LTBI treatment were higher for children ≥15 years of age (odds ratio, 1.6; 95% confidence interval [CI], 1.2 to 2.0), non-Hispanic ethnicity (odds ratio, 1.3; 95% CI, 1.1 to 1.5), symptoms of adverse reactions (odds ratio, 2.0, 95% CI, 1.1 to 3.0), and isoniazid hepatitis (odds ratio, 5.0, 95% CI 3.3 to 8.0).

Conclusions: Non-completion of isoniazid therapy in children was influenced by age, ethnicity, symptoms of adverse reactions, and isoniazid hepatitis. Parental and family involvement in the treatment process is particularly important for older children who function more independently in self-management of their isoniazid therapy.

INTRODUCTION

According to the American Thoracic Society (ATS), Centers for Disease Control and

Prevention (CDC), Infectious Disease Society of America (IDSA) guidelines, also

endorsed by the American Academy of Pediatrics (AAP), a 9-month course of isoniazid

is the standard regimen to treat latent tuberculosis infection (LTBI) in children and

adolescents to prevent progression of active TB disease.(1) Young children have higher

risk to progress to TB, and children have more years to develop TB.(2) Completion rates

of 9-month isoniazid, defined as 270 doses taken within a 12-month period, in pediatric

populations has varied from 40.3% to 76% in prior studies.(3-5) Similarly, completion

rates for 6-month regimen are reported to be slightly higher in some studies yet also

varied by study population. The 6-month isoniazid completion rate for children aged <15

years was 42.6% in Boston and 74% - 86.7% in San Diego.(6-8).

Previous studies have examined factors affecting completion rates for mixed-age

populations undergoing 9-month isoniazid therapy. Older age (6, 9-12), non-Hispanic

ethnicity (6, 7), experience with either isoniazid hepatitis or adverse reactions and

symptoms during the treatment (6, 13-16), and having low risk of TB (4, 17, 18) have

been associated with noncompletion of isoniazid therapy. However, it is not yet known

how these socio-demographic and clinical factors contribute to children's adherence to

isoniazid therapy. The study goal was to 1) determine the completion rate of 9-month

isoniazid therapy in children and 2) confirm the findings of existing literature on

predictors of isoniazid therapy and add knowledge about new predictors of treatment

noncompletion for children under 21 years of age in Northern California.

METHODS

Study Population

To determine completion rate of 9-month isoniazid therapy, a medical record review was conducted on an available sample of children less than 21 years of age who were referred to one of two sites in the county and initiated isoniazid therapy from January 2005 to August 2011. The study was approved by the Committee on Human Research at University of California, San Francisco (IRB# 11-08230, See Appendix 6) and the Institutional Review Board at Santa Clara County Valley Medical Center (IRB #11-059, See Appendix 7).

Children < 21 years of age who had a diagnosis of LTBI were included if they (1) had a positive tuberculin skin test, (2) had a normal chest radiograph, and (3) were prescribed isoniazid for 9 months. Cases were excluded from the study if they (1) were already receiving isoniazid therapy; (2) were previously treated and resumed isoniazid due to interruption in the treatment; (3) had active tuberculosis; (4) were placed on rifampin in place of isoniazid; or (5) had inadequate medical records.

Management of LTBI

Children (< 2 years) were referred to public health department for follow up on latent tuberculosis infection through completion of treatment. The medical management of these children was either by their primary care physician or was co-managed with public health nurses who followed up these patients with monthly home visits to assess medication adherence by pill count and to monitor for any adverse reactions from medication.

Children (between 2 -21 years), were evaluated and followed at the LTBI clinic by a nurse practitioner and had a complete history, physical examination, and assessment of compliance and adverse reactions, before receiving a one-month refill of medication. Patients with any risk factors of isoniazid-induced hepatitis received a baseline serum transaminase test prior to beginning therapy. No routine biochemistry testing was conducted. When a patient developed isoniazid hepatitis, elevation of serum transaminase exceeded 2 times the upper limit of normal, the test for liver enzymes was repeated within 24 hours to weekly until liver enzymes decreased or were stable. The chemistry monitoring practice was unknown for 1.5% patients (n = 24) treated by private primary care physicians or by a county tuberculosis clinic.

If pregnancy occurred, isoniazid was discontinued and deferred until 2-3 months postpartum to restart therapy. There were 8 postpartum patients in whom isoniazid therapy was discontinued until 2 to 3 months after delivery. There were no practice changes between 2004 and 2012 in the LTBI clinic.

For children who were lost to follow-up or failed to keep clinic or home visits, efforts were made to contact patients by telephone or letter. There was no mechanism to track children's completion of treatment status when a family moved out of county or state or transferred care to other medical providers in the community.

Definitions and Measures

A child was considered as <15 years of age based on the CDC guidelines (19). Completion of isoniazid therapy was defined as completion of 270 planned doses over a 9-month duration or within 12 months. Adverse reaction was defined as the frequency of

symptoms occurring after patient initiated treatment determined from a standard checklist of symptoms associated with an adverse reaction to isoniazid used by both the public health nurses and the LTBI clinic nurse practitioner. Accumulative numbers of symptoms from initiation to the end of treatment were recorded and divided by the number of home or clinic visits during treatment to obtain a rate of symptom experience adjusted by time. Retrieved variables consisted of age, gender, race, reasons for referral (TB risk classifications), induration of tuberculin skin test, symptoms of adverse reactions, serum transaminase levels, treatment time, status of completion, reasons for not completing treatment, having a family member on antituberculosis treatment, clinic location, and postal zip code.

Sample Size Estimation

Sample size estimation was based on multiple logistic regression analyses. It was determined that a sample size of 1,452 would be needed (nQuery Advisor, version 4.0, Cork, Ireland) for a two-group chi-square test with a 0.05 two-sided significance level and 80% power to detect a difference between a group with 85% completion rate and a group with 90% completion or an odds ratio (OR) of 1.59.(7)

Sample Independency

Several procedures were performed to ensure sample independency. When more than one child in a family was referred for evaluation and treatment, only the youngest child was entered as a case. To identify same-family children, the parent's name was used.

Quality Assurance

Intra-rater reliability of data entry was assessed in a double-entered random sample of 10% of all cases. The error rate was 8.9% for Public Health Department records, and 2.9% for all non-initiated patients at LTBI clinic. At the LTBI clinic, a random sample of 10% of the first 100 patients revealed a data entry error rate of 5%. Measures were then taken to reduce errors by refining the patterns of inconsistency in data entry and revising variable coding for data entry. The final error rate for the random sample from the last 100 patients was only 2.7%.

Data Analysis

Tabulations and correlations between variables were performed with SPSS Statistics (version 20.0, IBM Corp., Armonk, NY). The percentage of missing data for each variable of interest was examined and then excluded that variable from analysis if 20% was missing. All significant predictors were identified through the multivariable logistic regression based on $P > .05$. There was no collinearity among the predictors. The numbers of cases for categorical predictors of noncompletion were too small and the assumption of linear relationship between symptoms parameter and dependent variable was not met. To correct this problem, non-parametric bootstrap in SAS version 9.1 (SAS, Cary, NC) was used to report the odds ratio (OR) and the bias-corrected confidence intervals (95% CI) for each significant predictor.(20)

RESULTS

Completion Rate of Isoniazid Therapy

To assess the completion rate of isoniazid therapy, a total of 1,931 patients between 0 and 21 years of age with a diagnosis of LTBI, from the two sites (Figure 1) was identified. There were 219 patients (11%) who did not initiate isoniazid therapy. Patients who transferred care, moved, or were lost to follow-up accounted for 62% who did not initiate treatment (Table 1). There were 1,712 patients (89%) who initiated treatment and 1,626 patients who satisfied inclusion criteria. Of the 1,626 patients, 79% were Hispanic and 78% completed 9 months of isoniazid therapy (Table 2). There were 30 patients who developed adverse reactions to isoniazid and completed rifampin regimen. Among 357 who did not complete treatment, 31% moved or were lost to follow-up (Figure 1).

Table 2 shows demographic and clinical characteristics of patients who initiated treatment. Eight percent of patients were referred for having one TB risk factor (Tuberculin skin test conversion within 24 months or contact with active TB case) in addition to a positive tuberculin skin test. Half of the sample had experienced one or more symptoms of an adverse reaction. The most common symptom (29%) was loss of appetite or abdominal pain. The average number of clinic visits was nine, and 52 children (3%) had elevated serum transaminases during the course of treatment.

Predictors of Treatment Noncompletion

To evaluate factors with regard to treatment completion, retrieved variables included gender, reasons for referral for starting treatment (TB risk classifications), induration of tuberculin skin test, treatment time, having a family member on antituberculosis

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treatment, clinic location, and postal zip code. These factors had no significant effect in univariate analysis and were excluded from further analysis. Age ≥15 years, non-Hispanic ethnicity, adverse reaction symptoms, and isoniazid hepatitis were each independently associated with treatment noncompletion in multiple logistic regression analysis. In bootstrap analysis, age ≥15 years of age (OR=1.6; 95% CI 1.2 to 2.0), non-Hispanic ethnicity (OR=1.3; 95% CI 1.1 to 1.5), symptoms of adverse reactions (OR=2.0, 95% CI 1.1 to 3.0), and isoniazid hepatitis (OR=5.0, 95% CI 3.3 to 8.0) were significantly related to treatment noncompletion (Table 3).

DISCUSSION

Findings from this study show an overall completion rate of 79% for patients who initiated and completed a 9-month isoniazid therapy (Table 3). The rate of isoniazid therapy completion was higher (80%) in the younger aged group of 1,308 children under 15 years of age than in the older group (69%) of 307 children between 15 and 21 years of age. The completion rate for children ≤15 years is higher than what was reported in Columbus study, 54.4% of children ≤15 years of age completed therapy.(3) If a cutoff age of 18 years was used, the completion rate would have been 78.4%, which is similar to the Houston sample where 76% of children <18 years of age completed isoniazid therapy.(5)

In studies that defined treatment completion as a 6-month isoniazid therapy rather than 9 months, completion rates in children under 15 years of age ranged from 74% to 86.7%.(6, 7) If the 6-month definition was used, the completion rate would have been 83%, similar to the 87% rate found in a predominantly Hispanic population in San Diego.(7) Although

the results are similar to the Houston and San Diego studies, the Directly Observed

Therapy (DOT) used for half of the children in the Houston sample may have contributed

to their higher completion rate. In the San Diego study, 47% of the children received

behavioral intervention and 36% received source case investigation. In this sample, only

4 children received DOT and all of the remaining children were on a self-administered

therapy.

Several possible factors may contribute to our higher completion rate. First, pill counts by

the nurse practitioner may increase parental diligence and thus increase medication

adherence of children. Second, in our intensive follow-up efforts, phone calls and letters

were sent to remind patients of their appointments or to retrieve patients lost to follow-up.

Third, medical care was more accessible in the sample, with five LTBI clinic locations in

the county for families in different geographic areas and more readily accessible care

could influence completion rates.

In this study, age $\geq$15 years, ethnicity (non-Hispanic), and symptoms of adverse reactions

or isoniazid hepatitis were independently associated with not completing treatment for

LTBI (Table 3). Even for our full pediatric age range, older age was a factor in treatment

noncompletion. This finding is consistent with other studies (6, 9-12) supporting children

compared with adults are more likely to complete isoniazid therapy, perhaps because of

more intense parental supervision. The finding of this study suggest that Hispanic

children are more likely to complete treatment than non-Hispanic children is also

consistent with previously reports.(6, 7) The overall completion rate (78%) of therapy

may be attributed to the acceptance of LTBI therapy by parents born in South and Central

America than by parents from Eastern Europe or Asia.(3) Although these factors are

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associated with treatment noncompletion, caution should be exercised in interpreting these results due to the small number of children who failed to complete treatment in each of these factors categories (Table 3). A larger sample size is needed to confirm relationships among these predictors and treatment noncompletion in children.

This study confirmed that symptoms associated with adverse reactions to isoniazid is a major obstacle to completing therapy.(6, 13-16) Although patients reported symptoms, such as abdominal pain or loss of appetite, during the course of treatment, these symptoms can occur with many other minor illness episodes, yet a patient may have associated these symptoms with their isoniazid medication and prematurely discontinued treatment. Hepatitis, a common adverse reaction was, also confirmed as a factor associated with treatment noncompletion in this sample. Children with isoniazid hepatitis were required to have more blood tests and follow-up clinic visits, and therefore may be less likely to complete treatment. It is possible that patients themselves or their parents may be reluctant or perceive inconvenience for children to receive more venipuncture or additional clinic visits (18) or may be concerned about safety of the medication. Because of these reasons, the child or parents may have chosen to discontinue treatment on their own. Further study is needed to explore the child and parent perceptions of medication side effects and blood tests required to medically manage isoniazid-induced hepatitis.

Family members' involvement has been shown to promote adherence to treatment, including participating in screening for tuberculosis (21); however, this association was not found. Children in contact with people who have pulmonary tuberculosis, and therefore higher TB risk, are more likely to complete treatment.(4, 17, 18) However, the

finding of this study for this association is inconclusive to the small number of children in this sample who carried a high risk of TB.

This study has a few limitations to consider. First, a convenience sample of children with medical records from only one county was used and only 21% of this sample is non-Hispanic. The sample is also primarily from a specialty clinic in which many Hispanic children with public medical insurance are treated. Larger samples of ethnically diverse populations may be useful because ethnicity and socio-economic status may be confounding variables for adherence to treatment. The second limitation was the retrospective cohort study design, which can limit internal validity because of possible bias in recording outcomes of interest. Compared with other studies that lacked data on actual pill counts, the measure of this study was more valid, yet could still overestimate compliance because children can remove pills from bottles prior to the day of a pill count. Biomarker devices, for example urine strips (22, 23) or the Medication Event Monitoring System (MEMS) that records the date and time of bottle-cap openings (24), can generate more accurate results and could be used to monitor adherence, but practicality and cost are issues to consider in future research. Further study is needed to improve current measures of medication adherence; multiple outcome evaluations should be conducted without announcement during the course of treatment, and both subjective and objective methods should be used. The outcome of completion may also be biased by parents' responses to pill counts and the increased likelihood of adherence in the younger children supervised by a parent.

The third limitation is that data are unavailable for completion rates of 212 children who transferred care, moved, or were lost to follow-up. These three conditions accounted for 59% of the children who did not complete treatment (Figure 1). There have no mechanism to track their completion, so they are conservatively included in the noncompletion group. As such, this may result in an underestimation of completion rates if they completed therapy elsewhere. Similarly, for children who were lost to follow-up and who did not initiate treatment (Table 1), there were no data on reasons for not accepting isoniazid therapy.

The guidelines published by the ATS/CDC/IDSA/AAP recommend three types of interventions for promoting adherence to treatment of LTBI in children and adolescents: educational, organizational/support, and behavioral.(2) Our clinic provides organization support, with five convenient clinic sites and accessible open hours. Children obtain access to medical insurance for the clinical visits, and the public health department and LTBI clinic have the language capacity to communicate with Spanish-speaking patients. These provisions support children and their parents in accessing and completing LTBI treatment in a county with high TB rates.(25) According to American Academy of Pediatrics guidelines, diagnosing and treating LTBI is a crucial step to eliminate TB in children. The findings of this study support the need for public health intervention, particularly for older children aged may need better assessment of parental or family involvement in the medical decisions to initiate treatment for LTBI. The necessity for clinicians to facilitate parental and family involvement in the treatment decision and process is particularly important for older children who function more independently in self-management of their isoniazid therapy.

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Table 1. Reasons for Not Initiating Isoniazid Therapy

Reasons for not initiating isoniazid	LTBI Clinic	
	#	(%)
Has private primary care provider	51	(23)
Moved	43	(20)
Lost to follow-up	38	(17)
Refused	20	(9)
Completed therapy previously	15	(7)
Incarcerated	10	(4)
Other (including failure to comply)	10	(5)
Treated in a tuberculosis clinic	9	(4)
Repeated tuberculin skin test or QuantiFERON negative	7 *1	(4)
Unknown	6	(3)
Transferred care elsewhere	4	(2)
Did not start	3	(1)
Pregnant	2	(1)
Total	**219**	

*In addition to 218 children from LTBI Clinic, 1 child was from the Public Health Department.

Table 2. Demographic and Clinical Characteristics

Characteristic	Number (%)
Age*	
< 5 years	497 (30)
5 to 9 years	404 (25)
10 to 14 years	418 (26)
15 to 21 years	307 (19)
Sex	
Female	827 (51)
Male	799 (49)
Race†	
Hispanic	1277 (79)
Asian and Pacific islanders	197 (12)
Other	73 (5)
Black	36 (2)
White	30 (2)
Reasons for referral‡	
Positive tuberculin skin test (TST)	1148 (86)
TST conversion within 24 months	88 (7)
Positive TST under 24 months	42 (3)
Other reasons	37 (3)
Close contact to active TB case	13 (1)
TB skin test induration (mm)	14.2 ± 4.5 (5-50), 13
≥ 1 Adverse reactions	
Total	811 (50)
Loss of appetite or abdominal pain	465 (29)
Chill, fever, or night sweats	338 (21)
Nausea, vomiting, or diarrhea	299 (19)
Headache	272 (17)
Rash or itching	76 (5)
Serum transaminase ≥ 2 times upper limit of normal	52 (3)
Total clinic visits	8.0 ± 2.5 (0-14), 9
Treatment time (m)	9.7 ± 1.3 (1.0-22.1), 9.5
Family members on treatment	
Yes	157 (10)
No/unknown	1469 (90)
Completed therapy§	
Yes	1258 (78)
No	357 (22)

* Mean age 9 ± 5.2 (SD) years (range 0.5 to 20.8).
† Data on race available for 1613 patients (99%).
‡ Data on reasons for referral for 1328 patients (82%).
§ Completion data available for 1615 children (99%) of the 1626 children who initiated isoniazid therapy and were included in the analysis.

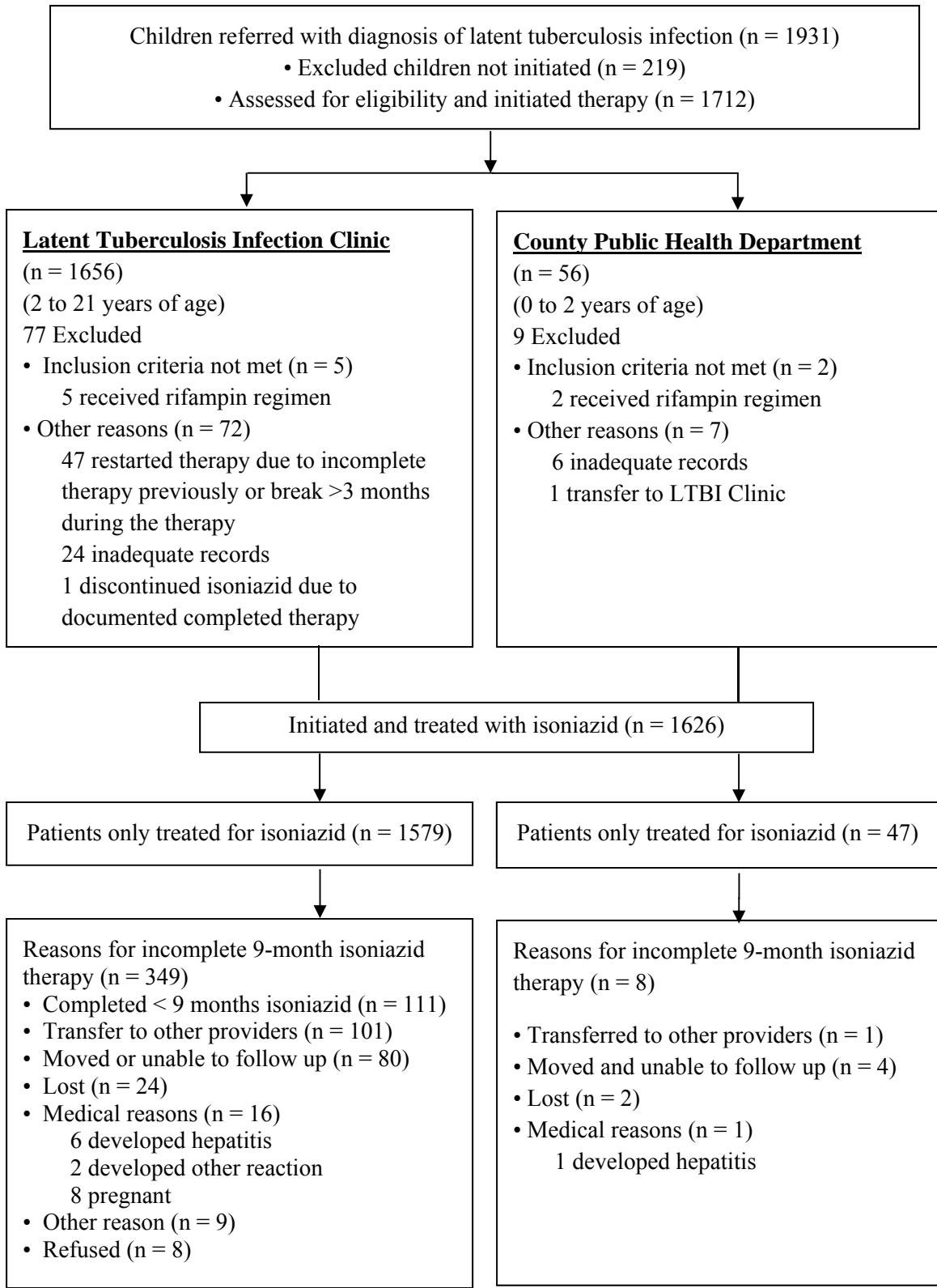Table 3. Factors Associated with Noncompletion of Isoniazid Therapy

Characteristic	Completed		Not completed		Total		Bootstrap analysis*	
	No.	(%)	No.	(%)	No.	(%)	OR	95% CI
	1258	(78)	357	(22)	1615	(100)		
Age(yrs) 0 - <5	394	(81)	93	(19)	487	(30)	Reference (1.0)	
5 - <10	321	(80)	82	(20)	403	(25)	0.9	0.7-1.1
10 - <15	331	(79)	87	(21)	418	(26)	1.0	0.8-1.2
≥15 - <21	212	(69)	95	(31)	307	(19)	1.6	1.2-2.0*
Race Non-Hispanic	236	(71)	95	(29)	331	(21)	1.3	1.1-1.5*
Hispanic	1011	(80)	260	(20)	1271	(79)	Reference (1.0)	
Isoniazid hepatitis†								
No	1251	(80)	312	(20)	1563	(97)	Reference (1.0)	
Yes	7	(14)	45	(86)	52	(3)	5.0	3.3-8.0*
Symptoms‡	0.16 ± 0.22 (0-1.2), 0.1		0.23 ± 0.40 (0-3), 0		0.17 ± 0.27 (0-3.0), 0.09		2.0	1.1-3.0*

* Bootstrap analysis, *significant effects by odds ratio (OR) and 95% Confidence Intervals (CI)

† Isoniazid hepatitis: serum transaminase (alanine aminotransferase or aspartate transaminase) greater than two times the upper limit of normal (ULN).

‡ Symptoms = total symptoms of adverse reactions divided by total clinic visits during course of treatment

Figure 1. Flow Diagram for Children < 21 Years Old with Latent Tuberculosis Infection

Children referred with diagnosis of latent tuberculosis infection (n = 1931)
- Excluded children not initiated (n = 219)
- Assessed for eligibility and initiated therapy (n = 1712)

Latent Tuberculosis Infection Clinic
(n = 1656)
(2 to 21 years of age)
77 Excluded
- Inclusion criteria not met (n = 5)
  5 received rifampin regimen
- Other reasons (n = 72)
  47 restarted therapy due to incomplete
  therapy previously or break >3 months
  during the therapy
  24 inadequate records
  1 discontinued isoniazid due to
  documented completed therapy

County Public Health Department
(n = 56)
(0 to 2 years of age)
9 Excluded
- Inclusion criteria not met (n = 2)
  2 received rifampin regimen
- Other reasons (n = 7)
  6 inadequate records
  1 transfer to LTBI Clinic

Initiated and treated with isoniazid (n = 1626)

Patients only treated for isoniazid (n = 1579)

Patients only treated for isoniazid (n = 47)

Reasons for incomplete 9-month isoniazid
therapy (n = 349)
- Completed < 9 months isoniazid (n = 111)
- Transfer to other providers (n = 101)
- Moved or unable to follow up (n = 80)
- Lost (n = 24)
- Medical reasons (n = 16)
  6 developed hepatitis
  2 developed other reaction
  8 pregnant
- Other reason (n = 9)
- Refused (n = 8)

Reasons for incomplete 9-month isoniazid
therapy (n = 8)

- Transferred to other providers (n = 1)
- Moved and unable to follow up (n = 4)
- Lost (n = 2)
- Medical reasons (n = 1)
  1 developed hepatitis

Chapter IV

Hepatotoxicity in Children Receiving Isoniazid Treatment for Latent Tuberculosis Infection

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Running head: Hepatotoxicity with isoniazid

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ABSTRACT

Background: Isoniazid hepatotoxicity has been found to be age-related and not common in children receiving isoniazid treatment for latent tuberculosis infection. Although the frequency of isoniazid hepatotoxicity is low in pediatric populations, children with liver failure and who have gone through liver transplant have been reported in the past. Characteristics of children with isoniazid hepatotoxicity are unclear. We describe the prevalence and demographic and clinical characteristics of children with hepatotoxicity associated with isoniazid treatment for latent tuberculosis infection.

Methods: Retrospective review of medical records in 1,626 children < 21 years of age who were referred to receive isoniazid treatment from January 2005 to August 2011 in one California county at two possible sites: the public health department, and a latent tuberculosis infection clinic of a county hospital.

Results: The prevalence of isoniazid hepatotoxicity (symptomatic elevation of amino transaminase > 3 times the upper limit of normal [ULN] with hepatitis and/or jaundice) was 1.2% (19/1,626). Of the 19 patients with isoniazid hepatotoxicity, 58% were female and most (79%) were Hispanic. The age distribution mean was 10 years (age range, 2.3 to 19.7 y). Thirty-two percent of children were overweight or obese. The median time from beginning isoniazid therapy to the date of diagnosis of hepatotoxicity was 95 days (range, 28 to 407 d). After stopping isoniazid, amino transaminase declined to normal range in a median of 46 days (range, 18 to 232 d). Sixty-three percent of the patients completed rifampin or isoniazid. There were no deaths. Age, sex, and race were not independently associated with development of isoniazid hepatotoxicity.

Conclusions: Hepatotoxicity in child < 21 years of age may be more common than previously thought, may occur in young children, and may be diagnosed by monitoring symptoms, physical examination, and serum transaminase levels. Hepatotoxicity is reversible with discontinuation of isoniazid.

Key words: Liver, rifampin, muscular dystrophy, transaminase

INTRODUCTION

A 9-month course of isoniazid is the standard regimen to treat children and adolescents with latent tuberculosis infection (LTBI).[1] Isoniazid hepatotoxicity is a major concern with isoniazid prophylaxis, and children who develop drug-induced liver injury may require liver transplant.[2] The current ATS/CDC guidelines define isoniazid hepatotoxicity as a symptomatic patient with an increase in liver enzymes, a serum concentration of alanine aminotransferase (ALT) greater than 3 times the upper limit of normal (ULN), and symptoms of hepatitis and/or jaundice; or an asymptomatic patient with ALT greater than 5 times ULN.[3] Studies have been conducted over decades to assess the occurrence of isoniazid hepatotoxicity in patients receiving isoniazid treatment.

Although different definitions of isoniazid hepatotoxicity are used in these studies, it is consistently shown that the occurrence of isoniazid hepatotoxicity is low in children. In 1978, a national sample of 2,473 patients < 20 years of age found 1 possible case of isoniazid-related hepatitis per 1,000 persons using a definition of isoniazid-related hepatitis as aspartate transaminase (AST) $\geq$ 250 Karmen units.[4] In 1999, in a Seattle–King County sample of 11,141 patients, Nolan and colleagues used a more stringent definition of isoniazid hepatotoxicity based on aspartate aminotransferase (AST) > 5 times the ULN with symptoms of hepatitis, and found no case of hepatotoxicity in 1,468 children under 14 years of age.[5] Similarly, in 2003 a San Diego county sample, LoBue and his colleague used the current ATS definition and found no case of isoniazid associated liver injury among 1,277 children under 14 years of age and 6 cases among 1,939 young adults between 15 to 34 years of age (0.3%).[6] Although the frequency of isoniazid hepatotoxicity is low in children, there are two reports on liver transplantation

and mortality outcomes. In a study of 20 children under 17 years of age, data collected between 1987 and 1997 on isoniazid-induced hepatic failure revealed a median age of 9 years, 4 children recovered, 10 underwent liver transplant and 6 died before receiving liver transplant.[2] The Centers for Disease Control and Prevention reported two children (11 and 14 years of age) of severe adverse events (SAEs) from 2004 to 2008.[7] One of the two children underwent liver transplant.

Characteristics of children with isoniazid hepatotoxicity remain unclear. Putative risk factors of TB drug-induced liver injury are associated with concurrent hepatotoxic medications, chronic alcohol consumption, viral or preexisting liver disease, previously abnormal serum transaminase or bilirubin, or within 3 months postpartum.[3] More descriptive data on risk factors related to pediatric isoniazid hepatotoxicity are needed. A retrospective, descriptive study from 2005 to 2011 examined the prevalence of isoniazid hepatotoxicity based on serum transaminase and reported symptoms, and the relationship to demographic and clinical characteristics of children receiving isoniazid treatment.

MATERIALS AND METHODS

To determine the prevalence rate of isoniazid hepatotoxicity, a medical record review was conducted on a sample of patients aged < 21 years, who had a diagnosis of LTBI and who were referred for and initiated isoniazid therapy from January 2005 to August 2011 in one of two sites: the public health department, and a latent tuberculosis infection clinic of a county hospital. Patients who were re-starters of treatment were excluded because their history of reaction to isoniazid was previously undetermined. The study was approved by the Committee on Human Research at University of California,

San Francisco (IRB# 11-08230, See Appendix 6) and the Institutional Review Board at Santa Clara County Valley Medical Center (IRB #11-059, See Appendix 7).

Patients who were under 2 years of age received LTBI treatment from their primary care physician and received monthly follow-up home visits by public health nurses from the Public Health Department to monitor treatment completion and side effects of therapy. Patients aged 2 to 21 years were evaluated and followed at the LTBI clinic under the Pediatric Department of a county hospital. Patients who were seen at the LTBI clinic run by a nurse practitioner had a complete history taken, including putative risk factors for isoniazid-induced liver injury including preexisting liver disease, human immunodeficiency virus (HIV) infection, concurrent injection-drug use, concurrent alcohol consumption, pregnancy or ≤ 3 months after delivery, and concurrent use of non-acetaminophen-containing medications with hepatotoxic potential. Patients with any of the abovementioned risk factors of isoniazid-induced hepatitis received a baseline serum transaminase test prior to beginning therapy. A chemistry-monitoring protocol was used to detect and treat patients with elevated liver function, in particular isoniazid-induced hepatitis. The nurse practitioner ordered liver function tests based on clinical findings from a physical examination for the signs and symptoms of adverse events reported by patients.

According to the clinic protocol, isoniazid hepatitis is defined as a patient developing elevated serum transaminases > 2 times the ULN. In such cases isoniazid was discontinued. Patients were tested weekly until liver enzymes decreased or were stable. When liver enzymes exceeded 5 times the ULN or jaundice was present, the patient had a repeat liver function panel, acute hepatitis panel, prothrombin time, and partial

thromboplastin time and then a pediatric gastroenterologist was consulted. After elevated

serum transaminases subsided, rifampin 6-month therapy was offered to patients.

Postpartum women did not receive isoniazid therapy until 2 to 3 months after delivery.

There have been no protocol or practice changes since 2005 at this LTBI clinic.

Serum transaminase testing at the LTBI clinic was conducted using a modular

analyzer (Roche/Hitachi Modular P800, Roche Diagnostic, Indianapolis, Indiana). There

were different normal range cut-offs by sex: female ALT (GPT) (0-31) U/L and AST

(GOT) (0-31) U/L; and male ALT (GPT) (0-40) U/L and AST (GOT) (0-37) U/L.

Bilirubin levels were set at 0.2–1.0 mg/dL for both males and females.

A standard checklist of symptom review was used by both the public health

nurses and the nurse practitioner to evaluate self-report symptoms occurring from the

start to the end of treatment, during monthly visits. To track symptoms related to

hepatotoxicity, a flow chart was kept of monthly monitoring for isoniazid adverse

reactions, and diagnoses related to hepatotoxicity were collected from the medical

records to reflect any symptoms, signs, or diagnoses during and 1 month after the therapy

course.

Definitions

In this study the pediatric population was distinguished by age as "child" less than

15 years old, and "young adult" as 15 to 21 years old.[8] The definition of isoniazid

hepatotoxicity used in this study is ALT greater than 3 times ULN with presence of

symptoms suggestive of hepatitis (nausea, vomiting, abdominal pain, jaundice, or

unexplained fatigue) and/or jaundice, or 5 times ULN without symptoms in line with the

current ATS guidelines. However, if patients developed nonspecific symptoms related to isoniazid treatment, the nurse practitioner ordered a liver function test. If the test results were greater than 2 times ULN, they were considered a hepatitis case and treatment was discontinued based on the clinic protocol. Therefore, these cases with nonspecific symptoms were included. Hepatotoxicity is defined as amino transaminase > 3 times ULN (male ALT (GPT) > 120 U/L and female ALT (GPT) > 93 U/L) with hepatitis symptoms or ALT > 5 times with or without hepatitis symptoms (male ALT (GPT) > 200 UL and female ALT (GPT) >155 U/L).

The rate of isoniazid hepatotoxicity for children beginning therapy in this sample was calculated by dividing the total number of patients with isoniazid hepatotoxicity (n = 19) by the number of patients who initiated treatment (n = 1626). The rate of isoniazid hepatotoxicity for children who completed a 9-month treatment (n=1258) was calculated by dividing the total number of patients with isoniazid hepatotoxicity by the number of patients completing the 9-month treatment (n = 1,258). The specific rates by age, sex, and ethnicity categories were calculated by dividing the number of children with isoniazid hepatotoxicity by the number of children in those categories. The age-, sex-, and race-specific rates of hepatotoxicity per 100 patients were used as appropriate for the size of this sample.

To describe demographic and clinical characteristics of patients with isoniazid hepatotoxicity, retrieved variables from medical records included age, sex, race, diagnosis related to isoniazid hepatotoxicity, height, weight, measurement date, isoniazid dose, date of treatment start, completion of treatment, adverse events associated with

treatment, concurrent medication, total dose taken, and laboratory serum transaminase test results during the treatment and entered these variables in a standardized database.

Statistical Analysis

Tabulations and correlations among the variables were conducted and were reported as mean ± SD (range, minimum to maximum) and median using SPSS statistical software (version 20.0, IBM Corp., Armonk, NY). To correct the problem of predicting a small number of hepatotoxicity cases (n=19), two measures were taken. First, the predicting variables were regrouped into dichotomous groups for age: child (1 y to < 15 y) and adolescent and young adult (≥ 15 y to < 21 y) and for race (Hispanic versus non-Hispanic). Second, exact logistic regression was used to examine potential predictors (age, sex, and race) in relation to development of isoniazid hepatotoxicity to produce more accurate estimates than possible with multivariable logistic regression.[9] Exact logistic regression was conducted by using Stata/SE Release 12.1 (StataCorp., College Station, TX). Statistical significance was set at $p \leq .05$.

Quality Assurance

Validity and reliability of data collection was established by a 10% random sample of medical records that were abstracted by a researcher and double-entered to compare for accuracy. Frequency distributions and variance measures were examined to discover aberrant values. Intra-rater reliability of data entry was assessed in a double-entered random sample of 10% of all records. The error rate was 8.9% for 47 initial records at the Public Health Department. For 1,633 initial records at the LTBI clinic, a random sample of 10% of the first 100 records revealed an error rate of 5% and then in a

random sample of 1.7% remaining records, the error rate was only 2.7%. The chemistry

monitoring practice was unknown for 1.5% patients (n=24) treated by private primary

care physicians or a county tuberculosis clinic.

RESULTS

Prevalence of Isoniazid Hepatotoxicity

There were 1,626 children between 0-21 years of age who initiated therapy and

13% of then transferred care or became lost to follow-up by the end of treatment. There

was no mechanism to ascertain whether these children develop isoniazid hepatotoxicity.

As seen in Table 1, 81% were under 15 years of age and most (79%) were Hispanic, and

half were female. There were 3.2% (n = 52) who developed isoniazid-related hepatitis,

with elevated amino transaminase or aspartate aminotransferase > 2 times ULN detected

during the course of treatment. After excluding one male who had Becker muscular

dystrophy and one child with an uncertain number of ingested doses, a total of 19 cases

of isoniazid hepatotoxicity were identified. The boy with Becker muscular dystrophy

confirmed with genetic testing was 6 years old and his serum transaminase failed to

return to normal. There was no child < 2 years of age treated by the Public Health

Department for whom hepatotoxicity was reported.

The rate of isoniazid hepatotoxicity for children *initiating* isoniazid therapy was

1.2% (19 of 1,626 cases) and the rate for children *completing* isoniazid therapy was 1.5%

(19 of 1,258 cases). The rate was higher for age between 15 to 21 years of age (6 of 307

or 2.0%) than for the children under 14 years of age (13 of 1,319 or 1.0%) (Table 2).

Exact logistic regression results indicate that age, sex, and race were not independently associated with development of isoniazid hepatotoxicity.

Demographic and Clinical Characteristics

In the 19 patients with hepatotoxicity, 11 (58%) were female and 15 (79%) were Hispanic and their mean age was 10.0 ± (5.8) years (Table 3). One used concomitant hepatotoxic medication; one was diagnosed with nonalcoholic steatohepatitis. Based on the U.S. guidelines[10] for child and adolescent body mass index (BMI), six cases (32%) were either overweight or obese. All of the 19 hepatotoxicity cases had an appropriate dose of isoniazid, with an average dose 9 mg/kg/d (range 3.0–13.8) and within the recommended range of 10–15 mg/kg/d.[11] Eleven of the 19 children (58%) had alanine aminotransferase > 5 times ULN including 6 patients had alanine aminotransferase exceeding 10 times ULN (Table 4).

Sixteen (84%) of the 19 children developed hepatitis symptoms during the course of treatment. There were 3 asymptomatic patients who were also tested for serum transaminase at the clinician's discretion based on physical exams. In these 19 patients, median peak alanine aminotransferase level was 170 U/L (range, 95–2925) and median peak aspartate aminotransferase level was 122 U/L (range 26–4139). The median time from start date of isoniazid therapy to onset of hepatotoxicity, diagnosed by elevated serum transaminase, was 95 days (range, 28 to 407 d). There were 6 patients (21%) in whom hepatotoxicity was detected after 6 months from start of treatment. Improvement of serum transaminases occurred within a mean of 67.9 days (median 46 days) after discontinuation of isoniazid. After discontinuation of isoniazid, alanine aminotransferase

decreased to normal range in all 19 children. There was no significant relationship between time to transaminase improvement and age (Pearson correlation $r = -0.05$, $p = 0.9$) or total dose taken ($r = -0.1$, $p = 0.7$). The most common symptoms reported among the symptomatic patients included abdominal pain or loss of appetite (Table 3) and 63% completed therapy with either rifampin (n=9) or isoniazid (n=3) and 37% did not initiate rifampin therapy or have unknown treatment outcome. There were no deaths reported in this sample.

DISCUSSION

Prevalence of Isoniazid Hepatotoxicity

The results indicate that isoniazid hepatotoxicity in children may be more common than previously thought; 19 patients with isoniazid hepatotoxicity was found. The rate of isoniazid hepatotoxicity for persons starting isoniazid was 1.2% (19 of 1,626 patients) and was 1.5% for persons completing isoniazid (19 of 1,258 patients). Specifically, the rate in children (1.0%) was half of the rate for our young adult age group (2.0%). The findings were compared with two previous studies with similar sample sizes of pediatric patients with different criteria for isoniazid hepatotoxicity. In the first study conducted in a similar Hispanic population in San Diego,[6] the case rate of isoniazid hepatotoxicity was reported as 0% of 1,277 children (0–14 years of age) and 0.3% of 1,939 adults (15–34 years of age). A possible explanation for our higher rates could be that we included in the hepatotoxicity cases children who developed nonspecific symptoms during treatment. Children who developed nonspecific symptoms or were unable to identify and verbalize symptoms, were tested and had serum transaminase > 3

85

times ULN. According to our clinic protocol, children with serum transaminase > 2 times ULN were considered as having isoniazid hepatitis, and therefore we included them as cases of isoniazid hepatotoxicity. Using the San Diego study criteria (alanine aminotransferase > 3 times ULN with presence of symptoms of hepatitis and/or jaundice; or alanine aminotransferase >5 times with no symptoms),[6] 5 of the cases with nonspecific symptoms (2 headache, 1 chest pain, 1 physical examination finding) would have been excluded leaving a total of 14 cases, decreasing the rate of isoniazid hepatotoxicity to 0.8% for 11 children (0–14 years of age) and 1.0% for 3 children (15–21 years of age). Nevertheless, these rates are still higher than reported in the San Diego study.

The second study conducted in the pacific northwest (King County, Washington State) used a more stringent isoniazid hepatotoxicity criteria (aspartate aminotransferase > 5 times ULN with the presence of hepatitis symptoms).[5] Nolan and colleagues reported no cases for children 0–14 years; n=1,468) and reported 0.08% (6 of 7,449 cases) for children 15–34 years old. The rate was 0.53% (7 of 1,319) for children of aged <15 years and 0.33% (1 of 307) for children aged between 15-21 years. Using the King County criteria, the rate of this study in children was higher by 5 more cases with symptoms.

In two previously published pediatric studies, a single cut-off level of serum transaminase was used rather than three-fold above normal range, which makes comparison across studies difficult. This is because the normal range of serum transaminases may differ among laboratories and a standard cut-off does not pertain to all laboratories. Two studies used alanine aminotransferase and aspartate aminotransferase > 100 IU/L for defining isoniazid hepatotoxicity. One study of 239 children (9–14 years of age) showed only 2 (0.8%) children had increased liver enzymes beyond this cut-off.[12]

The second study used similar criteria and found 0.18% of 564 children with isoniazid hepatotoxicity.[13] Although various definitions of isoniazid hepatotoxicity can affect reporting rates of isoniazid hepatotoxicity, more isoniazid hepatotoxicity cases in both the children was found in this sample.

In addition to the definitions used, there are other possible contributing factors in the higher rates of isoniazid hepatotoxicity in this study. For example, there was intensive follow-up of children at the LTBI clinic. A physical exam was done at each clinic visit and tests were ordered as needed. Children received follow-up phone calls to monitor adverse events and were brought back to clinic if closer follow-up was needed for elevated liver enzymes. Second, the clinic protocol used a conservative criterion of two times higher cut-off of serum transaminase. Once patients with isoniazid-related hepatitis (serum transaminases > two times ULN) were identified, a biochemistry testing schedule was instituted. Patients continued to receive follow-up transaminase tests to track serum transaminase levels, thus allowing us to identify children with 3 or more times ULN. A third possibility for the higher hepatotoxicity rates were the higher rate of treatment completion rate (77%) based on completion definition of 9 months (270 pills) in this study. Completion rate in the San Diego sample was 74% based on a definition of completion of at least 6 months of isoniazid, and the completion rate was 64% overall in the Seattle sample. When patients are adherent to their entire course of treatment and appointment schedules, it is more likely for clinicians to identify and prevent hepatotoxic reactions.

Clinical Characteristics and Putative Risk Factors

This study shows that all elevated alanine aminotransferase in children on isoniazid therapy were reversible within a median of 46 days (Table 4), except one patient with Becker muscular dystrophy in whom serum transaminase failed to return to normal despite medication discontinuation. High serum transaminase is common in boys with this condition, as previously described.[14, 15] This study was consistent with others studies in that the time from onset of isoniazid therapy to the development of hepatotoxicity was about 4 months (median 122 days).[2, 16] Most cases occurred within the first few months of treatment.[4] Most importantly, this study shows that late drug-induced liver injury may occur in pediatric populations (Table 3b). It is noted that 32% (6) of the 19 children were either overweight or obese. In a 2009 California Pediatric Nutrition Surveillance report, 13.8 % of 32,398 children aged less than 5 years were obese. For 16,514 children aged 5−20 years, 17.9% were overweight and 22.9% were obese in Santa Clara County.[18] The obesity rate of this sample can reflect the obesity epidemic in pediatric populations from which the sample was drawn. Obesity may not be a specific risk factor of hepatotoxicity. Nevertheless, nonalcoholic fatty liver disease can be seen with drug-induced liver injury.[3] Future study is needed to explore the relationship between obesity and nonalcoholic fatty liver disease related to drug-induced liver injury.

Threshold of serum transaminases need to be established in children. In Wu's study, 20% of children recovered spontaneously and 50% underwent liver transplant with fairly high serum transaminase levels.[2] Forty-five percent of their 20 children had as least one risk factors (viral hepatitis, multidrug therapy, and/or acetaminophen).[2] The mean serum alanine aminotransferase on admission was 1030 U/L (range 306–4822) and

aspartate aminotransferase level on admission was 1399 U/L (324–5952). Compared with their results, our mean peak alanine aminotransferase 552 U/L (95-2925) and aspartate aminotransferase 531U/L (26-4139) were 2 to 3 times lower, nevertheless, all of our patients recovered and there were no deaths. Even for our 6 patients (32%) had serum transaminase exceeding 10 times ULN, serum transaminases of these patients decreased to normal range (Table 4). Most of our children had no the abovementioned risk factors. In the condition of drug-induced hepatitis, serum transaminase reaches a certain threshold level, whether liver injury can be irreversible in children is unknown. Further study is needed to determine the threshold of serum transaminases for isoniazid for patients to guide the practice of monitoring isoniazid administration in pediatric populations.

The children in this study with isoniazid hepatotoxicity had none of the putative risk factors listed in CDC/ATS guidelines, except that one took concurrent acetaminophen, and one was diagnosed with nonalcoholic steatohepatitis.[17] However, his alanine aminotransferase levels were stabilized after medication was discontinued (ALT/AST 33/38) and he tested negative for viral hepatitis. It is noted that 32% (6) of the 19 children were either overweight or obese. Nonalcoholic fatty liver disease can be seen with drug-induced liver injury.[3] More study is needed to explore the relationship between obesity and nonalcoholic fatty liver disease related to drug-induced liver injury.

As for demographic characteristics, the findings suggest that age, sex, and race were independently not associated with development of isoniazid hepatotoxicity (Table 2). Studies have suggested risk factors of isoniazid hepatotoxicity including increasing age.[5, 6, 19] The findings of this study confirm that isoniazid hepatotoxicity occurs in young children aged <15 years and is even higher in children aged >15 years. The median age of

children in this sample is consistent with the mean age of 9 years previously reported.[2] In particular, evidence of this sample shows 11 patients (58%) under 10 years of age. Female sex seems to be another risk factor of isoniazid hepatotoxicity in early studies,[5, 16, 20] particularly for women of child-bearing age during and after pregnancy. Gender

(p=0.6) appears not to be risk factor in our young 19 patients; 11 (58%) were females. In our clinic protocol, once pregnancy is noted, isoniazid treatment is discontinued and re-evaluated at 2 to 3 months postpartum. A future study with a larger sample of pediatric patients is warranted to investigate if girls before or after puberty are at greater risk for isoniazid hepatotoxicity.

Several limitations are identified in this study. The first is lack of baseline tests and regular testing protocol. Therefore, whether some patients would have had abnormal baseline tests was unable to be ascertained. The second limitation is that if symptoms were directly caused by isoniazid was unable to be determined. Symptoms may concurrently exist for other minor illnesses. The third limitation is that 13% of all patients in this study who initiated treatment were lost to follow-up at the clinic or transferred care, and they may have had elevated serum transaminase that was not ascertained. The fourth consideration is that our sample consisted primarily of Hispanic children, which limited the ability to compare rates of isoniazid hepatotoxicity across different ethnic groups.

Communication with patients and family members is critical. Patients need to be advised to stop medications if experiencing certain symptoms and seek medical attention immediately. Studies of severe adverse events show that patients continued to take

isoniazid after onset of symptoms and patients who developed symptoms of hepatitis

waited until the onset of jaundice before seeking medical attention [7, 21] or were advised by

clinician not to stop medicine.[2] Our clinic advised patients to discontinue isoniazid on

their own if they experienced any symptoms, responded to patients' complaints of

symptoms, and brought patients immediately for clinical evaluation if experiencing

symptoms.

Communication among medical providers is also important. When our patients

develop elevated serum transaminase, their primary care physicians are notified

according to clinic protocol. Communication among prescriber, providers, and patients is

critical to detect severe adverse events early on, during the long course of treatment.[7]

Implications for Preventing Pediatric TB Cases

Isoniazid has been used to protect children with LTBI from progressing to active

TB.[11] Studies show that there are missed opportunities to treat children under 5 years old

and prevent pediatric TB cases. California's pediatric TB case rates were highest among

children 0 to 4 years of age, and minority children 0 to 14 years of age had case rates 6-

to 34-fold higher than did White children.[22] Hispanics account for the highest percentage

of TB cases among both foreign-born (46%) and US-born (39%) children and

adolescents.[23] This study was conducted in Santa Clara County where TB has been a

public health issue. In 2011, our case rate of TB was 10 cases per 100,000, two times

higher than the case rate of 5.8 per 100,000 in California.[24, 25] In communities with many

minority children, diagnosing and treating LTBI to prevent TB in children is paramount.

This study shows the importance of closely monitoring pediatric patients to prevent

irreversible liver failure. Symptom review, physical exam, and biochemistry testing remains necessary for pediatric populations. Clinicians need to have high awareness of symptoms of isoniazid hepatotoxicity.

CONCLUSION

This study shows that hepatotoxicity in child < 21 years of age may be more common than previously thought, occurs at a higher rate in older children (age 15-21 years) compared to younger children, and may be diagnosed by monitoring symptoms, physical examination, and serum transaminase levels. Hepatotoxicity is reversible with discontinuation of isoniazid. Further study needs to identify risk factors in children, especially adolescent females.

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Table 1. Incidence of Elevated Transaminases Levels and Ages* of LTBI-treated Female and Male Children

ALT/AST Levels§	No. (%)	Age, Females (n = 827)	No. (%)	Age, Males (n = 799)	No. (%)	Age, Total (n = 1626)
>2 x ULN	28 (3.4%)	10.6 ± 6.3 (2.2 – 20.2), 9.0	24 (3.0%)	7.6 ± 4.8 (0.6 - 17.6), 6.6	52 (3.2%)	9.2 ± 5.8 (0.6 – 20.2), 8.7
>3 x ULN	11 (1.3%)	11.7 ± 6.3 (2.2 – 19.2), 14.0	9 (1.1%)	8.4 ± 4.9 (3.9 – 16.7), 6.2	**20 (1.2%)	10.2 ± 5.8 (2.2 – 19.2), 8.7
>5 x ULN	6 (0.7)	9.5 ± 6.0 (2.2 – 17.2), 8.7	4 (0.5%)	6.6 ± 3.6 (3.9 – 11.8), 5.4	10 (0.6%)	8.4 ± 5.2 (2.2 – 17.2), 7.3

*Age at starting treatment

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

**Excluded 1 child with Becker muscular dystrophy and 1 child with uncertain ingested doses of isoniazid before elevated serum transaminase

Selection Criteria: any elevated serum transaminase during course of treatment >3 x ULN (Males with ALT>120 U/L or AST>111 U/L; Females with ALT>93 U/L or AST>93 U/L) or elevation >5 x ULN (Males with ALT>200 U/L or AST>185 U/L; Females with ALT>155 U/L or AST>155 U/L). ALT/AST levels (>3 times and >5 times ULN) were not independent; patients with >3 times ULN included patients who were also > 5 times ULN.

Table 2. Hepatotoxicity Rates by Sex, Age, and Race (N= 19 Cases)

Demographic characteristics	#	(%)	Cases of Hepatotoxicity #.	(%)	Rate of Hepatotoxicity (Cases per 100 persons)	P Value	Odd Ratio (95% CI)
Total	1626		19	(100)	1.2		
Age						0.2	
<5	497	(30)	6	(31.6)	1.2		Reference
5-9	404	(25)	5	(26.3)	1.2		
10-14	418	(26)	2	(10.5)	0.5		
15-21	307	(19)	6	(31.6)	2.0		2.0 (0.6– 5.7)
Sex						0.6	
Female	827	(51)	11	(57.9)	1.3		1.3 (0.5 – 3.8)
Male	799	(49)	8	(42.1)	1.0		Reference
Race †						1.0	
White	30	(2)	1	(5.3)	3.3		
Black	36	(2)	0		0		
Asian and Pacific Islanders	197	(12)	2	(10.5)	1.0		1.0 (0.2 – 3.3)
Others	73	(5)	1	(5.3)	1.4		
Hispanic	1277	(79)	15	(78.9)	1.2		Reference

Data for completion rates available for 1615 children (99%)

N = 1626 children who initiated isoniazid therapy and were included in the analysis; mean age 9 ± 5.2 years (range 0.5 – 20.8)
*Data for race available for 1613 children (99%).

P value and Odds Ratio is based on exact logistic regression.

Table 3. Clinical Features of 19 Patients with Isoniazid Hepatotoxicity

Age	Sex	Race	Concurrent medications	Body Mass Index	Isoniazid dose (mg/kg/d)	Last pill count	Treatment completion
2.3	F	4	Vitamin	16.7	150/13.0=11.5	81	Started rifampin. Transferred care.
3.9	M	4	Fluoride	15.9	200/15.5=12.9	143	Not wish to receive rifampin
4.1	F	6	0	16.4	200/17.7=11.3	*150	Complete rifampin
4.1	F	4	0	17.4 (OW)	200/18.5=10.8	20	Incomplete rifampin. Moved
4.2	M	4	0	15.5	200/17.0=11.8	16	Complete rifampin
5.0	M	4	0	Not Available	300/23.6=12.7	20	Did not start rifampin. Referred to GI clinic.
6.2	M	4	0	16.9	300/22.1=13.6	29	Complete rifampin
6.2	M	4	Acetaminophen	Not Available	300/21.7=13.8	180	Complete rifampin
7.1	M	4	0	17.0	300/22.4=13.4	149	Complete rifampin
8.5	F	4	Ibuprofen	18.3	300/34.7=8.6	240	Completed 8-month isoniazid
9.0	F	4	Vitamin	26.4 (OB)	300/47.8=6.3	103	Complete rifampin
11.9	M	3	0	24.7 (OB)	300/67.7=4.4	49	Did not start rifampin. Referred to further treatment.
14.1	F	4	Benadryl	29.6 (OB)	300/74.1=4.0	230	Complete 8 months isoniazid
15.2	M	4	Keflex	32.7 (OB)	300/101.1=3.0	205	Complete 7 months isoniazid
16.0	F	3	Ferrous	22.4	300/55.6=5.4	35	Complete rifampin
16.8	F	4	0	28.5 (OW)	300/67.7=4.4	106	Started rifampin and refused to continue
17.4	F	1	0	22.8	300/61.1=4.9	43	Complete rifampin
18.0	F	4	0	20.7	300/51.8=5.8	144	Complete rifampin
19.7	F	4	Oral contraceptives	23.6	300/58.5=5.1	102	Incomplete rifampin due to pregnancy

Age: date of birth subtracted from medication start date; Sex: F=female; M=male; Race: White (1), Black (2), Asian and Pacific Islander (3), Hispanic (4), Arab (6); Body Mass Index (BMI) values calculated by CDC BMI calculator for Child and Teen. Http://http://apps.nccd.cdc.gov/dnpabmi/Calculator.aspx?CalculatorType=Metric

OW= Overweight; OB= Obese.

Last pill count (*): doses family obtained at pharmacy, pill counts unavailable
Symptoms: 0 = child had no reported symptoms but the clinician identified signs through physical exam and ordered LFT test

Table 4. Clinical Features of 19 Children with Isoniazid Hepatotoxicity during LTBI treatment

Clinical Feature	# Patients	%
Age	10.0 ± 5.8 (2.3 – 19.7), 8.5	
Concurrent medication	9	(47)
Body mass index*	21.5 ± 5.4 (15.5 – 32.7), 20.7	
Viral hepatitis ‡		
Negative	11	(58)
Never tested	6	(32)
HBsAg negative only	2	(10)
HIV		
Negative	5	(26)
Never tested	14	(74)
Baseline serum aminotransferase		
Within normal limits	2	(11)
Never tested	17	(89)
Isoniazid dosage (mg/d)		
300	14	(74)
200	4	(21)
150	1	(5)
Average dose (mg/kg/d)	8.6 ± 3.9 (3.0 – 13.8), 8.6	
Times of serum aminotransferase ULN		
3 - <5	8	(42)
≥5 - <10	5	(26)
≥10	6	(32)
Peak ALT (U/L) §	552.1 ± 732.4 (95 – 2925), 170	
Peak AST (U/L) §	531.6 ± 1031.3 (26 – 4139), 122	
Time from treatment start to hepatotoxicity (d) ‡‡	134.5 ± 94.9 (28 – 407), 94.9	
Time to diagnosis of hepatotoxicity (m)		
< 3	6	(32)
3– 6	9	(47)
> 6	4	(21)
Time for ALT decline from onset hepatotoxicity (d) §§	67.9 ± 53.8 (18 – 232), 46.0	
Completion of therapy		
Rifampin 6-month	9	(47)
Rifampin not complete	3	(16)
Isoniazid 6-9 month	3	(16)
Rifampin not start, referred elsewhere	2	(11)
Rifampin not complete, transferred care	1	(5)
Rifampin decline	1	(5)

Data reported as number of patients, or mean ± SD with (range), median
*6 (32%) of children were overweight or obese.
‡Viral hepatitis: anti-HAV (IgM), anti-HBsAg, anti-HBc (IgM), anti-HCV (IgM)
§ ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.
‡‡ Time from start date of isoniazid therapy to diagnosis hepatotoxicity detected by elevated ALT (ALT > 3 times ULN)
§§ Time for ALT decline from peak levels to normal levels after isoniazid discontinued

CHAPTER V

IMPLICATIONS AND CONCLUSION

The overall aims for this dissertation project were to examine adherence issues to latent tuberculosis infection (LTBI) treatment. The goals were to examine knowledge, attitudes, and health responses in relation to TB and its stigma and to identify factors associated with noncompletion of isoniazid therapy and adverse reactions, such as hepatotoxicity, associated with therapy in children. In Chapter I, Piaget's child development theory was reviewed. Factors affecting pediatric medication adherence were discussed and incorporated in the conceptual framework for the research. Chapters II, III, and IV contained the three publishable papers emerging from the dissertation research process, and this chapter synthesizes that work within the context of the review of literature and theory and makes recommendations for practice and research.

The following three paragraphs briefly review the findings from this project in answering the research questions delineated in Chapter I.

Knowledge, Attitudes, and Health Responses related to Tuberculosis and Its Stigma

Stigma related to tuberculosis (TB) has been associated with lack of compliance to treatment. Individuals' perceptions of stigma differ by societal context. Limited data are available on cultural variation of TB stigma worldwide, particularly in countries with a high burden of TB. The review of 83 studies presented in Chapter II suggests that TB has different meanings to different cultural groups based on social context. Cultural variations exist across 35 countries with respect to knowledge of TB related to causes and

transmission routes, as well as attitudes and health responses. Tuberculosis stigma results from misperceptions of the causes of TB, association with human immunodeficiency virus (HIV) infection, and negative attitudes. Decisions on disclosing illness and choices between traditional healers and public/private providers were influenced by this stigma. Gender influenced perceptions and management of TB. Public health responses, such as isolation of exclusionary practices and stigmatization by medical professionals, contributed to TB stigma.

Completion Rates of Isoniazid Therapy and Factors Associated with Treatment Noncompletion

According to the American Thoracic Society/Centers for Disease Control and Prevention guidelines endorsed by the American Academy of Pediatrics, a 9-month course of isoniazid is the standard regimen to treat LTBI in children and adolescents to prevent progression of active TB disease (American Thoracic Society, 2000). Studies have been conducted to examine factors affecting completion rates for children undergoing 9-month isoniazid therapy. Older age, (Horsburgh et al., 2010; M. Hovell et al., 2003; LoBue & Moser, 2003; Minodier et al., 2010; Young, Edick, Klee, & O'Connor, 2012), non-Hispanic ethnicity (Cass, Talavera, Gresham, Moser, & Joy, 2005; LoBue & Moser, 2003), experience with either isoniazid hepatitis or adverse reactions and symptoms during the treatment (Berg et al., 2004; Kwara, Herold, Machan, & Carter, 2008; LoBue & Moser, 2003; Machado et al., 2009; Shukla, Warren, Woeltje, Gruber, & Fraser, 2002), and having low risk of TB (Goswami et al., 2012; Li, Munsiff, Tarantino, & Dorsinville, 2010; Shieh et al., 2006) have been associated with noncompletion of LTBI treatment. The goals of the study presented in Chapter III were to determine the

completion rate of 9-month isoniazid therapy in children and examine these factors previously identified in studies of adult populations in relation to treatment noncompletion for children under 21 years of age. The findings confirmed that successful completion of isoniazid therapy in children was influenced by age, ethnicity, symptoms of adverse reactions, and isoniazid hepatitis. Noncompletion rates of LTBI treatment were higher for age $\geq$ 15 years of age (odds ratio, 1.6; 95% confidence interval [CI], 1.2 to 2.0), non-Hispanic ethnicity (odds ratio, 1.3; 95% CI, 1.1 to 1.5), symptoms of adverse reactions (odds ratio, 2.0, 95% CI, 1.1 to 3.0), and isoniazid hepatitis (odds ratio, 5.0, 95% CI 3.3 to 8.0).

Isoniazid Hepatotoxicity, Prevalence Rate, and Demographic and Clinical Characteristics of Children with Hepatotoxicity

Isoniazid hepatotoxicity has been found to be age-related and not common in children receiving isoniazid treatment for LTBI. Although the frequency of isoniazid hepatotoxicity is low in pediatric populations, children with liver failure and who have gone through liver transplant have been reported in the past. Characteristics of children with isoniazid hepatotoxicity are unclear. The results presented in Chapter IV revealed that hepatotoxicity in children aged < 21 years may be more common than previously thought, may occur in young children, and may be diagnosed by monitoring symptoms, physical examination, and serum transaminase levels. Hepatotoxicity is reversible with discontinuation of isoniazid. The prevalence of isoniazid hepatotoxicity (symptomatic elevation of amino transaminase > 3 times the upper limit of normal [ULN] with hepatitis and/or jaundice) was 1.2% (19/1,626). The age distribution mean was 10 years (age range, 2.3 to 19.7 y). None of the patients had known putative risk factors. However, 32% of the

hepatotoxicity cases (n=6) were overweight or obese. After stopping isoniazid, amino transaminase declined to normal range in a median of 46 days (range, 18 to 232 d). Age, sex, and race were not independently associated with development of isoniazid hepatotoxicity.

State of Knowledge on Pediatric Medication Adherence

In this medical record review of 1626 children between 0 and 21 years of age at two sites in Santa Clara County, the overall completion rate was 79% for children who initiated therapy and completed a 9-month course of isoniazid therapy. The completion rate of isoniazid therapy was higher (80%) in the younger age group of 1,308 children under 15 years of age than in the older group (69%) of 307 children between 15 and 21 years of age. These completion rates are higher than those reported in other pediatric populations. Completion rates of 9-month isoniazid, defined as 270 doses taken within a 12-month period, in pediatric populations varied from 40.3% to 75% (Cruz & Starke, 2012; Li et al., 2010; Powell, Perkins, Wang, Hunt, & Ryan-Wenger, 2008). Similarly, completion rates for a 6-month regimen were slightly higher in some studies yet varied among study populations. The 6-month isoniazid completion rate for children aged <15 years was 42.6% in Boston and 74% to 86.7% in San Diego (Cass et al., 2005; LoBue & Moser, 2003; Parsyan, Saukkonen, Barry, Sharnprapai, & Horsburgh, 2007). In studies that defined treatment completion as a 6-month course of isoniazid therapy rather than 9 months, completion rates in children under 15 years of age ranged from 74% to 86.7% (Cass et al., 2005; LoBue & Moser, 2003). If a 6-month definition is used for this Santa Clara County sample, the completion rate would have been 83%, which falls within the range of rates reported in other studies.

Factors Affecting Medication Adherence of LTBI Treatment

Age

Even for the full pediatric age range, older age was a factor in treatment noncompletion. This finding is consistent with other studies (Horsburgh et al., 2010; M. Hovell et al., 2003; M. F. Hovell et al., 2003; LoBue & Moser, 2003; Minodier et al., 2010; Young et al., 2012), supporting that children are more likely than adults to complete isoniazid therapy. Studies have shown that for older children such as adolescents, age and risk behavior were negatively related to adherence to treatment for LTBI (M. F. Hovell et al., 2003). Parental involvement seems to promote adolescents' medication adherence. Adolescents who are adherent to counseling, have higher academic grades, being bicultural (M. Hovell et al., 2003), and live with both parents (Coly & Morisky, 2004) are more likely to complete treatment. Other studies on adherence to other pediatric medical regimens that demand long-term self management, such as asthma medications, provide examples similar to isoniazid therapy. Such studies consistently indicate that between ages 9 and 15, children perceive parental reminders as annoying but helpful for adherence, and feel that use of rewards can best reinforce their adherence (Penza-Clyve, Mansell, & McQuaid, 2004). Lack of parental involvement in medication routines and difficulty remembering doses has been associated with poor adherence for young people (mean age 13.5 years, range 6.9-18.9) on psychotropic medication (Dean, Wragg, Draper, & McDermott, 2011).

Ethnicity and Culture

Ethnicity was associated with completion and adherence in children who initiated isoniazid therapy. Compared to Hispanic children, non-Hispanic children were less likely

to be adherent to isoniazid therapy. The study sample included only 21% non-Hispanic children. The reasons why these children did not complete treatment need to be explored in future studies.

The finding that Hispanic children are more likely to complete treatment than non-Hispanic children is also consistent with previous reports(Cass et al., 2005; LoBue & Moser, 2003), and is in line with other studies showing that patients speaking Spanish, and being born outside the United States, were significant predictors of treatment completion (Bieberly & Ali, 2008; Cass et al., 2005; LoBue & Moser, 2003; Reichler et al., 2002). The overall completion rate (78%) of therapy may be attributed to the acceptance of LTBI therapy by parents born in South and Central America to a greater extent than by parents from Eastern Europe or Asia (Powell et al., 2008). These findings are in accordance with the conclusions reached in Chapter II about culture and stigma; TB can have different meanings and responses to treatment regimens within a cultural group based on social context. Cultural variations exist across 35 countries with respect to knowledge of TB related to causes and transmission routes, as well as attitudes and health responses.

Specifically, 8 studies (1% of 83 studies) from 6 countries with Hispanic/Latino samples including Columbia, Ecuador, Nicaragua, Peru, and the United States confirmed that TB stigma exists in the Latino culture. Studies reveal that Latinos feel stigmatized when receiving TB tests (Armijos, Weigel, Qincha, & Ulloa, 2008). Unfounded beliefs or misconceptions about TB transmission include sharing eating utensils or clothing, or exposure to blood fluid (Jaramillo, 1999; Joseph, Waldman, Rawls, Wilce, & Shrestha-Kuwahara, 2008). And fear of infection can result in stigmatizing TB patients, who

suffered health, economic, psychological, and social consequences (Armijos et al., 2008). This stigma has been reported to impact women more than men due to the low priority of health in society (Onifade et al., 2010). The small number of studies in the literature review on Hispanic/Latino populations shows a knowledge gap in stigma in Latino countries, which warrants future research to explore the meanings and impact of TB stigma in this ethnic group.

The Hispanic children in this study comprised a significant percentage of the sample (79%). As there is a growing population of Hispanic/Latino population in Santa Clara County, increasing from 21% in 1990 to 27% in 2010 (Santa Clara County Public Health Department, 2012), the sample reflects the prevalence of the population, but limits what can be generalized to Hispanic children and completion of isoniazid therapy.

Symptoms Associated with Adverse Reactions

Consistent with findings from other studies (Berg et al., 2004; Kwara et al., 2008; LoBue & Moser, 2003; Machado et al., 2009; Shukla et al., 2002), symptoms associated with adverse reactions to isoniazid in this sample of children are major obstacles to completing therapy. Some children reported symptoms such as abdominal pain or loss of appetite during the course of treatment. These symptoms can occur with many other minor illness episodes, yet a patient may associate these symptoms with their isoniazid medication and prematurely discontinue treatment.

Hepatitis, a common adverse reaction, was also confirmed as a factor associated with treatment noncompletion in our sample. Children with isoniazid hepatitis (defined as two times greater serum transaminase than normal for their sex) were required to have more blood tests and follow-up clinic visits, and therefore may be less likely to complete

treatment. It is possible that the children themselves or their parents may be reluctant, or perceive it as inconvenient, to receive more venipunctures or clinic visits (Shieh et al., 2006) or may be concerned about safety of the medication. Because of these reasons, the child or parents may have chosen to discontinue treatment on their own.
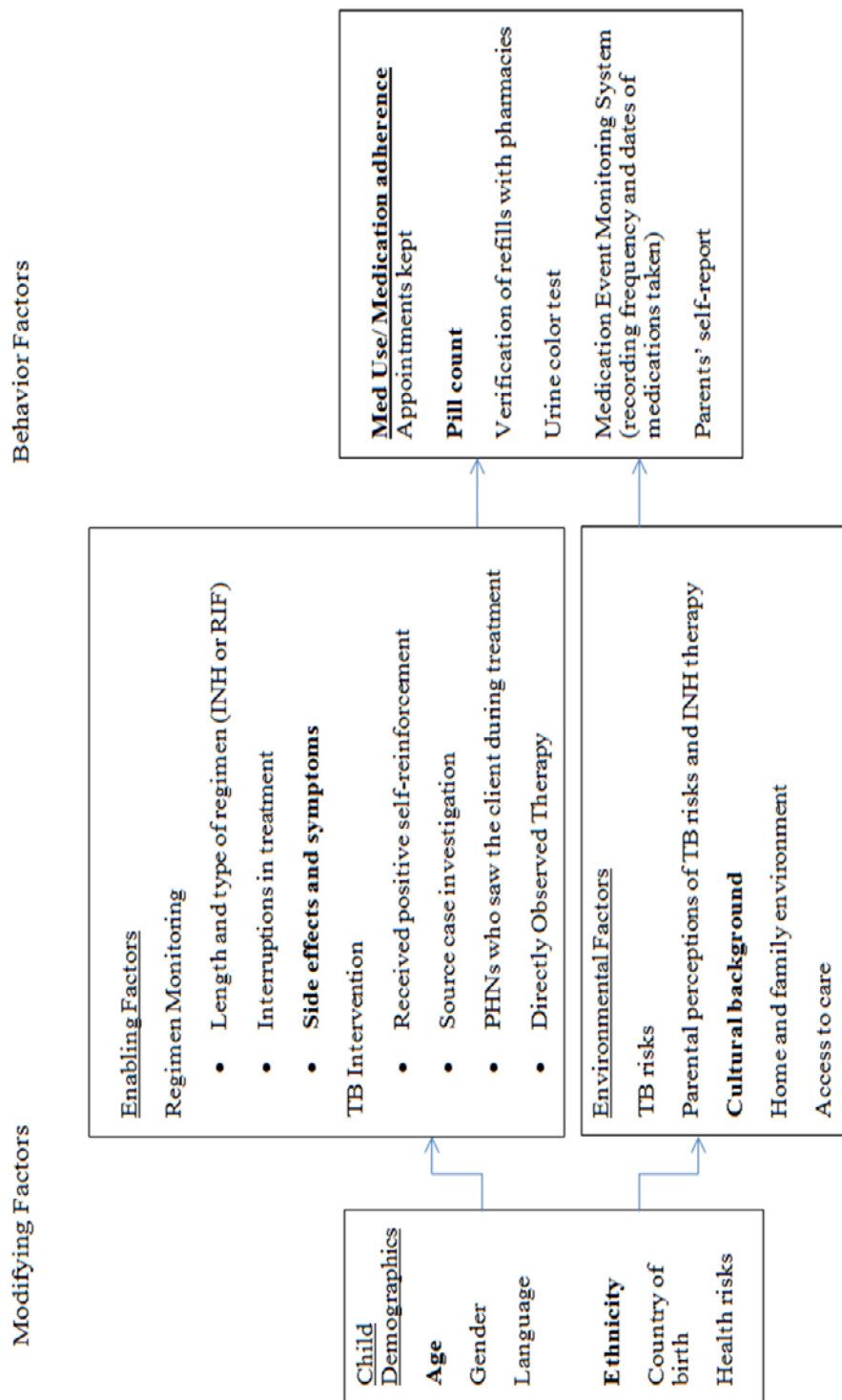
From Research to Theory

Using what is known about pediatric medication adherence, in particular for isoniazid therapy, the constructs in the Children's Health Belief Model (CHBM) were reevaluated. Although the CHBM acknowledges the psychology of health behavior, it fails to address perception of treatment experiences (e.g., the perception of side effects from INH), which contributes to nonadherence. The model does not fully capture treatment experiences, or symptoms related to adverse reactions to isoniazid. Little empirical evidence exists to support health behavior theories in promoting long-term medication adherence for TB or HIV (Munro et al., 2007). Characteristics of, and experience with, a regimen have been associated with adherence for asthmatic children (Rand, 2002; Shope, 1988). Experience of side effects can be a barrier for patients to continue with therapy, though young children have relatively lower likelihood of hepatotoxicity from isoniazid compared to adults (Pediatric Tuberculosis Collaborative Group, 2004).

The CHBM addresses environmental factors influencing a child's medication use, including perceived child's illness threat, perceived benefits of medicines, and expected child's medication use. However, the model fails to address parental supervision, which is critical for medication adherence for older children. For example, adolescents are beginning to learn to take responsibility for their own, medication, and at this stage of

development, parental supervision is important to their medication adherence. Also, the model was initially tested on school children (aged 8–14) (Bush & Iannotti, 1988), and more studies to test this model on older children's medication use are warranted.

Despite these limitations, the CHBM provides the theoretical perspective that age and socioeconomic factors have to be taken into consideration due to their impact on children's readiness for behavior change regarding medication use. Figure 1 reevaluates the key factors in the CHBM that were presented in Chapter 1, and highlights the findings from this dissertation research that support the model.

Figure 1. Revised Conceptual Framework of Predictors of Adherence to Treatment of Latent Tuberculosis Infection for Children

Modifying Factors

Behavior Factors

Child
Demographics

Age

Gender

Language

Ethnicity

Country of birth

Health risks

Enabling Factors

Regimen Monitoring

• Length and type of regimen (INH or RIF)

• Interruptions in treatment

• **Side effects and symptoms**

TB Intervention

• Received positive self-reinforcement

• Source case investigation

• PHNs who saw the client during treatment

• Directly Observed Therapy

Environmental Factors

TB risks

Parental perceptions of TB risks and INH therapy

Cultural background

Home and family environment

Access to care

Med Use/Medication adherence
Appointments kept

Pill count

Verification of refills with pharmacies

Urine color test

Medication Event Monitoring System (recording frequency and dates of medications taken)

Parents' self-report

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Implications for Clinical Practice

This dissertation research contributes to knowledge for clinical practice in three aspects. First, cultural variation needs to be considered in the development of interventions aimed at reducing stigma and improving adherence to treatment. Stigma manifests itself where there is a societal power imbalance in not only class, race, and gender, but also age, as seen in this study of younger and older children. The implications of these findings can be far-reaching for the provision of culturally sensitive TB treatment. Second, hepatotoxicity in children < 21 years of age may be more common than previously thought, occurring at a higher rate in older children. Communication with patients and family members is critical. Patients need to be advised to stop medications if experiencing certain symptoms and seek medical attention immediately. Communication among medical providers is also important. When a child develops elevated serum transaminase, the primary care provider should be notified according to clinic protocol. As seen in this medical record review, this type of clinic protocol was followed and may have minimized the occurrence of more severe adverse events like liver failure requiring transplantation. Communication among prescriber, providers, and patients is critical to detect severe adverse events early on, during the long course of treatment (Centers for Disease Control and Prevention, 2010).

Future Research Perspectives

In this dissertation, several questions were identified that need further research to expand our understanding of factors affecting medication adherence to LTBI treatment. Public health responses can be associated with stigmatization of TB in African countries.

Given the sample of children and this study design, a causal relationship between stigma and public health responses could not be addressed. Therefore, one question for further research is: Is there a causal relationship between stigma and public health responses?

Hepatitis, a common adverse reaction, was also confirmed as a factor associated with treatment noncompletion in our sample. Children with isoniazid hepatitis were required to have more blood tests and follow-up clinic visits, and therefore could be less likely to complete treatment. It is possible that patients themselves or their parents may be reluctant or perceive it to be inconvenient for children to receive more venipuncture or additional clinic visits (Shieh et al., 2006) or may be concerned about safety of the medication. A second research question for further investigation would be: What are child and parent perceptions of medication side effects and blood tests required to medically manage isoniazid-induced hepatitis?

All of the patients followed in this study recovered from isoniazid hepatotoxicity. Even for the 6 children (32%) who had serum transaminase exceeding 10 times ULN, serum transaminases decreased to within normal range when the medication was discontinued. In the condition of drug-induced hepatitis, when serum transaminase reaches a certain threshold level it is unknown whether liver injury can be irreversible in children. Therefore, a third research question would be: To guide the practice of monitoring isoniazid administration in pediatric populations, what should be the threshold or ULN for levels of serum transaminases for children receiving isoniazid?

Female sex was a risk factor of isoniazid hepatotoxicity in early studies (Franks, Binkin, Snider, Rokaw, & Becker, 1989; Millard, Wilcosky, Reade-Christopher, & Weber, 1996;

Nolan, Goldberg, & Buskin, 1999), particularly for women of child-bearing age during and after pregnancy. Gender appears not to be risk factor in our young 19 patients; 11 (58%) were females. In clinic protocols, once pregnancy is noted, isoniazid treatment should be discontinued and re-evaluated at 2 to 3 months postpartum. Future studies with a larger sample of adolescent females would be warranted to investigate this area. A final question that emerges from this dissertation research is: Are girls before or after puberty at greater risk for isoniazid hepatotoxicity?

Limitations of the Study

The retrospective nature of this research study poses threats to validity affecting inference of results and generalizability to the entire pediatric LTBI population (Shadish, 2002). The first issue is the possible threat to validity for outcome measures. Monthly pill count is utilized to calculate cumulative amounts of isoniazid taken. The drawback of this measure is that patients may remove pills from the bottle prior to their medical visit. Biomarker devices, for example urine strips (Ellis, Naar-King, Cunningham, & Secord, 2006; Salleras Sanmarti et al., 1993) or Medication Event Monitoring System (MEMS), an electronic monitoring system that records the date and time of bottle-cap openings (Berkovitch et al., 1998), generate more accurate results and could have been used in monitoring adherence, but at increased cost for families and the health care system. Design of further studies needs to improve current measures of medication adherence; multiple outcome evaluation visits should be conducted without announcement during the course of treatment, and both subjective and objective methods should be used to assess adherence.

Second, patients in this study are not representative because the majority were Medi-Cal recipients with low socioeconomic status. The majority of children were also from Hispanic families, which may differ in cultural perspectives and practices from other TB populations that include Asian and African American families. The dissertation study was also limited by a convenience sample of children with medical records from only one county. Larger samples from more geographically and ethnically diverse populations may be useful because ethnicity and socioeconomic status may be confounding variables for adherence to treatment.

Third, the retrospective study design has disadvantages such as lack of availability or poor accuracy of the medical records to demonstrate relationships between outcomes and other factors (Brown & Semradek, 1992). It is difficult to control bias and prevent confounded data, there is no randomization and no blinding, and it is difficult to establish cause and effect with this study design (D. R. Hess, 2004). To deal with the problems of a retrospective study design, in particular possible confounded data and the subsequent threat to validity, future prospective or quasi-experimental studies should be done that eliminate these threats and yield accurate outcome data.

Conclusion

To promote adherence to LTBI treatment in children, clinicians need to facilitate parental and family involvement in the treatment decision, have high awareness of symptoms of adverse reactions, and consider cultural variation in the development of interventions aimed at reducing stigma and improving adherence to treatment.

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APPENDIX 1. A summary of quantitative studies (n = 26) on Isoniazid therapy predictors and completion rates by types of design and chronological order

Selection criteria: Articles were chosen based on research questions designed to identify predictors of INH therapy completion.

Authors	Sample size and representation TB risks	Measure of adherence	Definition of dependent variable – medication adherence	Results (predictors and completion rates)
14 Retrospective Studies				
(Marks et al., 2000)	6225 contacts of 1080 patients with pulmonary, AFB smear (+) TB and age over 15 from 11 sites. 27 % of contacts were black/ non-Hispanic 24% of Hispanic.	N/A	Treatment for LTBI refers to a standard regimen of INH for 6 to 12 months for contacts of persons with drug-susceptible disease, or RIF or other drugs for contacts of persons with drug-resistant disease.	74% of 1725 contacts with TST (+) started LTBI Treatment, of whom 56% completed.
(Reichler et al., 2002)	2267 contacts of pulmonary TB cases from five health departments in the US in 1996. Five health departments in the US were selected as study sites. 630 contacts had newly documented positive TST; 31% black, 15% white, 12% Hispanic, 11% Asians; median age of these contacts was 37 years and 53% of male. 121 contacts were converters.	N/A	Completed >= 6 months LTBI treatment	Among 398 initiated treatment, 51% were documented to have completed a 6-month treatment.

(LoBu e & Moser, 2003)	3788 patents started INH between July 1999 and November 2002 from a San Diego county tuberculosis clinic. 34% age 0-14, 51% age 15 to 34. Limited number of patients 50 years and older, comprising only 3.8%. 80% White/ Hispanic. 21% US-born, 56% born in Mexico. 81% of patients were TST reactors, 10% were recent TST converters, 7% were close contacts to an active TB case.	Reported completion rates were based on prescriptio n refills.	Completed at least 6 months of INH	64% of patients completed at least 6 months of INH.
(Cass et al., 2005)	1582 participants 14 years of age or younger seen at SDCTBCP clinics, with positive TST who were started on LTBI treatment from July 1995 through December 1997.

Of 1582 patients, 1430 were Hispanic, 1323 spoke Spanish, 881 were foreign-born, 1135 were reactors, 299 were converters, and 576 received source case investigation. | Adherence to and completion of an appropriate LTBI therapy was measured by attendance at a minimum of 6 of 9 recommend ed clinic visits. | Adherence defined by at least 6 clinic appointments being kept | 1371 (86.7%) completed treatment. |
| (Brass ard, Steens ma, Cadieu x, & | School-based TB screening program, including associates investigation (also including family or household children | Adherence was also measured by nurse's pill count, patients' | Adherence was defined as taking over 80% of the total doses. | Of 342 children started on therapy, 316 (92%) demonstrated adequate |

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Lands, 2006)	with LTBI on therapy). There were 599 associates investigated from the 484 TST (+) school children seen at TB clinic. 82% started on LTBI therapy. 484 school children high percentage of eastern/southern Asians.	self-report, verification with pharmacies, and general attendance at medical appointments.		adherence.
(van Zyl et al., 2006)	335 children less than 5 years of age, identified as household contacts of TB cases. Mean age, 25 months (range, 2 days to 5 years).	N/A	Completion of treatment was defined as completing over 80% of treatment without interruption of more than 2 months.	Adherence to chemoprophylax is was 44.2% overall.
(Ailinger, Moore, Nguyen, & Lasus, 2006)	153 Latino clients seen at public health clinic for LTBI in 2004 to 2005. Samples were women (63%), with mean age of 26.1 years; 60% from Central America, 37% from South America; 3% from Mexico and Cuba. The majority came from El Salvador, Bolivia, or Guatemala. The mean time in the US was 4.58 years. 90% of clients were reactors, 6.5% were contacts of active TB cases, and 3.3% were converters.	The researchers noted the number of months that the client was adherent; that is, that he or she came to a clinic appointment and reported taking the INH. Clients were considered non-adherent if they did	Adherence was defined as the number of doses of INH taken, as reported by the client. Adherence reported here only included 8 months of therapy because clients did not have to return to this clinic after their ninth visit. They were given the INH for the 9th month.	47% patients completed 6 months of LTBI treatment.

		not show up for their clinic appointment and did not respond to the public health nurse's phone calls or letters.		
(Parsyan et al., 2007)	2621 subjects with LTBI were seen in 1998 and 1723 were offered treatment. Among 1091 who took treatment and less than 35 years of age, 457 were black and 335 Asians, 179 white and 119 Hispanic. Female and male almost equal percentage. About 80% patients are between 15 to 34 years of age. Patients came from China, Haiti, Vietnam, Bosnia, Dominican Republic, Cape Verde, and USA.	Patients were followed monthly and a one-month supply of medication was given at each visit. The patient was considered to have taken medication for that month unless otherwise noted in the chart. Completion of treatment was evaluated by comparing the number of months of LTBI treatment received	Patients who were less than 5 years old were defined as having completed treatment after taking INH for 9 months. Those older than 5 years were defined as having completed treatment after 6 months of INH.	Of the 1572 who completed, treatment was completed by 607(38.6%).

		with the treatment recommended.		
(Bieberly & Ali, 2008)	A total of 380 patients attending the Wetmore TB clinic between January 2006 and June 2007. Most patients were between ages of 19 and 55 years (74%), with a greater number of men being seen for LTBI than women (55% vs. 45%). 51% were Black, non-Hispanics. 27% were foreign-born. 29% were referred for contact investigation. 30% of patients were known contacts of active TB cases, and 17% recent TST converters.	N/A	Treatment completion was defined as the completion of at least 6 months of INH therapy or 4 months of RMP therapy.	Adherence rates for LTBI treatment were low at 19%.
(Kwara et al., 2008)	At the RISE TB clinic, Miriam Hospital, RI, from January 2003 to December 2003, 672 initiated INH therapy and were included in the analysis. 84.5% were born outside of the US, 57.3% were women, 54.8% Hispanic, 54.6% had a history of BCG, 51% had no insurance coverage, 43% were>= 35 years old. This study contained high-risk persons: 3 with HIV (+), 104	Treatment adherence was measured by the number of months in which pills were dispensed. Medications were dispensed on site, and patients were required to bring back	Completed 9 months of INH	Of 845 patients with LTBI, 81.6% initiated INH therapy, of whom 61.7% completed therapy.

	who had known contact, and 132 less than 20 years of age.	the pill bottle for a pill count at each visit.		
(Powell et al., 2008)	545 children from 54 different birth countries. Patients <= 15 years of age with LTBI referred to Nationwide Children's hospital TB clinic between August 2005 and July 2006.	Patients who failed to return to clinic for 3 consecutive months were deemed treatment failures.	Completion of therapy was defined as 270 doses of INH within a 12-month period of time. Patients who missed >= 3 consecutive months of therapy but eventually returned to the clinic were restarted on the full course of therapy.	The overall completion rate of the 545 patients evaluated was 54.4%.
(K. Hess, Goad, Wu, & Johnson, 2009)	348 participants were university students diagnosed with LTBI. Patients included in the analysis were those diagnosed with LTBI by student health clinicians, referred to the pharmacy LTBI clinic, and able to complete the full-9-month INH regimen by December 2005. The majority of patients were male (56.3%), mean age of 24.2 years, most of Asian ethnicity (63.5%). Patients were generally healthy, with	The number of tablets taken was assessed by the pharmacist's count or as self-reported by the patient if his or her medication vial was not available at the time of visit. Used dispensing records to	6-month completion was defined as taking 180 tablets in a 6-month period.	The 9-month completion rate was 59%, and the 6-month completion rate was 67%.

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	few comorbidities.	calculate adherence		
(Li et al., 2010)	Patients who were prescribed INH or RIF for LTBI therapy in any of the ten health department chest clinics during January 2002 to August 2004. 15035 patients (very large sample size) started LTBI treatment in chest clinic of New York City Health Department.	Based on medication dispensing on monthly visits Lack of data on actual amount of pills taken may lead to overestimation of compliance.	For adherence, patients of mean age >= 18 years took 6-9 months of INH daily, or twice weekly within a 9-12-month period, or >= 4 months of daily RIF doses within 6 months. Adherence of patients younger than 18 years: if they took INH for 9 or more months daily, or twice-weekly within a 12-month period, or 6 or more months of daily doses of RIF within a 9-month period. Failure to return for follow-up was considered nonadherence.	45.2% completed LTBI therapy.
(Horsburgh et al., 2010)	Retrospective, randomized two-stage cross-sectional survey of treatment and completion of LTBI at public and private clinics in 19 regions of the United States and Canada in 2002.	N/A	Completion of LTBI treatment was based on a specific number of doses to be completed within specific period of time for each regimen. For the 9-month daily INH regimen, completion was defined as 270	47% completed treatment regardless of what regimens.

				doses within 12 months; for 6 months of daily INH completion was 180 doses within 9 months; for 4 months of daily RIF, completion was 120 doses within 6 months; and for 2 months of daily RIF/Pyrazinamide, completion was 60 doses within 3 months.

9 Prospective (cohort) Studies

(Shukla et al., 2002)	An urban Midwestern teaching hospital in St. Louis, MO. Compliance data were available for 388 of 404 (96%) health care workers who were evaluated from January 1994 to May 2000 and initiated treatment. Of the 404 total workers, 52% were African American, 34% White, 12 % Asian, and 2 % Hispanic; 77% US-born, 43% new TST converters. Mean age 36 years. 62% female. 20% had a history of prior BCG vaccination.	Compliance data were cross-checked with outpatient pharmacy records. An occupational health database recorded the type of medications received, dates received, and the number of months the medications were received. Nurses were called monthly to assess side	Noncompliance was defined as receiving < 6 months of therapy or refusal of therapy.	Of these, 318 of 388 health care workers (82%) were compliant with 6 months of therapy.

		effects and compliance with the medication.		
(Eidlitz-Markus, Zeharia, Baum, Mimouni, & Amir, 2003)	105 patients aged 1 to 75 years who were treated with single daily dose of INH in Israel from September 1999 to April 2000. 105 patients (67 female) were examined. The mean age was 26.9 years. INH was prescribed for persons with LTBI who were at increased risk of developing active TB, which included 42 (40%) children and 25 (23.8%) with recent conversion. 36 patients (34.2%) had close contact with a patient who had TB.	Urine samples were collected on routine urine analysis and were tested for INH with the Arkansas color method. A subsample of 26 patients was randomly tested twice on separate visits.	N/A	71.5% adherence rate only 26 patients randomly tested twice on separate visits.
(Coly & Morisky, 2004)	A total of 766 low-income adolescents (79% participation rate), including 610 foreign-born, were recruited. Two health clinics in Los Angeles County, California. The age of foreign born participants ranged from 12 to 19 years, with a mean age of 15.3 (SD=1.9). Males comprised 52% of the foreign-born participants. The majority of the sample were Hispanics	The outcome variable, completion of treatment, was measured according to the discharge summary recorded in the patient's medical chart. For a patient to	Medical chart data were abstracted regarding clinic appointment keeping and completion of treatment.	Foreign-born adolescents were more likely to complete care than US-born adolescents, with 82% completion of care rate.

	(83.3%) followed by Asians (11.5%). Blacks and White/other represented 1.6% and 3.6%, respectively, of the population. The majority of Hispanics (72%) were born in Mexico. Participants were on average, 9.5 years of age when they arrived in the U.S. (SD=5.1, range 1-18).	complete medical treatment, a minimum of 6 months' treatment had to have been completed. All patients who did not have a measure regarding completion of care were assumed to have discontinued therapy and were coded as having not completed care.		
(Berg et al., 2004)	96 Latino adolescents recruited from school in San Diego county and mostly treated in community clinic. Ages ranged 12-19 years, 53.1% male. 66.7% born in Mexico, 73% had no health insurance at baseline. Mean age =15.42 years.	The 30-day medication adherence was assessed monthly up to 9 months by interview when the participants were asked how many pills in the last 30 days. Urine testing through unschedule	9 months	Somatic complaint over 9 months was the only significant predicator in pill-taking. Somatic complaints that occurred during 9 months of INH were significantly negatively related to cumulative adherence.

		d home visits.		
(Martinez Sanchis, Calpe Calpe, Llavador Ros, Ena Munoz, & Calpe Armero, 2005)	Between December 1996 and December 2002, 198 of 215 contacts prescribed with INH started INH and enrolled in the study at a hospital in Autonomous Community of Valencia, Spain. These contacts were found by following a system of concentric circles of HIVC-negative patients diagnosed with pulmonary TB in our public health care area from December 1996 to December 2002.	Patients were evaluated for adherence to treatment and side effects by being checked at 15, 30, 60, 120, and 180 days by a clinical interview with the physician, and by a blood test.	A patient was considered adherent to treatment if he or she attended scheduled check-ups.	79% completed the prophylaxis protocol.
(Shieh et al., 2006)	Academic medical center's TB clinic in Boston. Individuals 18 or more years of age prescribed at least 6 months of daily INH only for LTBI and who spoke English, Spanish, or Chinese from July 2002 to September 2003. 44.2% male, 51.6% less than 35 years old. 20.7 % White, 34.6% Black, 30.9% Asia/Pacific Islander. 90.3% foreign-born.	N/A	At least 6 months of daily INH. Completion of 6 months of INH within 9 months.	28.6 % finished at least 6 months of INH.
(Machado et al., 2009)	101 household contacts of hospitalized TB patients in Salvador, Brazil between	Contacts who did not complete treatment	Household contacts who completed LTBI treatment were defined as those	Of 101 household contacts who initiated LTBI therapy, 53.5%

	November 2006 and February 2008. All ages. Mean age 23. 44% male. 52% Black, 38% multiracial, 10% White.	were defined as those who missed at least one but not all of the follow-up visits and missed an INH refill.	who returned to hospital every 30 days for 6 months and received 30-day supplies of INH.	completed the 6-month regimen. 28.7% were immediately lost to follow-up.
(Minodier et al., 2010)	777 immigrant children with positive TST. Mean age of screened children was 146 months; 52% were males. Data analysis for 724 immigrant children with LTBI.	Adherence to INH was evaluated by 1) self-reported adherence at each appointment, 2) by pill counts wherever possible, 3) by phone calls to pharmacies during treatment to verify regular medication supplies.	Adherence was considered adequate if the child took >= 80% of the prescribed doses in a time <= 120% of the duration planned at the first visit.	Adequate completion of treatment was noted in 61.3%.
(Coreli, 2010)	90 enrolled patients were of Haitian origin in Florida and adults diagnosed with LTBI who began preventive therapy through the Broward County Health Department or the Palm Beach County Health Department and enrolled from August 2005 to July 2007.	Adherence to prescribed regimen was monitored through monthly follow-up appointments where patients came in for a check-up	9 months INH	74.4% had chart-documented completion of therapy.

	Some of the patients, including children and HIV co-infected persons, were monitored through DOPT. 22.2% referred due to contact of TB cases. 7.8% referred due to HIV-co-infection.	and to receive a month's supply of medication. Stigma scale, an interview questionnaire.		

3 Quasi-Experiment or Randomized Controlled Trials

(Menzies et al., 2005)	104 patients from a tertiary-care, university affiliated hospital specializing in respiratory diseases between January 21 to October 1, 2002. Personal and baseline clinical characteristics are not significantly different between patients who fell into these three categories.	Medication Event Monitoring System (MEMS) recorded the date and house each time the bottle was opened. Adherence based on MEMS information after 4 weeks of therapy. After the 4th week, adherence was evaluated based on patient's self-report and punctuality. They are	Adherence completers: patients who took more than 80% of doses within 43 weeks for INH. Non-completers: patients who took less than 80% of prescribed doses. Cut-off of 80% has been associated with efficacy of INH.	82.6% (86 out of 104 patients) took more than 80% of doses within the expected interval.

		also estimated by whether the pills remaining corresponded approximately to the number that should have been left.		
(Hirsch-Moverman, Bethel, Colson, Franks, & El-Sadr, 2010)	Participants in Study A (n = 191), conducted in 1996-1999, self-administered daily Isoniazid (INH) for 6-12 months; while participants in Study B (n = 123), conducted in 2002-2005, self-administered daily INH for 9 months. Overall, participants were more likely to be male (64.3%), African American or Latino (72%), aged <40 years (55.4%), unemployed (68.2%), and not married (70.1%). The majority of participants were foreign-born (52.9%).	Questionnaire and the studies differed in the use of electronic monitoring devices (EMDs), which recorded opening times of medication bottles in Study B but not in Study A.	Based on CDC guidelines	Overall, 44.6% of participants completed therapy, with significantly higher completion rates in Study B than Study A (37.0% vs. 56.1%, p = 0.001).
(Trajman et al., 2010)	Randomized controlled trial of latent tuberculosis infection (LTBI) treatment in 10 clinics in Canada, Saudi Arabia and Brazil.	Adherence to treatment was measured according to three different criteria: the number of	Patients randomized to 4 months of RMP (n = 420) or 9 months of INH (n = 427) were monitored for adherence using an electronic device.	583 (73%) completed treatment and were further analyzed for time to complete.

doses taken (treatment completion), the allotted time to complete treatment and the time interval between doses (regularity).

Adherence was monitored by an electronic devise in the pill bottle cap that recorded the date and time the bottle was opened (micro-electro-mechanical system [MEMS] device, Aprex Corporation, Fremont, CA, USA), and by pill count by the attending physician or nurse. Whenever

Outcomes were 1) treatment completion, defined as intake of >or=80% of the prescribed doses, and further categorized as completed within the allotted time or not; and 2) treatment regularity, measured by the time interval between doses.

results
were
discordant,
doses taken
were based
on MEMS
recordings,
given the
published
evidence of
their better
correlation
with
treatment
outcomes.

APPENDIX 2. Modifying Factors

Variable	Study Findings
Age	Age appears to be a predictor of adherence to INH therapy. Poor adherence to treatment was associated with age over 16 years, OR = 1.82, 95% CI [1.82, 2.99] (Minodier et al., 2010) and an age of 15 years and older was associated with failure to complete treatment, OR= 1.49, 95% CI [1.14, 1.94] (Horsburgh et al., 2010). Similarly, persons 19 to 34 years of age had the highest nonadherence rates in another study (Bieberly & Ali, 2008). However, it has been reported that an age of 35 years and older was associated with increased likelihood of completion of treatment, adjusted Relative Risk (aRR) = 1.2, 95% CI [1.1, 1.2] (Li, Munsiff, Tarantino, & Dorsinville, 2010). Another study found higher completion rates in younger age groups (0 to 14), 74% completion, OR = 4.1, $p < .01$, 95% CI [2.2, 7.8] (LoBue & Moser, 2003).
Gender	While most studies suggest that adolescents and young adults have poor adherence, gender does not seem to be associated with completion of INH therapy. One study found higher completion rates associated with female sex, OR= 1.2, $p = .03$, 95% CI [1.0, 1.4] (LoBue & Moser, 2003).
Language, ethnicity, and country of birth	While results are somewhat mixed, speaking Spanish, ethnicity, country of birth, and immigrant status appear to be associated with adherence rates. In one study, speaking Spanish was a significant predictor of treatment completion (Cass, Talavera, Gresham, Moser, & Joy, 2005). The nationalities of parents who refused to have their children start LTBI therapy were 54% and 80% of Eastern Europeans and Asians, respectively, compared with less than 10% of parents from Sub-Saharan Africa, Central and South America, and the United States, $\chi2 = 102.67$, $p = .001$, which led to their children's non-completion of treatment (Powell, Perkins, Wang, Hunt, & Ryan-Wenger, 2008). Another study showed that failure to complete therapy was associated with birth in Haiti, OR = 2.17, 95% CI [1.49, 3.17] or the Dominican Republic, OR = 1.93, 95% CI [1.08, 3.43] (Parsyan, Saukkonen, Barry, Sharnprapai, & Horsburgh, 2007). A study found the rate of adherence with treatment of LTBI was lower in immigrants (approximately 11% of subjects from Ecuador, Peru, Morocco, United Kingdom, and Italy), than in non-immigrants, OR = 3.42, $p = .02$, 95% CI [1.03, 11.04] (Martinez Sanchis, Calpe Calpe, Llavador Ros, Ena Munoz, & Calpe Armero, 2005). It is unclear if variation among completion rates across different ethnic or immigrant groups could be due to attribution of positive Tuberculin Skin Test to BCG vaccination or

their ability to accurately understand the need for LTBI therapy in their host country.

Health risks Health risk factors such as alcohol or drug use may predict poor adherence to TB therapy. Alcohol use was a significant predictor of nonadherence in an inner-city cohort of African Americans or Latinos, 72% completion rate, OR = 0.53, 95% CI [0.32, 0.88] (Hirsch-Moverman, Bethel, Colson, Franks, & El-Sadr, 2010). It has also been found that the greater the alcohol use, the less adherent adolescents were to INH therapy, $F (4, 91) = 3.35$, $p < .05$ (Berg et al., 2004). Injected drug use was a risk factor for failure to complete LTBI treatment, OR = 2.13, 95% CI [1.04, 4.35] (Horsburgh et al., 2010).

APPENDIX 3. Enabling Factors

Variable	Study Findings

Length and
type of
regimen

Shorter regimens have been shown to be correlated to adherence to
LTBI treatment. A 3-month chemoprophylaxis regimen of INH and
RMP (3HR) was adhered to significantly better than a 6-month
chemoprophylaxis regimen of INH (van Zyl et al., 2006). Similarly,
treatment completers were more likely to be those who received the
Rifamycin-based alternative regimen (60%) than INH regimen, aRR
= 1.2, 95% CI [1.1, 1.3] (Li et al., 2010). Another study found
completion of treatment was higher with 4 months of RMP
compared with INH, aOR = 4.3, 95% CI [2.7, 6.8] (Trajman et al.,
2010). In one study, the risk factor for failure to complete was
starting a 9-month INH protocol compared with 6 months of INH, 4
months of RIF, or 2 months of RIF/Pyrazinamide (PZA), OR= 2.08,
95% CI [1.23, 3.57] (Horsburgh et al., 2010).

Interruption
in treatment

The first 3 months are the best time to identify nonadherence issues,
because completion rates continue to decline during the course of
treatment. Interruption has been defined as missing more than 2
weeks of DOT or more than 1 month of self-administered treatment,
and then resuming treatment (Marks et al., 2000). It has been
reported that 3,748 patients (47.8%) failed to return for INH
treatment after the first month of clinic medication dispensing (Li et
al., 2010). In a study evaluating the usefulness of urine dipsticks for
monitoring adherence to INH therapy, two thirds of patients
discontinued treatment in the first 2 months (Meissner, Musoke,
Okwera, Bunn, & Coulter, 2002), and another study of patients under
18 years of age reported that 66% stopped INH treatment at or after
2 months (Li et al., 2010). More evidence to show that nonadherence
can be seen early in INH treatment came from a study which showed
that nearly two thirds (65.9%) of the participants self-discontinued
LTBI treatment either by declaration or by not returning to the clinic
within 3 months of starting treatment (Shieh et al., 2006).

Time to
completion

Adherence continues to decrease as time progresses. One study
showed that adherence of Latino immigrants treated at public health
clinic dropped off in a linear fashion from the first month (84%) to
the eighth month (34%) (Ailinger, Moore, Nguyen, & Lasus, 2006).
Another study reported that the 6-month completion rate was 67%
while the 9-month completion rate dropped to 59% (Hess, Goad,
Wu, & Johnson, 2009). Time to completion of the expected number
of doses is a predictor of adherence; adherence during the first
month, based on the number of doses and variability of times when
taken, may be useful to predict completion of LTBI treatment
(Menzies et al., 2005). Early predictors (at the first follow-up visit)

of nonadherence were late attendance, RR=0.9 for completion in time, 95% CI [0.8, 0.98], more than 20% of doses being missed, RR = 0.4, 95% CI [0.3, 0.6], and greater variation of hours between doses (0.209 vs. 0.131, p < .001) (Trajman et al., 2010). The length of time since the last self-reported INH dose had a stepwise increase in probability of having a negative urine test with no detectable INH metabolites, OR = 1.33, p = .0007, 95% CI [1.13, 1.57] (Szakacs et al., 2006). However, barriers to treatment and receptiveness to treatment should be further explored in relation to the initial stage of treatment; such research may explain these treatment interruptions more clearly.

Side effects and symptoms

Side effects and symptoms are included under regimen monitoring, which is among the enabling factors in the conceptual framework. This is because side effects and symptoms (if they occur) due to medications are assessed and monitored on a monthly basis, by clinicians who determine whether the regimen should be discontinued or changed. Table 3 lists the possible side effects of INH. These include: asymptomatic elevation of serum liver enzyme concentration, clinical hepatitis, and peripheral neuropathy; allergic reaction; fatigue; nausea and vomiting; loss of appetite; abdominal pain; yellow skin or eyes; dark urine; numbness or tingling in hands or feet; and blurred vision (Centers for Disease Control and Prevention, 2010b). Side effects of RIF treatment may include hepatotoxicity, cutaneous reactions, gastrointestinal symptoms, and orange discoloration of body fluids (Centers for Disease Control and Prevention, 2010b).

Liver toxicity is the most serious side effect of TB drug therapy. For INH-associated liver injury, one of two additional criteria must be met: 1) greater than three-fold elevation of transaminases above normal in the presence of symptoms compatible with liver injury; or 2) elevation of transaminases greater than five times normal in the absence of symptoms (LoBue & Moser, 2003). The occurrence of side effects was one of the factors significantly associated with adherence (Parsyan et al., 2007). Low completion rates were associated with having experienced at least one adverse effect other than hepatotoxicity, OR = 0.8, p = .03, 95% CI [0.7, 0.9] (LoBue & Moser, 2003). Side effects were also found to be associated with non-completion of treatment, OR = 3.6, 95% CI [2.2, 6.2] (Kwara, Herold, Machan, & Carter, 2008). Increased symptoms while receiving therapy were significantly associated with noncompliance, OR = 4.5, 95% CI [2.0, 10.1] (Shukla, Warren, Woeltje, Gruber, & Fraser, 2002). This is supported by another study reporting that the risk of treatment non-completion was significantly higher in the household contacts who reported side effects to INH, RR = 2.69, p

	= .01, 95% CI [1.3, 5.8] (Ailinger et al., 2006). Somatic symptoms (i.e., headaches, acne, and dandruff) other than the side effects of medications, also impeded treatment completion in Latino adolescents, resulting in a significant negative association with cumulative adherence (Berg et al., 2004).
TB intervention	Factors associated with adherence are positive self-reinforcement, source-case investigation, the number of different Public Health Nurses (PHNs) seeing the client during treatment, and DOT. Receiving source-case investigation, and a behavioral intervention that included self-monitoring and positive reinforcement whereby children were rewarded for taking INH, were significant predictors of treatment completion (Cass et al., 2005). In a related study it was found that the number of different PHNs who saw the client during treatment was related to rate of adherence in Latino immigrants, r = 0.646, p ≤ .001 (Ailinger et al., 2006). The mean number of different PHNs who clients saw during their treatment was 3.39 (range = 1-7, SD = 1.5) for the population with low TB risk. Although PHNs were involved in providing TB intervention, overall 47% of patients completed 6 months of LTBI treatment in this relatively low-TB-risk sample group. Another study concluded that treatment completers were more likely to be treated in a DOT protocol, 71.4% completion, aRR = 1.3, 95% CI [1.2, 1.3] (Li et al., 2010).

APPENDIX 4. Environmental Factors

Variable	Study Findings

TB risks

Direct contact with a patient with active TB was shown to increase adherence in three studies (Bieberly & Ali, 2008; Li et al., 2010; Reichler et al., 2002). Patients with a higher TB risk include those who are in close contact with an active TB patient and recent skin test (TST) converters. This type of contact appears to be a reliable predictor of adherence. Contact with pulmonary TB cases resulted in an increased likelihood of treatment completion (57.4%), aRR = 1.5, 95% CI [1.4, 1.7] (Li et al., 2010). A completion rate of 51% was reported in people who were in contact with active TB patients, and completion rates were higher among skin test converters (Reichler et al., 2002). Similarly, another study showed that patients with recent TST conversion were significantly more likely to adhere to treatment compared to LTBI patients without that risk factor (Bieberly & Ali, 2008). However, some of these high-risk completers received DOT, which could affect results. During the course of contact investigation, clients who receive screening and TB education may also unexpectedly have increased adherence.

Parental perception of TB risk and INH therapy

A limited number of studies have shown that patients' perceptions or beliefs of TB risks affect adherence to INH therapy. Patients who perceived a low risk of developing active TB without LTBI treatment were significantly less likely to complete LTBI treatment, RR = 0.35, p = .001, 95% CI [0.18, 0.67], as well as those who did not value regular visits to healthcare professionals for health maintenance, RR = 0.27, p = .019, 95% CI [0.07, 0.85] (Shieh et al., 2006). In support of the idea that patient perceptions affect adherence, it was shown that patients' belief in INH safety was associated with a positive urine test for medication adherence (INH metabolite present) (Szakacs et al., 2006). However, this urine test was only performed once without follow-up testing.

Other factors

Two additional predictors associated with nonadherence include BCG vaccination and reluctance to have a venipuncture. BCG vaccination was significantly associated with noncompliance, OR=3.5, 95% CI [1.8, 7.1] (Shukla et al., 2002). In another study, approximately half of the respondents who did not want, or were unsure if they wanted venipunctures in order to monitor liver toxicity, were significantly more likely to fail to complete treatment, OR = 0.43, p = .015, 95% CI [0.22, 0.85] (Shieh et al., 2006).

Cultural background	How individuals perceive INH therapy can impact adherence, especially in relation to aspects of culture. The perception in Vietnamese culture of the therapy's side effects as "hot," causing an imbalance in the body system and leading to illness, increased the likelihood of nonadherence (Ito, 1999).
Home and family environment	Home environment has been documented to be a predictor of adherence. Homelessness was associated with low completion rates, $OR = 0.2$, $p < .01$, 95% CI [0.1, 0.5] (LoBue & Moser, 2003). Patients in overcrowded homes were less likely to be adherent than those were not from overcrowded homes, $aOR = 0.71$, $p = .02$, 95% CI [0.54, 0.95] (le Roux et al., 2009). Another risk factor for failure to complete treatment was residence in a communal setting such as a nursing home, shelter, or jail, $OR = 2.94$, 95% CI [1.58, 5.56] (Horsburgh et al., 2010). There is limited evidence that family involvement or marriage status is associated with LTBI completion. For children's adherence to LTBI therapy, having two or more family members brought in for TB screening was associated with treatment adherence, $aOR = 2.0$, 95% CI [1.3, 3.3] (Brassard, Steensma, Cadieux, & Lands, 2006). For adolescents, living with both parents was associated with treatment completion, $OR = 1.74$, 95% CI [1.02, 2.97] (Coly & Morisky, 2004). Marriage was a significant predictor of completion, $aOR = 2.15$, 95% CI [1.30, 3.56], particularly among married persons of foreign birth (Hirsch-Moverman et al., 2010). Support from family members and peers (direct and indirect peer pressure to stop INH or opposition or no support from family member) was related to rate of nonadherence (Ito, 1999).
Access to care	Barriers to access to care are associated with nonadherence and include a lack of medical insurance, no primary-care physician, or no transportation. Lack of medical insurance was associated with treatment nonadherence, $OR = 1.7$, 95% CI [1.1, 2.7]. Not having a primary-care physician was a univariate predictor of treatment non-completion, $RR = 0.48$, $p = .013$, 95% CI [0.25, 0.87] (Shieh et al., 2006). Another study showed that the risk of treatment non-completion was significantly higher in household contacts if they had to take two buses for a one-way trip to the hospital, $RR = 1.8$, $p = .04$, 95% CI [1.01, 3.3] (Machado et al., 2009).

APPENDIX 5. UCSF Committee on Human Research Application Approval Letter

UCSF
University of California
San Francisco

Human Research Protection Program
Committee on Human Research

Notification of Expedited Review Approval

Principal Investigator
Kathryn A Lee

Co-Principal Investigator
Shiow-Huey Chang

Type of Submission: Initial Review Submission Packet
Study Title: Adherence to Treatment of Latent Tuberculosis Infection Among Children
IRB #:   11-08230
Reference #:   036991
Committee of Record: Laurel Heights Panel
Study Risk Assignment: Minimal

Approval Date: 02/08/2012   **Expiration Date:** 02/07/2013

Regulatory Determinations Pertaining to this Approval (if applicable):

This research satisfies the following condition(s) for the involvement of children:
45 CFR 46.404, 21 CFR 50.51: Research not involving greater than minimal risk.

The research meets conditions of 45 CFR 46.205 for the involvement of neonates.

The research meets all conditions of 45 CFR 305(a), and is permissible under the following category:
HHS Secretarial Waiver (68 FR 36929, 6/20/03) Epidemiological research with prisoners: The research must have as its sole purpose (i) to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease. The study poses no more than minimal risk and presents no more than an inconvenience to the prisoner subjects, and prisoners are not the focus of the research.

The requirement for individual HIPAA authorization is waived for all subjects. The use or disclosure of the requested information does not adversely affect the rights and welfare of the individuals and involves no more than a minimal risk to their privacy based on, at least, the presence of the following elements: (1) an adequate plan to protect the identifiers from improper use and disclosure; (2) an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or if such retention is otherwise required by law; (3) adequate written assurances that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule; (4) the research could not practicably be conducted without the waiver; and (5) the research could not practicably be conducted without access to and use of the requested information.

A waiver or alteration of informed consent is acceptable because, as detailed in the application: (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation. The waiver or alteration of informed consent applies to all subjects.

APPENDIX 6. Santa Clara Valley Medical Center IRB Application Approval Letter

SANTA CLARA
VALLEY
MEDICAL
CENTER

751 South Bascom Avenue
San Jose, CA 95128

www.scvmed.org
Office of the Institutional Review Board
Old Main Building, Room 3C018
Telephone: (408) 885-3115
Fax: (408) 885-4834
E-mail: Whitney.Touserkani@hhs.sccgov.org

January 4, 2012

Shiow-Huey Chang, RN, CNS
P.O. Box 403
Cupertino, CA

RE: New project entitled "Adherence to Treatment of Latent Tuberculosis Infection Among Children"
        IRB Reference #11-059

The following action was taken by the Research and Human Subjects Review Committee of Santa Clara Valley
Medical Center regarding the above-referenced project. The Committee is a duly constituted Institutional Review
Board [IRB] that operates in compliance with the Common Rule under a Federalwide Assurance #00001437. Review
was conducted in accordance with Title 45, Part 46, Subpart C, §46.301- 46.306 of the Code of Federal Regulations,
which pertains to research involving individuals who are involuntarily being confined or detained in a penal
institution.

Action Taken

Having resolved all issues raised in review of this project, the Committee hereby grants final approval to conduct the
research. The project was approved for a period of one year with the proviso that you agree to comply with the
conditions for approval set forth below. Approval was granted with the understanding that all precautions will be
followed regarding protecting patient identifiable information as outlined in the revised proposal and data sheet
submitted to the IRB office through e-mail on December 16, 2011.

Approval was granted through the expedited review process allowed under Title 45, Section 46.110 of the Code of
Federal Regulations. The official date of approval is December 21, 2011.

IRB Reference Number: The number assigned to this project is **11-059** and should be referenced when
corresponding with the Committee regarding this project.

CONDITIONS FOR APPROVAL

Informed Consent: This project qualifies for waiver of informed consent in accordance with Title 45, Section 46.116
(d) of the Code of Federal Regulations.

HIPAA: This study qualifies for waiver of authorization of HIPAA in accordance with Title 45, Section 164.512
(i)(2)(ii)(A), (B), and (C) of the Code of Federal Regulations.

Expiration: This project's approval will expire **12/20/12**. If the project is to continue beyond the expiration date, it
must be renewed in accordance with the Committee's renewal instructions. As a courtesy reminder, a renewal
application will be e-mailed to you approximately one month prior to the expiration date. Note: If the project is
terminated or completed prior to the expiration date, the Committee must be notified in writing and provided with
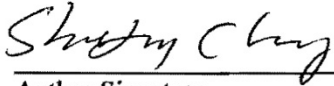a final report.

APPENDIX 7. Publishing Agreement

Publishing Agreement
*It is the policy of the University to encourage the distribution of all theses,
dissertations, and manuscripts. Copies of all UCSF theses, dissertations, and
manuscripts will be routed to the library via the Graduate Division. The library will
make all theses, dissertations, and manuscripts accessible to the public and will
preserve these to the best of their abilities, in perpetuity.*

Please sign the following statement:
*I hereby grant permission to the Graduate Division of the University of California, San
Francisco to release copies of my thesis, dissertation, or manuscript to the Campus
Library to provide access and preservation, in whole or in part, in perpetuity.*

_____   04/17/13
Author Signature   Date