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Factors Associated With Tuberculin Skin Test Positivity Prevalence in U.S. Medical Laboratory Microbiologists

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Walden University
2013

Abstract

Factors Associated With Tuberculin Skin Test Positivity Prevalence

in U.S. Medical Laboratory Microbiologists

by

Julie Ann West

BS, The University of the State of New York (Excelsior College), 1989

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

December 2013

Abstract

Prior research has indicated that healthcare personnel (HCP) who work in areas where *Mycobacterium tuberculosis* poses an occupational hazard are at high risk of tuberculin skin test (TST) positivity and subsequent conversion to active tuberculosis (TB). U.S. medical laboratory microbiologists confront similar hazards but have not been studied outside of the HCP aggregate. The purpose of this study was to fill this gap by examining the relationships between the predictor variables of self-reported history of bacille Calmette-Guérin (BCG) immunization, place of birth, and years of laboratory experience and the outcomes of self-reported lifetime TST positivity, preventive treatment noninitiation, and barriers to treatment adherence for this subgroup. This quantitative, cross-sectional study was guided by the epidemiologic triad model. A researcher-designed self-administered questionnaire including Part A of the Brief Medication Questionnaire was mailed to 4,335 U.S. microbiologist members of the American Society for Clinical Pathology. From the 1,628 eligible respondents, results showed that prevalence of positive TSTs (17.0%) and treatment noninitiation (9.8%) was low. Multivariate analysis identified BCG and foreign birth, as well as age, nonoccupational exposure, history of TB, work in mycobacteriology, and work outside of microbiology as predictors of a positive TST; foreign birth was a predictor of treatment noninitiation. Additional research is needed to identify other laboratorian groups at increased risk for developing TB. These results enhance positive social change by helping to inform recommendations in the global fight to stop the spread of TB, as well as improve allocation of resources among this specific group of HCP.

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Dedication

For many years, my dear mother has been the cornerstone of our family. She has encouraged the furthering of my education at every opportunity. In honor of her many sacrifices, steadfast love, and support, I dedicate this work to her.

Acknowledgments

My many thanks to the faculty at Walden University for making this experience a learning tool, second to none. Special thanks go to Dr. Hadi Danawi, Committee Chair, for guiding me through the dissertation process. Dr. Danawi always exemplified the traits of professionalism and encouragement necessary to keep me on the dissertation path. A special thank you to Dr. Angela Prehn for providing continued guidance. Dr. Prehn unknowingly set me on this dissertation path several years ago, when she provided recommended readings on my chosen topic.

Thank you to the American Society for Clinical Pathology (ASCP); without their permission, the mailing of this survey would not have been possible. My profound thanks to those ASCP members who chose to participate in the volunteer survey. For without the responses of this group of U.S. medical microbiologists, data collection and analysis would not have been possible.

Finally, many sincere thanks go to my former laboratory supervisor and mentor, Linda Townsend, who taught me everything I know about medical microbiology. She has been a great teacher to me, in the ways of laboratory medicine as well as in many associated life lessons. Her mentorship has made me a better microbiologist, as well as a better person. Thank you.

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Chapter 1: Introduction to the Study

Background of the Study

Active tuberculosis (TB) disease is a significant public health problem at the global level. Statistics regarding the transition from inactive or latent tuberculosis infection (LTBI) to active TB disease remain relatively unknown because the priority of the World Health Organization (WHO) has been to detect and prevent active forms of TB disease (WHO, 2011b). Worldwide in 2010, 1.1 million people died from TB and 8.8 million new TB cases were reported (WHO, 2011b). In addition to serious morbidity and mortality, control of TB is expensive, predicted to reach almost 5 billion U.S. dollars in 2011 (WHO, 2010b), and 1-4 million U.S. dollars with each national prevalence survey worldwide (WHO, 2011a; WHO, 2011b). Expenses incurred in WHO-guided prevalence surveys are derived from chest x-rays, interviews, and laboratory testing of sample sizes in populations, usually numbering > 50,000 people each (WHO, 2011a, 2011b).   In the United States, cases of active TB reported in 2009 numbered 10,893 (Centers for Disease Control and Prevention [CDC], 2010b). While not every individual infected with inactive or latent tuberculosis infection becomes sick, about 5% to 10% of persons with normal immune systems will develop active TB disease at some point in their lives; this risk is the highest in the first 2 years after infection (CDC, 2005a, 2011a, 2011b).

TB is spread among individuals via the forceful exhalation (coughing or sneezing) of aerosolized droplet nuclei containing viable tubercle bacilli (TB bacteria) in cases of active disease. Risk of infectivity depends upon exposure and host factors (Heymann, 2008). After a period of incubation, infection results as active disease lesions or inactive

(latent) disease. While active TB disease is diagnosed using culture and direct microscopy techniques, inactive disease has been diagnosed historically using the tuberculin skin test (TST). The TST has been used to evaluate close contacts of individuals with active TB disease, to screen high-risk groups (immigrants, the immunosuppressed), and to screen healthcare personnel (CDC, 2005b). The TST screen examines an individual's antibody response to TB antigens present in purified protein derivative (PPD) tuberculin solution (National Tuberculosis Curriculum Consortium [NTCC], 2010). Although the TST continues to be utilized as a test of choice in the targeted tuberculin testing of inactive (latent) TB infection, the risk of false-positive or false-negative reactions is possible, as is a risk of misreading the test. In the United States, a low-incidence country, TST sensitivity is 0.59 to 1.0 and specificity is 0.95 to 1.0 (Rose, Schechter, & Adler, 1995). TST positivity is considered a hypersensitivity response, indicative of exposure to the TB bacterium and the presence of some form of inactive (latent) or active infection, warranting further investigation by a healthcare provider.

The percentage of active TB cases among healthcare personnel (HCP) in the United States reached 3.8%, second among occupations only to unemployed and retired individuals (CDC, 2010b). Because the latent period from initial infection to active TB disease can be long, infection rates and fatalities from TB disease as reported to the Occupational Safety and Health Administration (OSHA) may be underrepresented (Sepkowitz & Eisenberg, 2005). In the United States, occupational deaths due to active TB are infrequent compared with those in high-incidence, underdeveloped countries.

However, during the late 1980s and early 1990s, the TB-related deaths of at least 10 HCP contracting the infection occupationally were reported (Sepkowitz & Eisenberg, 2005). A resurgence of TB during this time coincided with the HIV/AIDS epidemic, contributing to health care facility outbreaks (Field, 2001). Many U.S. HCP remain at risk today for activation of inactive TB to active TB disease due to these past exposures (Sepkowitz & Eisenberg, 2005). While the risk of activation appears no greater for HCP than for the general public, the risk of latent and active infection globally due to occupational contact does appear higher (Baussano et al., 2011). The risk of progression from latent to active TB disease and the subsequent spread of TB among coworkers, patients, and families can create a public health problem (CDC, 2000, 2005b; Drobniewski et al., 2007). Several high-profile cases among HCP have prompted major contact investigations (Fitzpatrick et al., 2005; Hickstein et al., 2004; Nania et al., 2007), making the targeting of certain HCP groups for latent TB infection a priority (CDC, 2005b).

Researchers such as Baussano et al. (2011) have reported that globally, rates of new active TB cases (incidence) for HCP are higher than for the general population, representing TB as an occupational disease. While occupation alone cannot predict TST results, certain occupational factors involving contact with TB-contaminated patients or specimens remain well-known risk factors (CDC, 2005b, 2009). Among HCP, medical laboratorians are at high risk for TST positivity, indicating inactive TB infection, as well as for developing active TB. Since the 1940s and 1950s, laboratory workers repeatedly exposed to sputum or postmortem specimens from tuberculosis case patients have been at

greater risk for incidence of TB infection (inactive and active) when compared to the general public (CDC, 2005b; Reid, 1957). Exposures typically occur in the microbiology laboratory; very high (11.4%) incidence of new TST positivity (conversion within 2 years) among high-risk work settings including the microbiology laboratory was recorded in one study (Kraut, Coodin, Plessis, & McLean, 2004). CDC has targeted laboratory workers in guidelines for TB screening programs at the level of the health-care setting, and anyone participating in aerosol-generating procedures or in specimen-processing procedures (including processing for *Mycobacterium tuberculosis*) should take part in regular TST screening protocols (CDC, 2005b). In addition, specific factors further increasing risk include (a) place of birth (immigration from endemic countries); (b) location of work (working in hospitals or other congregate health-care facilities); (c) type of work, such as microbiology staff in a mycobacteriology laboratory (CDC, 2000, 2005b); and (d) years of work experience in the lab setting (Menzies, Fanning, Yuan, Fitzgerald, & the Canadian Collaborative Group, 2003; Rafiza, Rampal, & Tahir, 2011).

LTBI prevalence, a potential precursor to active TB (CDC, 2005a, 2011a, 2011b), has been associated with working in laboratories, especially in low-income countries (Joshi, Reingold, Menzies, & Pai, 2006). In Russia, LTBI prevalence has been documented at 40.8% in HCP staff but 61.1% in laboratory workers (Drobniewski et al., 2007). A Malaysian study was the exception; no laboratorians were positive (Rafiza et al., 2011). In U.S. HCP, LTBI prevalence (reported as TST positivity) rates have been reported to range from 11.3% (Bailey, Fraser, Spitznagel, & Dunagan, 1995) to 32% (Cook, Maw, Munsiff, Fujiwara, & Frieden, 2003), with higher LTBI prevalence rates

linked to an increase in foreign-born HCP (Cook et al., 2003). Among microbiology

laboratory healthcare workers in New York City, a baseline TST positivity rate of 57%

was reported (Garber, San Gabriel, Lambert, & Saiman, 2003), compared to a baseline

TST positivity rate of 36.2% among health department HCP in the same locale (Cook et

al., 2003). Risk factors of history of BCG immunization (a vaccine used to reduce risk of

TB in highly endemic countries), foreign birth, and employment in the mycobacteriology

laboratory have been found to be significantly associated with TST positivity in the U.S.

microbiology laboratory workers (Garber et al., 2003).

Preventive treatment for latent tuberculosis infection (LTBI) is of great interest

for slowing or stopping the spread of TB from inactive TB infection to active TB

infection. Prescribed treatment is important because it is thought to prevent latent TB

infection from becoming active TB disease (Heymann, 2008), thus breaking the chain of

disease transmission. HCP diagnosed with LTBI are at risk of not initiating and not

adhering to prescribed treatment for reasons of inaccessibility of easy treatment regimens

(treatment site hours, ease of obtaining medications), long treatment duration, stigma

associated with treatment, and barriers associated with adverse drug effects (Bieberly &

Ali, 2008; Gershon, McGeer, Bayoumi, Raboud, & Yang, 2004). Preventive treatment

completion rates among HCP have been reported as inconsistent, ranging anywhere from

48% in one retrospective analysis to 93% in a separate post intervention analysis (Hirsch-

Moverman, Daftary, Franks, & Colson, 2008). The general public's completion rate

approximates 60% (CDC, 2000). Preventive treatment among microbiology

laboratorians may be even more challenging; Gershon et al. (2004) reported HCP as

having an initiation rate of 58% overall, which compares to 20% reported among microbiology lab workers (Garber et al., 2003). As many as 11.4% of HCP who did not complete treatment in the Camins, Bock, Watkins, and Blumberg (1996) study reportedly stopped because of real or perceived drug effects. Preventive treatment noninitiation and treatment nonadherence (due to the presence of barriers such as medication side effects) in medical laboratory microbiologists as a subgroup of HCP are yet to be described at the national level. This subgroup has been largely ignored in literature referencing HCP (Bailey, Fraser, Spitznagel, & Dunagan, 1995) or misclassified as part of a larger group (Louther, 1998).

For this study, a U.S. medical laboratory microbiologist subgroup was accessed through the national registry known as the American Society for Clinical Pathology (ASCP, 2009). Results from this study will make an important contribution and enhance social change by helping inform recommendations in the global fight to stop the spread of TB, decrease TB deaths and disabilities, and improve allocation of resources among this specific group.

Chapter 1 will present (a) a statement of the problem, (b) the purpose of this study, (c) the nature of this study, and (d) the research questions. In addition, a discussion of the study's theoretical base, important terms, assumptions, limitations, delimitations, and significance will be presented. A detailed discussion of the literature and a summary of that research as it pertains to the study will follow in Chapter 2.

Problem Statement

Globally, millions of individuals continue to become infected with and die from TB or complications of TB every year (WHO, 2011). The elimination of TB infection in the United States is an overarching goal of the Institutes of Medicine (IOM, 2000) and the CDC (2002). The U.S. Healthy People 2020 document (U.S. Department of Health & Human Services, n.d.) has deemed at-risk groups important in the targeted treatment of latent and active TB infection (CDC, 2003a, 2005a). Additionally, guidelines for preventing the transmission of *Mycobacteria tuberculosis* in health-care settings, specifically targeting persons at risk (including employees having contact with infected patients, foreign-born HCP, and mycobacteriology laboratory workers) have been provided by the CDC (2005b). Healthcare personnel (HCP) diagnosed with LTBI are at risk of conversion to active tuberculosis (TB) disease status (CDC, 2000; Drobniewski et al., 2007) and may create conditions for the spread of TB among coworkers, patients, and families (CDC, 2005b). In the United States, several high-profile cases of active TB in HCP have been documented, and at least two were the result of LTBI treatment noninitiation (Fitzpatrick et al., 2005; Hickstein et al., 2004; Nania et al., 2007). In addition, HCP with LTBI may be at higher risk of treatment nonadherence (Bieberly & Ali, 2008; Gershon et al., 2004). This may complicate the spread of TB by introducing drug-resistant strains (CDC, 2011e). Among HCP, those working in mycobacteriology and emigrating from TB-endemic countries may be at high risk of LTBI as identified through TST screenings (CDC, 2000; Garber et al., 2003).

An initial review of the literature revealed that (a) tuberculin skin test (TST) positivity is used as a surrogate in the literature to represent prevalence of LTBI or unsuspected active TB infection and (b) HCP as a group have already been studied for TB-related epidemiologic purposes. Therefore, the problem is that while researchers have reported conglomerate data on the prevalence and risk factors associated with TST positivity among HCP, a gap in the current literature remains regarding prevalence and risk factors of (a) self-reported lifetime TST positivity, (b) treatment noninitiation, and (c) treatment nonadherence (presence of barriers) among any U.S. subgroup of HCP in its entirety, specifically among U.S. medical laboratory microbiologists. In addition, new and shortened preventive treatment guidelines have been published (Jereb, Goldberg, Powell, Villarino, & Lobue, 2011), further promoting a need to determine baseline data in target populations. Baseline data such as those collected in this study will assist in determining effectiveness of these new LTBI treatment guidelines in future research. Results are expected to add to the existing literature on HCP by reporting an analysis of the self-reported data assembled through surveying an entire national registry of medical microbiologists in the Unites States.

Purpose of the Study

The purpose of this cross-sectional quantitative study is to fill in the gap detailed above and describe the population of U.S. medical laboratory microbiologists in terms of prevalence and

- Independent variables, including risk factors of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and the

dependent dichotomous variable of self-reported lifetime TST positivity
status,

- Independent variables, including risk factors of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and the dependent variable of preventive TB treatment noninitiation (past or present) among those acknowledging ever having had a positive tuberculin skin test, and

- Independent variables, including risk factors of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and the dependent variable of barriers to treatment adherence (presence of medication side-effect barriers as measured by the Brief Medication Questionnaire) among those acknowledging ever having had a positive tuberculin skin test and initiating preventive TB treatment.

In addition, gender, age, type of laboratory work, nonoccupational exposure, and history of TB disease have been assessed as covariates or confounders. An evaluation of how each outcome varied across demographic and work-related factors took place. It was reasonable and anticipated that risk factors such as a history of BCG immunization and place of birth (nonoccupational), as well as years of work experience (occupational), might be associated with self-reported lifetime TST positivity. However, not much was known with regard to preventive treatment noninitiation and barriers to treatment adherence in this subgroup of HCP.

Nature of the Study

The rationale for this study was based on research by Garber et al. (2003) (*n* =

342), which has appeared as the largest and most recent study of medical laboratory

microbiologists in the United States. This and other studies identified through this

literature review used survey questionnaires of HCP or of the laboratorian subpopulation

for the gathering of data on the prevalence or incidence of active TB (Harrington &

Shannon, 1976) or prevalence of LTBI (Alonso-Echanove et al., 2001; Drobniewski,

Balabanova, Zakamova, Nikolayevskyy, & Fedorin, 2007; Garber et al., 2003; Menzies

et al, 2003; Rafiza et al., 2011). The cross-sectional design was chosen for this study

because the baseline TST prevalence of U.S. medical laboratory microbiologists as a

whole is relatively unknown. Findings indicated that the prevalence of a positive TST in

the Garber et al. (2003) group was 57%, while only 20% received Isoniazid preventive

treatment; multivariate analysis in this study revealed age, foreign birth, BCG

immunization, and employment in the mycobacteriology laboratory as risk factors for

positive TST (Garber et al, 2003). This study builds on (a) previous TST positivity

prevalence and associated risk factor research by Garber et al. (2003) and (b) related

nonadherence and medication side-effect barriers as researched by Garber et al. (2003),

Shukla, Warren, Woeltje, Gruber, and Fraser (2002), and others by surveying U.S.

medical laboratory microbiologists certified with a nationally recognized registry.

In this cross-sectional quantitative study, a dichotomous dependent variable of

self-reported lifetime TST positivity status was evaluated against a set of independent

variables including history of BCG immunization, place of birth (U.S. or foreign), and

years of laboratory experience. These items were chosen because they have appeared as proposed risk factors in prior TST research involving laboratory personnel (Garber et al., 2003) and elsewhere in the literature. Any history of self-reported preventive treatment initiation as reported on the questionnaire provided an opportunity to examine additional dichotomous dependent variables of (a) treatment noninitiation, and (b) barriers to treatment adherence as the presence of medication side-effect barriers (measured using a screening section of the Brief Medication Questionnaire [BMQ], devised by Svarstad, Chewning, Sleath, and Claesson in 1999) against the same independent variables above. The research tested the above-reported independent variables in subsequent hypotheses about whether specific factors were associated with the constructs of interest as represented by the epidemiologic triad model theory. A questionnaire survey was used in this process.

The nature of this study was a quantitative cross-sectional survey design using a one-time written self-administered questionnaire (Appendix A). The single-stage questionnaire using closed-ended questions targeted eligible U.S. medical laboratory microbiologists, a cohort of approximately 5,138 registrants at the time of the research proposal, registered as members of the national professional association known as the American Society for Clinical Pathology (ASCP). ASCP is the principal registry for most U.S. medical laboratory personnel (ASCP, 2009). For the purposes of this study, the U.S. medical laboratory scientist population registered with the ASCP and reportedly working in area of responsibility referred to as "Microbiology/Mycology/Parasitology/ Virology" is referred to as *medical laboratory microbiologists*. This area of designation

was chosen for cross-sectional study because medical laboratory microbiologists include

mycobacteriology workers, those most likely to perform high-complexity specimen

processing and TB testing on patient specimens (CDC, 2005b). U.S. mailing addresses

were accessed through INFOCUS Marketing (2011). The ASCP mailing list is updated

monthly, and addresses are run through the National Change of Address database,

resulting in an estimated loss of no more than 1% of addresses (S. Blake, INFOCUS

Marketing Consultant, personal communication, September 17, 2012). Calculation of

sample size justified use of the entire cohort in order to statistically satisfy all research

questions as posed (Appendix B). An announcement postcard including a scholarship

donation incentive (Appendix C) was mailed 1 week prior to the survey packet. Two

items from the Brief Medication Questionnaire (BMQ) Part A were included in the

written survey (Appendix D). Statistical methodologies, including univariate, bivariate,

and multivariate statistics, were used in the data analysis. The end product of the survey

was that of lifetime prevalence involving any self-reported lifetime TST positivity

outcome, risk factors of self-reported TST positivity, risk factors of preventive TB

treatment noninitiation, and risk factors of barriers to treatment adherence from an

individual's past or present (lifetime) history. More detail regarding research methods is

presented in Chapter 3 of this dissertation.

Research Questions and Hypotheses

This study seeks to supply new data on a subset of HCP (the medical laboratory

microbiologist) who may be at higher risk for developing LTBI but have been

understudied. Descriptive study output includes the overall self-reported tuberculin skin

test positivity rate and how it varied across demographic and work-related characteristics. In addition, the proportion of (a) infected workers who self-reported as having been prescribed preventive treatment, (b) those initiating this treatment, and (c) those initiating treatment who encountered barriers to treatment adherence (medication side effects), as well as how these measures varied across demographic and work-related characteristics, have been reported in this dissertation study.

Specific research questions addressed in this quantitative study are as follows:

- Research Question 1: What is the relationship of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience with self-reported lifetime tuberculin skin test (TST) positivity?

  o Null Hypothesis: There is no statistical association between self-reported individual independent variables of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience and the dependent variable of self-reported lifetime TST positivity.

  o Alternate Hypothesis: There is a statistical association between self-reported individual independent variables of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience and the dependent variable of self-reported lifetime TST positivity.

The three independent variables were analyzed using bivariate analysis to determine odds ratios and were evaluated as a group using the individual statistically

significant associations in a multiple regression analysis predicting the most

parsimonious model for self-reported lifetime TST positivity.

- Research Question 2: What is the relationship of history of BCG

  immunization, place of birth (U.S. or foreign), and years of laboratory

  experience with preventive treatment noninitiation among those individuals

  prescribed treatment for a positive tuberculin skin test?

  - o Null Hypothesis: There is no statistical association between self-reported

    individual independent variables of history of BCG immunization, place

    of birth (U.S. or foreign), and years of laboratory experience and the

    dependent variable of preventive treatment noninitiation.

  - o Alternate Hypothesis: There is a statistical association between self-

    reported individual independent variables of history of BCG

    immunization, place of birth (U.S. or foreign), and years of laboratory

    experience and the dependent variable of preventive treatment

    noninitiation.

The three independent variables were analyzed using bivariate analysis to

determine odds ratios and were evaluated as a group using the individual statistically

significant associations in a multiple regression analysis predicting the most

parsimonious model for treatment noninitiation.

- Research Question 3: What is the relationship of history of BCG

  immunization, place of birth (U.S. or foreign), and years of laboratory

experience with barriers to treatment adherence (medication side effects) among those initiating preventive treatment for a positive tuberculin skin test?

- o Null Hypothesis: There is no statistical association between self-reported individual independent variables of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and the dependent variable of barriers to treatment adherence (medication side effects) as identified using the Brief Medication Questionnaire (BMQ) in those respondents ever having initiated preventive treatment for a positive tuberculin skin test.

- o Alternate Hypothesis: There is a statistical association between self-reported individual independent variables of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and the dependent variable of barriers to treatment adherence (medication side effects) as identified using the Brief Medication Questionnaire (BMQ) in those respondents ever having initiated preventive treatment for a positive tuberculin skin test.

The three independent variables were analyzed using bivariate analysis to determine odds ratios and were also evaluated as a group using the individual statistically significant associations in a multiple regression analysis predicting the most parsimonious model representing barriers to treatment adherence (presence of medication side effects) by analysis of BMQ scores.

Table 1 represents a summary of the research questions, variables, scale of measure, and analysis used in this study. For more detail, please refer to Chapter 3 and the study code book (Appendix E).

Table 1

Summary of Research Questions, Variables, Scale of Measure, and Analysis

Research questions	Variables	Scale of measure	Analysis
Research Question 1: What is the relationship of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience with self-reported lifetime tuberculin skin test (TST) positivity?	Dependent: Self-reported lifetime TST positivity (no/yes)	Dichotomous/nominal	Bivariate analysis, logistic regression
	Independent: History of BCG immunization (no/yes)	Nominal	
	Place of birth (U.S. or foreign)	Nominal	
	Years of laboratory experience (years as range categories)	Nominal	
Research Question 2: What is the relationship of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience with preventive treatment noninitiation among those individuals prescribed treatment for a positive tuberculin skin test?	Dependent: Self-reported initiation of preventive treatment (no/yes)	Dichotomous/nominal	Bivariate analysis, logistic regression
	Independent: History of BCG immunization (no/yes)		
	Place of birth (U.S. or foreign)	Nominal	
	Years of laboratory experience (years as range categories)	Nominal	
		Nominal	
Research Question 3: What is the relationship of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience with self-reported barriers to treatment adherence (medication side effects) among those initiating preventive treatment for a positive tuberculin skin test?	Dependent: Barriers to treatment adherence (using the Brief Medication Questionnaire: BMQ score of ≥ 1 is positive for presence of medication side-effect barriers (Svarstad et al., 1999) (barriers absent/no; barriers present/yes)	Dichotomous/nominal	Bivariate analysis, logistic regression
	Independent: History of BCG immunization (no/yes)	Nominal	
	Place of birth (U.S. or foreign)	Nominal	
	Years of laboratory (years as range categories)	Nominal	

Theoretical Base

The research was conducted as a quantitative study based on the epidemiologic triad theoretical model. The epidemiologic triad is used to describe the occurrence of disease as linked to host and environment. Texts have articulated use of this triangle in several ways involving spread of infectious diseases from an epidemiologic perspective (Rockett, 1999; Smith, 2002; Williams & Nelson, 2007). Constructs of the triad model originated in the mid-1800s (Smith, 2002). One of the first pieces of literature supporting the development and formal use of the epidemiologic triad involved studies of infectious diseases of fish (Snieszko, 1974). (More detail regarding theory and this literature review may be found in Chapter 2.) In the epidemiological triad model, emphasis is on the relationship between agent, host, and environment (Rockett, 1999; Smith, 2002). Constructs as related to the survey questionnaire are as follows:

1. Agent: Tuberculosis bacterium is considered the agent. Presence of the agent was measured by asking these written survey questions of the survey respondent:

   o Lifetime history of positive TST? (Research Question 1)

   o Ever received an interferon gamma-releasing assay (IGRA) blood test and was the result "positive"?

   o Lifetime history of active TB?

   o Nonoccupational contact with anyone diagnosed with active TB?

2. Host: The host is the human reservoir who becomes infected and sheds the bacterium (through sputum or expelled fluids) by coughing or through other

contact, thereby shedding and spreading the infection to new hosts (Rockett, 1999). Host characteristics may include factors of resistance (strengthened resistance may occur through BCG immunization or preventive treatment initiation to stop infection once an individual has been diagnosed). Information regarding the construct of host was collected through the following questions:

o Ever received a BCG immunization? (Independent Variable 1)

o Ever initiated preventive treatment for a positive TST? (Research Question 2)

3. Environment: Environmental conditions contribute to the spread of agent and include overcrowding, poor ventilation, and bad sanitation (usually present in developing countries, according to Heymann [2008]). Environmental conditions might also include exposure to agent through lack of, or improper use of, engineering controls or personal protective equipment in the microbiology lab setting (CDC, 2009). Barriers to preventive treatment initiation may also be considered environmental (medication side effects) and act as barriers to treatment adherence (Svarstad et al., 1999). Information regarding the construct of environment was collected through the following questions:

o Place of birth (U.S. or foreign)? (Independent Variable 2)

o How many years worked in a laboratory setting? (Independent Variable 3)

o What type of laboratory work was performed?

o   If anti-TB medication was ever initiated, how well did it work? Were the

medications bothersome? (Taken from the Brief Medication

Questionnaire, Svarstad et al., 1999; Research Question 3)

These interconnected factors can lead to disease. In this research, TB infection

(latent or active) is the disease outcome of interest (Figure 1):
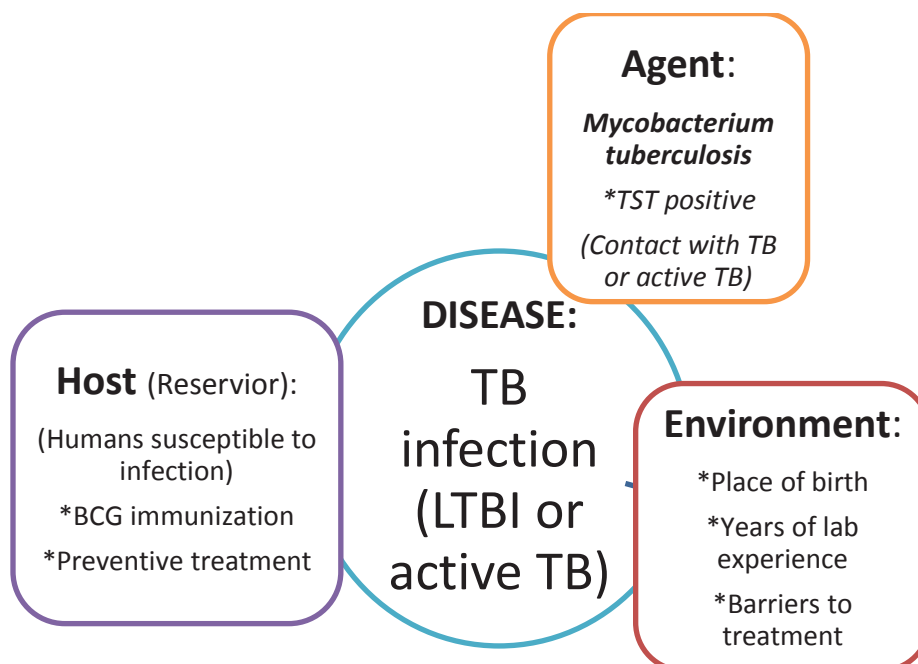
Figure 1. TB infection (LTBI or active TB) as an outcome of the constructs associated
with the epidemiologic triad model.

With regard to the dependent and independent variables of this study, the research

tested hypotheses as they related to the theory of the epidemiologic triad model by first

identifying presence of agent by measuring lifetime prevalence of self-reported tuberculin

skin test (TST) positivity and TST positivity risk factors in the selected U.S. medical

laboratory microbiologist subpopulation of HCP. TST has been used historically in the

identification of the latent (and sometimes, active) TB infection agent in humans.

Second, in those respondents self-reporting a lifetime history of TST positivity, the

remaining host and environmental variables were measured (see Table 2).

Table 2

Summary of Constructs and Relationship to Epidemiologic Triad Model

Research questions	Variables (Constructs)	Relationship to the model
Research Question 1: What is the relationship of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience with self-reported lifetime tuberculin skin test (TST) positivity?	Dependent: Self-reported lifetime TST positivity	Agent
	Independent: History of BCG immunization	Host
	Place of birth (U.S. or foreign)	Environment
	Years of laboratory experience	Environment
Research Question 2: What is the relationship of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience with preventive treatment noninitiation among those individuals prescribed treatment for a positive TST?	Dependent: Self-reported initiation of preventive treatment	(Where agent has already been established) Host
	Independent: History of BCG immunization	Host
	Place of birth (U.S. or foreign)	Environment
	Years of laboratory experience	Environment
Research Question 3: What is the relationship of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience with barriers to treatment adherence (medication side effects) among those initiating preventive treatment for a positive TST?	Dependent: Barriers to treatment adherence: using the Brief Medication Questionnaire score; a score ≥ 1 is positive for medication side-effect barriers (Svarstad et al., 1999)	(Where host preventive initiation of treatment has already been established) Environment
	Independent: History of BCG immunization	Host
	Place of birth (U.S. or foreign)	Environment
	Years of laboratory experience	Environment

The epidemiologic triad model is relevant to this research for three reasons. First, given the increase in foreign-born immigrants entering the HCP pool (Clearfield & Batalova, 2007) and the increased exposure (contact) with TB in specific workplaces (CDC, 2005b), it was reasonable to surmise that medical laboratory microbiologists in the United States might be at greater risk of reporting TST positivity than other HCP groups (Garber et al., 2003). Second, given the inconsistencies in numbers of U.S. HCP who do not initiate preventive treatment (Garber et al., 2003; Hirsch-Moverman et al, 2008), it was reasonable to surmise that this subpopulation could also be at risk of treatment noninitiation. And finally, given the reports that barriers to treatment adherence such as medication side effects prevent treatment completion in HCP (Camins et al., 1996), it was reasonable to surmise that this subpopulation might also be at risk for experiencing these barriers. In all three scenarios, the risk of acquiring TB infection (disease outcome reflected as TST positivity) was conjectured to be associated with (a) the exposure to tubercle bacilli (agent); (b) a lack of preventive treatment (host); and (c) place of birth, years of exposure, and barriers to treatment (environment).

The final analysis leading to summarization of descriptive data on the chosen study population and parsimonious models pertaining to the research questions have been discussed as they relate to the triad model. The resulting conclusion comments more broadly on the relevance of this study's findings to the epidemiologic triad model as it pertains to the overarching problem of identifying and halting the spread of tuberculosis among U.S. HCP, specifically medical laboratory microbiologists.

Definition of Terms

The following terms are definitions of technical terms, jargon, or special word uses found in this study. Some terms are operational in nature and will be so designated. Detail of coding terms will be described in Chapter 3.

Acid-fast bacilli (AFB): Bacteria belonging to the genus *Mycobacteria*, distinguished by their ability to retain specific stains after an acid solution rinse. AFB may include *Mycobacterium tuberculosis complex*, as well as nontuberculosis mycobacteria. Additional testing is needed in order to differentiate *Mycobacterium tuberculosis* (MTB) from other mycobacteria (NTCC, 2010).

Active tuberculosis: Illness in which TB bacteria actively multiply. These bacteria usually attack the lungs of the body. The case patient is infectious and symptomatic and may cough up blood and present with chest pain. The infected individual may spread TB to others while in this active disease state (NTCC, 2010).

American Society for Clinical Pathology (ASCP); ASCP Board of Registry (BOR): A U.S. certification registry established in 1928 for medical laboratory professionals, composed of members from different specialties or areas of responsibility within the medical laboratory scenario (ASCP, 2009).

Bacille Calmette-Guérin immunization (BCG): A vaccine for tuberculosis named after French scientists Calmette and Guérin. This vaccine has been used to reduce risk of TB disease in infants and children. Commonly used in highly TB-endemic countries, BCG use in adults is controversial (NTCC, 2010). For the purposes of this study, BCG immunization refers to the self-reported lifetime history of ever receiving BCG.

Biological safety cabinet (BSC): A BSC is a laminar flow hood used in biosafety levels greater than Level 2, where aerosol-generating manipulations are contained.

Brief Medication Questionnaire (BMQ): The BMQ is a validated survey questionnaire tool used for screening patient adherence to treatment, as well as barriers to adherence (Svarstad et al., 1999).

Contact: Refers to individual who has been exposed to *M. tuberculosis* infection, and possibly contaminated, by the sharing of air space with an individual sick with active TB (NTCC, 2010).

Culture: Laboratory test in which patient specimens (sputum, body fluids, or tissues) are processed and plated to special media in order to grow TB bacteria. Growth of MTB on culture media typically takes 2-4 weeks (NTCC, 2010).

Directly observed therapy (DOT): Strategy designed to help with adherence to LTBI treatment. A healthcare worker witnesses the patient swallow each dose of prescribed medication (CDC, 1999; NTCC, 2010).

Droplet nuclei: Small droplets (1 to 5 microns in diameter) that may be expelled into the air as an individual with active TB coughs or sneezes. Droplet nuclei can remain airborne for several hours, depending on environmental conditions (NTCC, 2010).

Drug-resistant TB: TB disease caused by MTB bacteria that are resistant (cannot be killed) to at least one of the first-line antituberculosis drugs (NTCC, 2010).

Epidemiological triad: A model used to describe the occurrence of disease as linked to host and environment. By breaking one of the three triad links, the occurrence of disease is stopped (Rockett, 1999; Smith, 2002).

Exposure: Condition of being subjected to or in contact with an infectious agent, such as the TB organism; exposure does not guarantee infection (NTCC, 2010).

Extensively drug-resistant tuberculosis (XDR TB): TB disease caused by infection with a TB strain that is resistant to INH and RIF, plus additional resistance to any fluoroquinolone antibiotic and at least one of the following: amikacin, kanamycin, or capreomycin (NTCC, 2010).

First line TB drugs: Initial drug therapy for treatment of TB. Includes isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin (CDC, 1999).

Foreign-born persons: Individuals born outside the United States; foreign-born persons from TB-endemic countries are "more likely to become exposed to and infected with TB" (NTCC, 2010, p. 9). For TB surveillance, a *U.S.-born person* is defined as someone born in the United States or its associated jurisdictions (U.S. territories include American Samoa, C.N.M.I. [Commonwealth of Northern Mariana Islands], Guam, Puerto Rico, U.S. Virgin Islands), or someone born in a foreign country but having at least one U.S.-citizen parent (CDC, 2012). For purposes of this study, foreign-born persons are not U.S.-born.

Health belief model (HBM): A model used to explore why populations tend not to complete LTBI treatment (Glanz, Lewis, & Rimer, n.d.).

Healthcare personnel (HCP); healthcare worker (HCW): Workers in healthcare organizations such as hospitals, clinics, nursing homes (NTCC, 2010). The preferred terminology is *HCP*, where HCP refers to "all paid and unpaid persons working in health-care settings who have the potential for exposure to case patients and/or to

infectious materials, including body substances, contaminated medical supplies and equipment, contaminated environmental surfaces, or contaminated air" (U.S. Department of Health and Human Services, 2008, para. 1).

Induration: In the skin test reaction, the area of firmness produced by immune-cell infiltration in response to intradermal introduction of tuberculin antigen. The area is measured by palpation. Results are recorded in millimeters in order to classify as a positive or negative skin test (NTCC, 2010).

Interferon-gamma release assay (IGRA) or Interferon (IFN)-γ assay: Recently described in vitro whole blood test used to detect a component of cell-mediated immune reactivity to the *M. tuberculosis* bacteria. Interferon-gamma is released from sensitized lymphocytes in specially processed whole blood (NTCC, 2010).

Isoniazid (INH): A first-line treatment agent for latent and active TB (NTCC, 2010).

Laboratory work: For this study, *years of laboratory work* refers to clinical or medical laboratory experience and includes training as well as paid and unpaid work in areas where testing was performed on clinical specimens, controls, or isolates.

Latent tuberculosis infection (LTBI): Known as *TB infection*; the infected carry the TB organism but do not have TB disease; the infected are asymptomatic and noninfectious. These individuals usually demonstrate a positive tuberculin skin test reaction (CDC, 1999). LTBI is inactive TB; however, latent infection may lead to active TB if preventive treatment is not received (NTCC, 2010).

Lifetime prevalence (period prevalence): For the purposes of this study, lifetime prevalence refers to the proportion of the population with self-reported TST positivity (a given condition) over a specified time period (past and present lifetime of the individual study participant).

Medical laboratory microbiologists: For the purposes of this study, this terminology refers to the group of members registered with and designated by ASCP as primarily working in the area of the laboratory known as *Microbiology/Mycology/ Parasitology/Virology.*

Microbiology/Mycology/Parasitology/Virology: Primary area of work responsibility as designated by ASCP (INFOCUS Marketing, 2011). For the purposes of this study, ASCP member registrants designated as working in the area of *Microbiology/Mycology/Parasitology/Virology* will be referred to as *medical laboratory microbiologists*.

Multidrug-resistant tuberculosis (MDR TB); multi-drug resistant latent tuberculosis infection (LTBI): TB caused by a strain resistant to more than one anti-TB drug; usually resistant to isoniazid and rifampin. May also refer to LTBI caused by contacts of confirmed resistant cases (NTCC, 2010).

Mycobacteriology: Laboratory department responsible for processing and testing specimens for *Mycobacteria* (MTB and nontuberculosis).

N-95 respirator: Personal protective equipment device; a particulate respirator used to remove 95% or more of TB infected particles from air inhaled by individual wearing the respirator (NTCC, 2010).

Rifampin (RIF): A first-line agent for treating TB (NTCC, 2010).

Rifapentine (RPT): An antibiotic used for treating TB (Jereb et al., 2011).

Treatment adherence: Following a recommended course of treatment by taking all prescribed medications for the entire length of time (CDC, 1999).

Treatment barrier; treatment adherence barrier; barriers to treatment adherence: Anything that prevents a case patient from adhering to a treatment regimen (CDC, 1999). For the purposes of this study, screening for possible barriers to treatment adherence (leading to nonadherence) was measured as the reporting of medication side effects using the Belief Screen portion (Part A) of the Brief Medication Questionnaire (Svarstad et al., 1999).

Treatment initiation; preventive treatment initiation: Begin taking prescribed anti-TB medications. For the purposes of this study, treatment initiation refers to starting or beginning treatment, even if treatment was not completed. For this study, *noninitiation* refers to never commencing prescribed anti-TB treatment.

Treatment of LTBI: Treatment with medication that prevents development of active TB disease (CDC, 1999; CDC, 2005).

Treatment nonadherence: Inability or refusal to take TB drugs as prescribed (CDC, 1999). For the purposes of this study, treatment nonadherence was measured in terms of self-reported completion of an entire prescribed course of treatment.

Tuberculin skin test (TST); Mantoux skin test method: A skin test performed by intradermal injection of 0.1 mL of purified protein derivative (PPD) tuberculin solution to the forearm. Skin area is read for reaction 48 to 72 hours after injection. Conversion

from a negative to a positive reading occurs in an individual undergoing repeated testing. An increase in reaction size by $\geq$ 10mm within 2 years is considered positive and indicates recent MTB infection. A positive (reactive) result may also occur on the very first attempt at TST testing of an individual. False-negative reactions may occur in a person having a recent infection or in a child under 6 months of age; false-positive reactions may occur because of infection with nontuberculosis mycobacteria or by history of BCG immunization (NTCC, 2010).

Tuberculin skin test (TST) convertor: For this study, a TST convertor was identified as an individual who ever received a verbal or written report of a positive TST result from a healthcare or occupational services provider, and had received a negative TST result prior to that point in time.

Tuberculin skin test (TST) positivity or TST status: For the purposes of this study, TST status refers to a self-reported lifetime history of positive TST by the survey participant. The respondent was asked if he or she was ever told by a health department employee, occupational health department employee, or other provider (doctor) that his or her TST was positive. The term *status* may refer to a history of either positive or negative TST.

Tuberculosis: Symptomatic disease caused by *Mycobacterium tuberculosis* bacteria (tubercle bacilli).

Tuberculosis Adherence Determination Questionnaire (TBADQ); Tuberculosis General Adherence Scale (TBGAS): Validated survey questionnaires in which self-reported adherence to tuberculosis medication treatment is gauged using a Likert scale

(McDonnell, Turner, & Weaver, 2001). (These scales were discussed but not used in this research because of lengthy questionnaire presentations and applicability to patients with active TB disease and not latent disease.)

Assumptions

The following assumptions are facts assumed to be true but not actually verified:

- The postal list addresses on file of ASCP registrants were assumed to be current and correct for use in mailing the marketing packet designated for this survey campaign. Addresses on file were obtained from ASCP's only approved source, INFOCUS Marketing, Inc. This marketing source has reported an estimated loss of no more than 1% of addresses (S. Blake: INFOCUS Marketing Consultant, personal communication, September 17, 2012). I calculated the actual rate of returned mail. (Please refer to Chapter 4.)

- Correct and timely postal delivery service (with no mail lost) was assumed. All surveys placed in U.S. mail by respondents were assumed returned to the address as listed on the self-addressed return envelopes in a timely manner.

- The Brief Medication Questionnaire (BMQ) survey tool section used in this survey was assumed to have been validated as reported by its authors.

- This cohort had contact with case patient specimens in the work environment. These data were collected by asking respondents to designate the specific microbiology sections (or other areas of the laboratory) in which they worked or had worked in the past.

These assumptions are necessary in the context of this study in order to address response rate as a function of the mailing process, to avoid revalidating the BMQ questions, and to justify use of the chosen cohort's occupational specimen contact.

Limitations

The following limitations were potential weaknesses of the study:

- The complete research survey tool is a questionnaire designed for the study population of ASCP professional health care personnel and is not necessarily generalizable to other groups. U.S. medical laboratory microbiologists belonging to other registry groups were not included in this survey.

- Questions on the questionnaire may be inherently flawed. To avoid problems associated with the question structure, the questionnaire was pretested and pilot tested. (Refer to Chapter 3 for detail.)

- The questionnaire design involved self-report, which may have caused inherent confusion in comprehension and interpretation of survey questions. Possible confusion was decreased by use of the same survey question syntax as used in previous research by Garber et al. (2003) and in the Svarsted et al. (1999) validated BMQ survey research.

- Use of a portion of the BMQ in the survey questionnaire, while useful in past research on general medication nonadherence, has not been implemented in anti-TB medication studies (Lavsa, Holzworth, & Ansani, 2011; Svarstad et al., 1999) until now. The question syntax was slightly modified in the questionnaire to reflect past rather than current medication use.

- Lack of willingness to respond to questions about self-reported TST may have led to attrition. (Questionnaires of those who chose not to participate in the survey were not included in the analysis.) Confidentiality was stressed on each survey cover letter. Information on nonrespondents was not collected for several reasons: (a) this survey was anonymous; (b) ASCP management reported collecting individual demographic data as they pertained to the individual member profile but did not allow access to this data; and (c) ASCP does not assess demographic data as it pertains to the group demographic (J. Johnson: ASCP Customer Service Representative, personal communication, September 9, 2012).

- Self-reported nature of the study: Interpretation of what survey respondents were told in the past about TST status may have led to recall bias. Although educated health care personnel, these respondents may have comprehended the questions but not remembered correctly (or at all) with regard to TST results, history of BCG immunization history, preventive treatment prescription or initiation, or treatment adherence barriers as having transpired in the past. In addition, records detailing millimeters of TST induration were not collected, nor did any medical records undergo review.

- Misclassification bias: Some workers may have performed microbiology duties in past work although their work was not characterized as such. An attempt to assess and document both past and present microbiology work in this study took place in order to decrease misclassification bias.

- Low response rate may have occurred due to the nature of the single-stage mail questionnaire process. An announcement postcard preceded mailing of the actual survey packet by 1 week in an attempt to improve response rate. In a different questionnaire mailing to an ASCP study population, response rate was only 22.5% (Clark, 2008). Historically, low response rate may lead to selection bias and may limit precision among results as they apply to the full population. An incentive, a contribution to the ASCP Scholarship Fund, was added in order to improve survey response. With every 1,000 completed surveys returned on time, $250 (U.S.) was donated on behalf of the study group to the ASCP Scholarship Fund. A charitable contribution was chosen as an incentive because incentives have been known to increase survey response rates by up to 78% (Mangione, 1995).

- Study results were based only on those questionnaires returned within the allotted time frame. Late responses postmarked more than 1 month past due date were not included, eliminating a portion of the survey sample results. Notation in large case letters was made on the front of each survey consent form and on the questionnaire itself to denote the time frame by which surveys were due.

- Limitations of the use of tuberculin skin test (TST) as a tool include possible reporting of false results due to BCG immunization interference and misreading of skin reactions leading to false positive and false negative

results. These problems are inherent in the use of the TST and have been reported as such in previous research.

Delimitations

The scope of this study includes addressing the following specific aspects of the research problem:

- Choice of study population: Medical laboratory scientists were chosen as a focus for this study because prior literature sporadically addressed regional subpopulations of health care personnel and laboratory personnel in the United States. The ASCP membership provided an opportunity to access a national board of registry whose participant members actively work in the medical laboratory field. The cohort with the area of responsibility of "Microbiology/Mycology/Parasitology/Virology" was chosen as the subpopulation of microbiologists for this study because a literature review revealed that this group is at high risk of infection with tuberculosis due to repeated exposure to actual case patient specimens. This group was accessed through the only marketing firm approved by ASCP to provide mailing lists, INFOCUS Marketing. Postal mailings were used rather than email lists because the email list on file with INFOCUS Marketing did not represent the complete cohort. At the time of this study, current email lists represented approximately one-third to one-half of the cohort only (INFOCUS Marketing, 2011). INFOCUS Marketing allowed access to the mailing list based on prior approval of the intended survey packet by ASCP. I paid processing fees based

on a written agreement with INFOCUS Marketing (INFOCUS Marketing, 2011). INFOCUS Marketing reprinted all required survey packet materials and mailed them to the ASCP mailing list of members on my behalf.

- Choice of method: A quantitative, cross-sectional survey design using a structured written questionnaire composed of closed-ended questions was used because this method is inexpensive and provides an easy way to obtain data. Self-reported data were expected to include some bias (see section on limitations). However, the use of educated medical laboratory personnel (who have knowledge of tuberculosis and use of the TST) in this survey decreased some of the variability in reporting confusion as compared to use of other HCP populations.

The scope of this study has been hereby bounded by both aspects of the study population and study design:

- The population of interest was the ASCP cohort of registrants known as members of the "Microbiology/ Mycology/Parastiology/Virology" area of responsibility with U.S. mailing addresses that were most currently on file with ASCP during Spring 2013. Other ASCP categories of members were not included in this study. The reason for focusing on the full cohort of those members reported to work primarily in microbiology was that these medical laboratory scientists have a greater occupational exposure to tubercle bacilli by virtue of the type of work they perform (direct handling and processing of case patient specimens). The full complement of the group at the time of

initial inquiry numbered at least 5,138 records (INFOCUS Marketing, 2011);

the actual membership cohort numbered 4,335 at the time of mailing. The

focus on using ASCP certified registrants was due to the presence of the

ASCP Board of Registry as the most prevalent registry for all medical

laboratory scientists in the United States (ASCP, 2009).

- The cross-sectional nature of this survey design, allowing for prevalence of

  self-reported lifetime TST-positive status reporting, is not a reflection of

  incidence. This study was intended to serve as a single-stage sampling

  method, a snapshot in time of an individual's status to date. This survey

  design may be referred to as a lifetime prevalence of any past and present TST

  positivity, preventive treatment initiation (and subsequently calculated

  noninitiation), and barriers to treatment adherence (medication side effects).

- The scope of self-reported demographics and history studied in this population

  (in order of questionnaire sections) included (a) gender, (b) age, (c) type and

  years of laboratory experience, (d) place of birth (U.S. or foreign), (e) history

  of prior BCG immunization, and (f) history of active TB and/or

  nonoccupational exposure. These items have been the basis of previous

  research. In addition, history of ever receiving an interferon gamma-releasing

  assay (IGRA) was explored, as it is a new blood test used now by many

  occupational health providers to replace the TST (Jereb et al., 2011).

- Self-reported lifetime TST-positive individuals who indicated ever initiating

  preventive treatment responded to two additional closed-ended questions

allowing assessment of barriers to treatment adherence (which included drug

side effects and bothersome features). These two questions were derived from

one validated section of the Brief Medication Questionnaire (BMQ). The

BMQ has been found to be brief and valid in screening for treatment

nonadherence barriers (Lavsa et al., 2011).

- This study was bounded by the epidemiologic triad model and the model's associated characteristics of infectivity.

- Time: Respondents were instructed to return study questionnaires within 4 weeks of receipt of mail delivery, in line with acceptable time lines for data collection (Mangione, 1995). Returns postmarked more than 1 month late (8 weeks after [first class] mailing of study packet) were not analyzed. Handling of incomplete questionnaires is discussed in Chapter 3.

Because this study was limited to ASCP professional health care personnel

reportedly working in the primary area of responsibility of Microbiology/Mycology/

Parasitology/Virology, results are not necessarily generalizable to other health care

professionals or to other groups.

Significance of the Study

These results make an important contribution to the existing literature, enhancing

social change initiatives through identifying prevalence and associated risk factors of

self-reported lifetime tuberculin skin test positivity, preventive treatment noninitiation,

and barriers to treatment adherence (presence of medication side effects) in the U.S.

medical laboratory microbiologist subpopulation of healthcare personnel. Strategies to

promote improved understanding of TB prevention treatment in this high-risk

subpopulation may be achieved by using knowledge obtained from this research.

Positive social change at this level results in the improvement of human and social

conditions by contributing to decreases in TB disease mortality and morbidity and proper

stewardship of ever-decreasing resources. Targeted strategies intended to reduce

prevalence of positive TSTs among healthcare personnel and improve treatment initiation

rates, as well as reduce barriers to treatment adherence, are important in preventing TB

reactivation to active TB disease (CDC 2005a, 2005b; Charles P. Felton National

Tuberculosis Center, 2005; Fitzpatrick et al., 2005). For example, one connection

between actual results that this study has generated and how specific use of these results

in making changes may occur is within the ASCP professional registry itself. This

research has demonstrated that this group of HCP is indeed at great risk for increased

TST positivity and that foreign birth is one associated risk factor. Educational strategies

designed to target specific personnel when first certifying with ASCP or upon

membership renewal may assist in promoting treatment initiation. Any barriers to

treatment adherence (such as medication side effects) in this same group may be

addressed by educational interventions designed to alleviate these barriers. Additional

research among other certification groups of ASCP might follow, adding to the initiative

among all laboratorians to halt the spread of TB.

This research is significant in order to assist in identification of subpopulations at

risk of developing active TB. The literature has addressed prevalence and predictors of

tuberculin skin test positivity in several subpopulations of healthcare personnel.

However, a literature review has revealed that a single study has neither addressed U.S. medical laboratory microbiologists nor been conducted from the perspective of a national registry cohort. This study differs from previous studies by addressing the U.S. medical laboratory scientist population identified by ASCP as working in the area of responsibility known as "Microbiology/Mycology/Parasitology/Virology." By identifying the prevalence of (a) self-reported lifetime tuberculin skin test (TST) positivity, (b) preventive treatment noninitiation, and (c) barriers to treatment adherence (the presence of medication side-effect barriers as measured by the Brief Medication Questionnaire) and predicting models of associated risk factors for each in this subpopulation, the overall health of medical laboratory HCP, families, patients, and coworkers will improve due to focused preventive treatment with recommended regimens (Lambreghts, 2008). In addition, this study assesses gender, age, type of laboratory work, and nonoccupational contact as confounders or modifiers. An evaluation of how each outcome varies across demographic and work-related factors has taken place and is represented in Chapters 4 and 5. The collection of these data and subsequent analysis support an epidemiologic model for describing this ASCP subpopulation.

The sharing of research findings with the ASCP and its membership, other healthcare professionals, and the public health community at the close of this study will assist in bringing the issue of TST positivity from an historic lifetime prevalence perspective and aspects of preventive treatment noninitiation and adherence barriers to light. In addition, published findings will be shared with the owners of the BMQ survey instrument (Svarstad et al., 1999). Although newer interferon-gamma blood tests

promise more accurate identification of LTBI status, at present, the TST remains a

recommended, inexpensive method for detecting LTBI among healthcare personnel

(CDC, 2005a). Gauging TST positivity among a national HCP group such as this ASCP

subpopulation aids public health professionals in further understanding LTBI among U.S.

medical laboratorians.

The first step in controlling the burden of active TB disease is to identify LTBI

and active TB disease in at-risk populations and initiate appropriate treatment (CDC,

2000). As a result of this study, positive social change is expected to occur through the

description of an at-risk population in order to assist in reducing TB mortality and

morbidity and improving stewardship of TB control resources. An overall decrease in

monetary costs of TB may follow. The Centers for Disease Control and Prevention

(CDC, 2002) have estimated that TB-related costs approach $1 billion in the United

States each year.

This study promotes greater understanding of LTBI (prevalence as measured with

TST history) among the cohort of medical laboratory microbiologists, a subpopulation of

healthcare personnel in the United States. The CDC (2002) has reported that to maintain

the current decline in TB incidence in the United States, timely treatment management of

TB by "prevention of transmission through infection control" (CDC, 2002, p. 6) is of

great importance.

Summary and Transition

In summary, this research study is intended to provide a snapshot of TST

positivity prevalence, risk factors, treatment noninitiation, and quantitative exploration of

barriers to treatment adherence (medication side effects) among a subpopulation of U.S. HCP known as medical laboratory microbiologists. Access to the scientists registered with ASCP has provided an opportunity to compile and analyze new data on laboratorians while comparing results to other well-documented studies, such as those reported by Garber et al. (2003). The key points of this research were to

1. Survey this HCP subpopulation for prevalence of self-assessed TST results throughout the lifetime and determine risk factors of self-reported lifetime history of TST positivity;

2. Determine treatment initiation rates among self-reported TST ever-positive individuals who were prescribed preventive treatment and predict a model for risk factors of preventive treatment noninitiation;

3. Determine barriers to treatment adherence (medication side effects) among those ever initiating preventive treatment using the belief screen portion (Part A) of the BMQ and predict a model for barriers to treatment adherence (due to medication side effects) using BQM scores; and

4. Evaluate how each outcome varied across demographic and work-related factors.

The remainder of this study is described in Chapters 2 and 3, following prescribed guidelines of the Walden University School of Health and Human Services. Chapters 4 and 5 of the dissertation cover study results and final discussion, describing data collection and analysis. Raw data table examples are provided.

Chapter 2, the literature review, addresses pertinent TB and LTBI literature as it pertains to descriptive epidemiology of (a) global, (b) U.S., and (c) HCP populations, and drill-down to the level of (d) the medical laboratory microbiologist. History of the tuberculin skin test and specifics on treatment initiation and nonadherence among HCP and the subpopulation of laboratorians are reviewed. Literature referring to the independent and dependent variables is scrutinized. Survey instruments used to determine adherence to treatment regimens and related barriers to treatment are explored and compared. A review of the literature as it pertains to public health prevention and control, as well as LTBI and TB theory and methods is presented.

Chapter 3, Research Method, discusses the intended use of the self-administered mail questionnaire for this quantitative survey method research. A thorough review and discussion of the operationalized definitions, questionnaire tool, as well as the validated survey tool, the BMQ (Svarstad et al., 1999) follow. Sample size requirement calculations are demonstrated. Intended methods for univariate, bivariate, and multivariate analysis are described in detail.

Chapter 4, Results, covers the actual research results as obtained during the mail survey of medical laboratory workers. Results are presented in table format, and analyses using Epi Info™ software (CDC, 2011c) are provided.

Chapter 5, Discussion, Conclusions, and Recommendations, discusses the interpretation of the research results in detail. Conclusions from this study and recommendations for future research are provided.

Chapter 2: Literature Review

Introduction

Halting the global spread of tuberculosis (TB) is one of the significant public health challenges of this century (IOM, 2000; StopTB Partnership, n.d.; World Health Organization [WHO], 2010b). Identification and treatment of individuals at risk for developing LTBI and active TB are of the utmost importance in stopping TB's spread (CDC, 2002, 2003a), as well as in controlling costs. "In New York City alone, for example, the monetary costs for losing control of TB proved to be in excess of $1 billion" (IOM, 2000, p. 1). Losing control of the spread of TB has led to emergence of drug-resistant strains (Bradford et al., 1996; WHO, 2001a, 2001b). These costs and resistance have been described as threats to "global stability and national security" (WHO, 2001b, p. 1).

For years, the tuberculin skin test (TST) has been the screening test of choice for identifying individuals infected with the latent (inactive) form of TB. Once identified, these individuals are targeted for preventive treatment. Although treatment is usually indicated in these cases, many individuals resist initiation of treatment or adherence to a prescribed course of treatment; identification of barriers to completion of treatment is needed to maintain control of TB (CDC, 2003a). Healthcare professionals (HCP), especially medical laboratory microbiologists, comprise a group of individuals thought to be at higher risk of acquiring TB infection than the general population, either through occupational exposure or from exposures outside the work area.

This chapter presents an overview of the following: (a) the historical background of *Mycobacterium tuberculosis* (TB) infection (including descriptive epidemiology and TB infection prevalence and risk factors drilled down from global to U.S. levels), (b) aspects of TB infection in healthcare personnel (HCP) and the laboratorian subpopulation, (c) the public health impact of TB infection, (d) the study's research variables, (e) relevant theories in TB research, and (f) design, research, and analysis methods. Addressing these topics is necessary in demonstrating the gap found while researching the literature: the lack of current information regarding TST positivity, treatment noninitiation, and treatment nonadherence (medication side-effect) barriers in specific groups of U.S. healthcare personnel, such as U.S. medical laboratory microbiologists. The content of this literature review will address TST-positivity prevalence among HCP, specifically what is known regarding the HCP subgroup of medical laboratory microbiologists. In addition, this review will focus on research methods used in obtaining TST positivity (prevalence) and risk factors compared with TST conversion (incidence) statistical data, preventive treatment initiation, and treatment nonadherence (barrier) data from several populations, but mainly focused on different HCP populations. Finally, the medical laboratory microbiologist population will be addressed.

Review of the Literature

Organization of the Review

The review of the literature begins with a brief description and background of the history of tuberculosis, the discovery and etiology of the *Mycobacterium tuberculosis*

(MTB) bacteria, clinical characteristics of TB infection, diagnosis, testing for TB infection, treatment, and descriptive epidemiology of TB as an infectious agent. Understanding prevalence and incidence, and risk factors as they pertain to the general population will be covered. More detail on the healthcare personnel (HCP) and then the laboratorian subpopulation follows, including literature pertaining to occupational risk, prevalence (TST-positivity) and incidence (TST-conversion), preventive treatment initiation, treatment nonadherence, and treatment barriers. Current recommendations for TB prevention and control are also discussed in detail.

A thorough description of the research variables as risk factors is presented, as well as a description of this study's specific research variables. Past research and history of theory as it applies to the current literature are reviewed, and current research regarding risk factors for infection with active and inactive TB infections is discussed in the context of the hypotheses under study. Finally, comparisons of relevant research and analysis methods are discussed in detail, and the gap is explained.

Search Strategy

Pertinent scholarly, peer-reviewed literature was identified through a search of databases using the search terms *TB* or *tuberculosis* and *tuberculin skin test* or *TST,* and/or *healthcare worker* or *HCW,* and/or *healthcare personnel* and/or HCP. A separate search was performed using the term *tuberculin skin test positivity*. Additional search terms included *mycobacteriology* or *laboratory,* as well as *self-reported. LTBI treatment* plus *initiation* or *adherence* or *nonadherence* and *healthcare worker* were also used in searching for scholarly articles. To obtain information on the validity of the self-reported

TST, the search terms *self-reported tuberculin skin test* plus *validity* were used. Initial

searches were limited to publications between January 1, 1980, and January 1, 2012.

Individual publications were first searched, including *Emerging Infectious Diseases*

(EID) and *Clinical Infectious Diseases (CID)*. PubMed, Academic Search Premier

within the EBSCO database, CINHAL within the EBSCO database, Google Scholar

database, and the dissertation database for ProQuest were searched using the search terms

listed above. If at any time an article was not located using traditional databases, the

Walden Library Document Delivery Service (Illiad) was used. Of great use was the

special search query using the phrase "*What's new for 'tuberculosis'*" in PubMed. I

received periodic emails from the My NCBI "*What's new*" search for results from the

National Center for Biotechnology Information (NCBI) at the U.S. National Library of

Medicine (NLM).

In addition to journal and database searches, reference lists of selected peer-

reviewed journal articles were reviewed to identify additional studies pertinent to this

review. This process was used most frequently. (Some historic and sentinel theory

articles dating from the 1940s, 1950s, 1960s, and 1970s were located using this latter

method.)

Inclusion criteria were as follows: articles with abstracts that focused on LTBI or

active TB among healthcare personnel (HCP), as well as among subgroups of clinical or

medical laboratorians. Article abstracts describing occupational risk factors were also

perused prior to retrieving the entire article from the source. TST positivity or TST

reactivity in cases of LTBI, especially among HCP, were added to the search inclusion

criteria. Studies related to TST conversion were added later, in an attempt to compare research methods and gain additional information on risk factors. Inclusion criteria included articles with a focus on LTBI or active TB treatment initiation (noninitiation) or treatment adherence (nonadherence). Later attempts at expanding the search criteria to include treatment adherence barriers among different populations and different disease outcomes were also added. Articles focusing on cross-sectional research methodologies (surveys and questionnaires) and epidemiologic triad models were highly desirable, as were articles using other research and analysis methods for purposes of comparison.

Relevance of the Literature to the Research Questions

This literature review is intended to evaluate the historical and current literature with regard to an overview of the different aspects of tuberculosis infection (latent and active), as well as with regard to the research questions as described in Chapter 1 of this study. In addition, a focus on the HCP subpopulation of medical laboratorians, specifically that of medical laboratory microbiologists as a subgroup, will take place. Much of the literature regarding etiology, epidemiology, and treatment was extracted from CDC and WHO resources. Those resources and the primary journal articles will be used to explain what is known about tuberculosis infection. This review will also attempt to answer the following questions: What is the relationship between history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and

- Self-reported lifetime history of tuberculin skin test (TST) positivity?
- Preventive treatment noninitiation among those individuals prescribed treatment for latent or active TB?

- Treatment adherence barriers (medication side-effects measured with the

    BMQ) among those initiating treatment for latent or active TB?

Overview of Clinical Tuberculosis

Discovery of Tuberculosis Bacteria

Tuberculosis, also known as TB, is considered an ancient disease. Egyptian

mummies dating back 4,000 years have produced evidence of tubercular decay

(Nobelprize.org, 2012). For centuries, TB has been described in the literature (CDC,

2011e). Hippocrates once noted that consumption was the most widespread and fatal

disease of his time (Nobelprize.org, 2012). Considered a death sentence to anyone

diagnosed with the disease (CDC, 2011e), TB became treatable after the 1940s and 1950s

with the development of antibiotics (Nobelprize.org, 2012).

Mycobacterium tuberculosis (MTB) bacteria were first described by Robert Koch,

a German physician and scientist. Koch's discovery and presentation of TB involved a

new staining method, which he demonstrated to an audience in 1882 during a medical

lecture (Nobelprize.org, 2012). Koch's staining method remains in use by laboratory

microbiologists to this day.

Following the establishment of tuberculosis as an infectious disease, antibacterial

drugs were developed, a significant landmark in the fight to control TB infection. Three

Nobel Laureates, Paul Ehrlich, Gerhard Domagk, and Selman Waksman, have been

largely credited for this early work. From 1944 to 1954, three drugs—streptomycin,

para-aminosalicylic acid (PAS), and isoniazid—became available for use in treating TB

(Nobelprize.org, 2012). The curative impact of these three drugs against inactive and

active TB infection was significant among individuals who could take a combination of drugs for an extended period of time. Today's anti-TB medications continue to require this combination of drugs taken over several weeks or months.

Etiology of Tuberculosis

Tuberculosis bacteria belong to the genus *Mycobacterium*, where over 150 different species have been identified to date (Behr, 2010). The majority of the *Mycobacteria* are nonpathogenic. Tuberculosis (TB) infections are caused by the species *Mycobacterium tuberculosis* (MTB) complex. The complex includes subspecies *M. tuberculosis, M. bovis (*cow*), M. africanum, M. canettii,* and occasionally *M. microti, M. caprae,* and *M. pinnipedii* (Heymann, 2008). Although the vast majority of human clinical cases are caused by *M. tuberculosis*, all of these organisms may produce clinically similar symptoms (Heymann, 2008). Many different strains of MTB exist worldwide, complicating all aspects of TB disease (Behr, 2010).

The *Mycobacterium tuberculosis* genome has been sequenced, revealing over 4,000 genes (Heymann, 2008). The complete genome sequence of *Mycobacterium tuberculosis* was published in 1998, accelerating the study of MTB pathogenesis (Cole et al., 1998; Mathema, Kurepina, Bifani, & Kreiswirth, 2006). The belief at the time was that human TB originated with the domestication of cattle, as linked to *M. bovis* (to be mentioned later in the discussion on immunization). However, Mostowy and Behr (2005) determined this to be improbable; rather, MTB belonged to the *Mycobacterium tuberculosis* complex. In 2009, researchers derived a phylogeny, a lineage for the *Mycobacterium* genus, in order to understand why MTB developed as a pathogen when

many other species within the genus are nonpathogenic (Veyrier, Pletzer, Turenne, &

Behr, 2009).

Clinical Characteristics of Tuberculosis Infection

   Manifestations. Clinical manifestations of tuberculosis infection may take one of

two forms: latent or active TB disease. Initial infection may go unnoticed. Although

individuals with either form are considered infected with bacterium belonging to the

Mycobacterium tuberculosis complex, clinical characteristics differ. For the purposes of

the remainder of this literature review, and because most public health research involving

tuberculin skin testing is in agreement on this point (CDC, 2005a, 2010a), discussion will

relate only to the *Mycobacterium tuberculosis* organism within the MTB complex.

   Latent infection. Latent TB infection (LTBI) is a condition in which persons

infected with the tuberculosis bacteria may harbor the bacteria without displaying

symptoms. The bacteria are inactive in this state, or dormant, and kept in check by the

body's immune system (Nobelprize.org, 2012). Although the individual does not feel

sick, the dormant bacteria may become active in the future for many different reasons.

Reports have indicated that "as many as one-third of all living beings are latently

infected" (Nobelprize.org, 2012, p. 2). While not every infected individual becomes sick,

about 5% to 10% of persons with normal immune systems will develop TB disease at

some point in their lives; this risk is the highest in the first 2 years after infection (CDC,

2011a, 2011b). Latent TB infection may persist throughout the entire lifetime of an

individual (Heymann, 2008).

Active infection. Active TB infection is a disease condition in which persons

infected with the tuberculosis bacteria harbor the bacteria and do indeed display one or

more symptoms. The TB bacteria have created a state of active disease after a short

period of incubation, or after reactivation of latency. The activation of latent TB may

occur in individuals with a weakened immune system, as in HIV-infected individuals.

"About one-third of the more than 40 million HIV/AIDS patients are co-infected with TB

bacteria" (Nobelprize.org, 2012, p. 2). During this time frame, these individuals begin to

exhibit symptoms of active disease and may be able to spread TB bacteria to others

(CDC, 2011e).

Although different parts of the human body can be affected in TB infection

(active disease), the lungs remain the primary cause for concern. General symptoms of

active TB disease may include (a) fever, (b) chills, (c) night sweats, (d) weight loss, (e)

loss of appetite, (f) fatigue, and (g) malaise (CDC, 2011b). According to CDC (2011b),

the primary symptoms of pulmonary TB disease include (a) cough lasting for 3 or more

weeks, (b) chest pain, and (c) coughing up blood or sputum. In extrapulmonary TB

disease, spinal TB disease may cause back pain, while TB disease of the kidneys may

present with blood in urine, and TB in lymph nodes may present as neck swelling (CDC,

2011a, 2011e).

Diagnosis: Medical Evaluation and Testing

A thorough medical history to detect risk factors for developing TB (active

disease) should include an individual's social, family, medical, and occupational

information (CDC, 2011b). A description of any symptoms or exposures to persons with

infectious TB should be documented. In addition, history of latent TB infection

(previous positive tuberculin skin test or blood test result) and information on any

treatment initiation and completion should be documented. If any of these risk factors

are present, a medical professional should suspect TB disease (CDC, 2011a, 2011e).

Once active TB disease is suspected, a physical exam should follow and include a chest

x-ray and bacteriological examination (tests for smear and culture).

The bacteriological examination is performed by a microbiology laboratory that

performs identification and/or susceptibility testing of *Mycobacteria tuberculosis* (MTB)

and other *Mycobacteria* species. Specimens are collected at a health center, clinic, or

hospital setting and sent to the laboratory for testing. (Of note, this examination and

subsequent handling of specimens poses a point of possible exposure to the laboratorian.)

CDC (2011b) guidelines for testing of the specimen (usually sputum) include the

following:

1. Proper collection of a specimen representative of the sputum, body fluid, or
   tissue under study,

2. Processing the specimen for microscopic examination of acid-fast bacilli
   (AFB) on smears,

3. Direct identification of specimen (using nucleic acid amplification test
   methods),

4. Culture (growth) and identification (of AFB bacteria), and

5. Drug susceptibility testing of the AFB bacteria.

Testing is intended to rule in or rule out MTB as soon as possible in order to implement infection control guidelines and initiate proper treatment of patient. Characteristics associated with active tuberculosis include cough persisting 3 weeks or more, insufficient treatment for a latent TB infection, cavitations on chest X-ray, positive AFB smear result, or positive AFB culture where MTB has been definitively identified (CDC, 2011a). While active TB disease is diagnosed using culture and direct microscopy techniques, inactive disease has been diagnosed historically using the tuberculin skin test (TST).

To test for TB infection (infection with *M. tuberculosis*), specific diagnostic tests may include the following:

- Mantoux tuberculin skin test (TST),

- Interferon-gamma release assays (IGRAs)—blood tests, and/or

- Smears and cultures, as mentioned in the previous section on Medical Evaluation.

CDC (2011e) has reported that a positive TST or IGRA indicates infection, but cannot serve to identify an active state of disease. Further medical evaluation is recommended at this stage.

Tuberculin skin test (TST). The tuberculin skin test (TST) has been used as an initial screening test for detecting LTBI and active TB in the United States. LTBI has been diagnosed historically using the tuberculin skin test (TST). The TST has been used to evaluate close contacts of individuals with active TB disease, to screen high-risk groups (immigrants, the immunosuppressed), and to screen healthcare personnel (CDC,

2005b). The TST has been used to examine an individual's antibody response to

Mycobacterium tuberculosis antigens present in purified protein derivative (PPD)

tuberculin solution (NTCC, 2010). The test, performed using the Mantoux technique, has

required injecting 0.1ml of 5 TU purified protein derivative (PPD) solution under the

forearm skin intradermally. A delayed hypersensitivity reaction is detectable and read

within a 48-72 hour time frame by a trained professional. The hypersensitivity reaction is

detectable within 2-8 weeks after initial infection (CDC, 2010a). In the United States, a

positive TST is determined by measuring zone size and combining these results with risk

of exposure to TB and risk of progression to active TB disease (Heymann, 2008).

According to CDC (2010a), the TST should be

- Interpreted the same as for individuals having received the BCG vaccine.

- Read in millimeters of skin induration and based on risk of exposure.

- Performed on HCP (and especially on mycobacteriology laboratory
  employees) considered to be at high risk of exposure.

Proper interpretation of the TST zone of induration size determines the need to begin

preventive treatment (Heymann, 2008).

Positivity. TST positivity is the consequence of an initially positive TST result or

conversion from a negative to a positive TST result over the long-term. An individual

may present with a positive TST result on the first attempt at skin testing or may have

converted from negative to positive status. (Conversion is discussed further in the next

section.) A positive TST result is considered a response indicative of exposure in some

form of latent or active infection with the TB organism and warrants further investigation by a healthcare provider (CDC, 2010a).

At present, prevalence of LTBI is estimated using the TST or the IGRA blood test and is useful as a baseline indicator. The resulting TST- or IGRA-positive result (indicating positivity) is a gauge of prevalence in a population provided the individual does not display characteristics of active TB disease. Examples of TST positivity and prevalence data will be discussed later in this chapter.

Conversion. Incidence of LTBI is currently estimated through a documented *conversion*, using the TST or the IGRA blood test. Use of the TST to determine conversion includes performing a two-step test with a negative baseline (CDC, 2010a). A subsequent positive TST indicates that conversion has occurred. This conversion means that the individual has experienced an exposure leading to infection, and this infection is usually latent (but may become active TB disease in some at-risk individuals). The conversion period must be documented, as it is a test reaction change occurring over a set time frame.

Examples of TST conversion have been well-documented in the literature. Among HCP at low risk of TST conversion are administrative personnel, demonstrated to have a TST conversion rate of 0.3% when compared with the clinical staff conversion rates of 1.1% to 1.5% reported in an Atlanta hospital from 1994-1998 (Larsen et al., 2002). In the same study, TST conversions among the BCG-vaccinated reached 20.0% (an increase suspected to be due to boosting), while nonBCG-vaccinated conversions were reported at 1.2%. Clinical laboratory staff convertor rates were as high as 6.6%

(second only to nurses) in one retrospective cohort study (Miller, Tepper, & Sieber, 2002). Years of employment within the same occupation were also a factor in the Miller et al. research. In the microbiology laboratory, considered a high-risk setting, a very high 11.4% TST conversion rate was reported in one study (Kraut et al., 2004).

Tuberculin skin test imitations and usefulness. Although the TST continues to be utilized as a test of choice in detecting inactive (latent) TB infection, the test is subject to several limitations. First, difficulty in proper placement of the purified protein derivative (PPD) or reading the results properly may lead to false positive or false negative results (CDC, 2011a). Second, false positive results can result from cross-reactivity caused by host exposure to other mycobacteria such as those included in the BCG vaccine (CDC, 2011a). No studies involving laboratorians and cross-reactivity exposures were located while performing this literature review. However, one study reported an absolute false positive prevalence rate of 0.1% (Canada) to 2.3% (India), depending on a country's prevalence of sensitization to nontuberculosis mycobacteria (Farhat, Greenaway, Pai, & Menzies, 2006). Third, immunosuppression of the host (such as in cases of HIV infection) may cause a falsely decreased response to the PPD (CDC, 2011a, 2011e).

One such example was a study in which a falsely elevated TST conversion rate was reported to be as high as 9.8% among a group of medical students. Only half of those were true TST convertors, determined by repeat testing with a different PPD material and read by a trained individual upon retesting (Wurtz, Fernandez, & Jovanovic, 1994). More detail on test limitations is presented in Chapter 3 of this dissertation.

Interferon-gamma assays (IGRA blood tests). In recent years, new IGRA blood tests have entered the market with the intended role of improving sensitivity and specificity over the TST for diagnosis of tuberculosis infection. These blood tests measure immune reactivity to *M. tuberculosis*. An infected individual's blood should release interferon-gamma (IFN-γ) from white blood cells when mixed with proteins derived from *M. tuberculosis* antigens. One visit to the laboratory for testing (as opposed to two for TST) and less cross-reactivity with BCG immunization and nontuberculosis mycobacteria (Mazurek et al., 2001) are definite advantages. High expense and special specimen processing requirements are limitations to using this test over the TST. In addition, these blood tests are like the TST in that impaired immune function in an individual may decrease test sensitivity, leading to indeterminate or false negative screening test results (Heymann, 2008). The IGRA tests are available in limited use at present, and several researchers have stated that these assays are now widely recognized as "the 100-yr up-grade on tuberculin skin test for diagnosis of latent tuberculosis infection" (Lalvani & Millington, 2008, p. 1429). The IGRA tests deserve mentioning, but at the time of this literature review, remain an evolving test protocol.

Research to date has determined that the IGRA tests have a place in diagnosing LTBI in high-risk groups and in countries where BCG vaccination is routinely performed (Ozekinci, Ozbek, & Celik, 2007), as well as in the hospital setting (Ferrara et al. 2005). In low-risk populations, these tests may be useful in helping to diagnose both LTBI and active TB (Tahereh, Alireza, Massoud, & Amina, 2010). However, IGRA blood tests may be adversely affected in immunosuppressed individuals, presenting as indeterminate

results (Ferrara et al., 2005). In one study, the difference between diagnostic confidence

of one IGRA blood test (QuantiFERON™-TB Gold) and the TST were determined as a

(a) Positive Predictive Value (PPV) of 52% for the blood test and 54% for the TST, and a

(b) Negative Predictive Value (NPV) of 86% for the blood test and 67% for the TST

(Tahereh et al., 2010). The importance of gauging a useful NPV is justified in the

knowledge of high costs involved in treating a case of LTBI over many months.

Among healthcare personnel, one particular study demonstrated differences that

have been observed between one blood test method and the TST. In Denmark, a low-

incidence tuberculosis country, TST positivity among a group of 192 infectious disease

department workers was reported at 34%, while the same group demonstrated a positivity

rate of 1% by IGRA blood test method (Soborg et al., 2006). The differences were linked

to prior BCG immunization as the only significant risk factor in the study. Soborg et al.

(2006) reported that in contrast, these differences are much less in countries with

medium- or high-risk.   An example of this scenario was found in research where

participants living along a Turkish region of the Mediterranean demonstrated a BCG

vaccination rate of 94.2%, but TST-positivity rate of 7.4% (Kazanci et al., 2010). In

Turkey, where TB disease remains prevalent, BCG vaccination is compulsory for all

infants (Kazanci et al., 2010; WHO, 2011b).

Although promising, the IGRA blood test is not logistically practical in many

settings. At present, the TST remains the most widely used and cost-effective screening

test. No literature was found indicating prevalence of this test among U.S. medical

laboratory microbiologists.

Treatment of Inactive (Latent) and Active Infections

In addition to knowledge of TST positivity and related predictive factors, it must be stressed that preventive treatment for latent tuberculosis infection (LTBI) is of great interest in slowing or stopping the spread of TB. Prescribed treatment is important because it is thought to prevent latent TB infection from becoming active TB disease (Heymann, 2008). Candidates for treatment of LTBI include certain high-risk groups identified through targeted public health programs, such as immigrants (especially those from TB-endemic regions), injection drug users, residents and employees of high-risk congregate settings (such as correctional facilities, homeless shelters, hospitals), and persons with decreased immune system functionality (CDC, 2011e). Of importance to this study, CDC has recommended treating personnel from mycobacteriology laboratories who have demonstrated a positive TST (or IGRA blood test) or conversion (CDC, 2005b, 2011e).

Treatment of LTBI is presently restricted to three generally accepted options, depending on age and presence of comorbidity (CDC, 2011e):

- Isoniazid (INH) taken daily for a total of 9 months.

- Isoniazid (INH) and rifapentine (RPT) given in 12 doses (once-weekly).

- Rifampin (RIF) daily for a total of 4 months (or use of Rifabutin [RBT]).

As noted, proper preventive treatment takes many months and many doses in order to sustain TB control and prevent development of resistance (Larson, 2007; WHO, 2001a). This long treatment duration may be why treatment noninitiation and nonadherence are prevalent among many populations. A new option recently described

by Jereb et al. (2011) has provided a more efficient regimen, intended to improve treatment adherence. The recommended LTBI treatment consists of a 12-dose regimen, whereby 12 once-weekly doses are given over 3 months. Two drugs, Isoniazid and Rifapentine, given as directly observed treatment, have been found just as effective as the standard 270-dose 9-month treatment (Jareb et al., 2011).

No matter which course of preventive treatment is prescribed, all patients should be educated to recognize adverse reactions to the medications (CDC, 2011a, 2011e). In addition, completion of treatment should be documented and retained with the individual (CDC, 2011e).

Treatment for active TB disease will last from 6 to 9 months in drug-susceptible individuals, and longer (up to 24 months) if multidrug-resistant TB has been identified (CDC, 2011e). CDC (2011e) reported that the preferred treatment regimen for treating drug-susceptible active TB disease in persons not infected with HIV includes a combination of several anti-TB medications taken over many weeks. However, current global community prevalence of resistance to isoniazid and rifampin is about 0.7% for both drugs combined (Larson, 2007). It is important to note that drug susceptibility results may not be available for many weeks due to the slow-growing nature of MTB bacteria and the individual laboratory's processing-to-result turnaround time.

Costs involved with treating MDR TB and XDR TB are several times higher per patient than costs involved with treating drug-susceptible strains of MTB (WHO, 2011b). In the United States for year 2010, cost per TB patient treated with first-line drugs was estimated at more than $5000; 2009 TB control cost in the United States was ≤ 1% of

total health expenditures by the entire public sector (WHO, 2011b). In other regions

around the world, costs ranged from $100 to $500 per patient for treatment, while TB

control cost was typically > 7% of total health expenditures by the public sector (WHO,

2011b).

The Infectious Diseases Society of America (IDSA, 2004) reported that some

serious diseases have no treatment except for supportive care. For diseases (like active

tuberculosis) that do have effective treatments, complacency may delay new research

causing existing treatments to be ineffective when resistant strains arise. TB is an

example of a disease where over 30 years have passed since a new class of antibiotic was

approved for treatment (Larson, 2007). In addition, TB treatment for inactive and active

infections is complex and sometimes toxic, adding to the difficulty in ridding the world

of this disease.

Descriptive Epidemiology

Geography. Every country is affected with over 95% of infections occurring in

developing countries (Heymann, 2008, p. 643). Worldwide in 2010, incident cases

reached 6.2 million people diagnosed with active TB; 5.4 million had TB for the first

time and 0.3 million had recurrence of TB after receiving prior treatment (WHO, 2011b).

Forty percent of the world's incident cases of active TB in 2010 were located in India and

China, while Africa accounted for 24% (WHO, 2011b). Of note, twenty-two high

incidence countries accounted for 82% of the total incident cases (WHO, 2011b). Cases

are defined by WHO as confirmed *Mycobacterium tuberculosis* (MTB) isolated from

culture of a clinical specimen (WHO, 2011b). In addition, a high prevalence of resistant

TB strains has been identified in countries of Eastern Europe, Latin America, Africa, and Asia (WHO, 2001a, 2011b).

In the United States, active TB has been reported in almost every state and while increasing in some geographical areas (CDC, 2011b, 2011d), the total number of active TB cases has decreased (CDC, 2011d). According to CDC (2011b), other issues related to antimicrobial resistance have become problematic.

Age. U.S. cases of active TB by age demonstrated a downward trend in all age groups from 1993 to 2009 (CDC, 2010b). In 1993, the highest incidence rate of active TB cases (per 100,000) reported was 17.7 in the > 65 year age group (this group had highest exposure occurring before the advent of treatment), while the four age groups denoting ages 0-14, 15-24, 2-44, and 45-64 years averaged rates of 2.9, 5.0, 11.5, and 12.4, respectively (CDC, 2010b). In 2009, incidence rates of active TB dropped to 5.8 for the > 65 year age group, and 1.0, 3.0, 4.7, and 4.3 for divisions representing age groups 0-14, 15-24, 2-44, and 45-64 years, respectively (CDC, 2010b). According to ASCP, the average age of the U.S. medical laboratory workforce was nearing 50 years in 2008 (ASCP, 2008) making this subgroup of HCP at greater risk based on age alone.

Gender. In high-incidence countries, morbidity is highest among adult males (Heymann, 2008). In the industrialized countries, mortality and morbidity have been trending downwards but have recently stagnated due to HIV infection, poverty, and the dismantling of TB control services (Heymann, 2008). Males remain at a higher rate of 11.8 per 100,000 and females at a rate of 5.1 per 100,000 for cases of active TB in the United States, generally because males engage in work outside the home, or because of

unemployment and the associated higher chances of contact with TB (McKenna, Hutton, Cauthen & Onorato, 1996). ASCP (2008) reported that nearly three-fourths of the U.S. medical laboratory scientist workforce in 2005 was female, and therefore not as high-risk a group based on gender alone.

Reservoir. The reservoir of M. TB complex is primarily that of humans, and rarely found in other primates (Heymann, 2008). The reservoir of *M. bovis* is cattle and other mammals (Heymann, 2008).

Transmission. TB is spread among individuals via forceful exhalation of aerosolized droplet nuclei (microscopic droplets) containing viable tubercle bacilli (TB bacteria) from individuals with active cavitary pulmonary or laryngeal disease (Mathema et al., 2006). The risk of infectivity depends upon exposure and host factors (Heymann, 2008).

In laboratory workers, skin, eyes, alimentary tract, and respiratory tract have long been known as portals of entry for the airborne tuberculosis bacilli (Long, 1951). Since the 1950s, many healthcare engineering controls have been implemented that have decreased this risk. In addition to transmission between individuals via respiratory route, examples of portals of entry in laboratorians were first described by Long (1951) as skin (incision or glass puncture wounds, abrasives, prolonged contact with pus, finger in eye), alimentary tract (inhaled, then swallowed), respiratory tract (droplets), and intravenous (needle prick). Although rare in number, and preventable through measures employed in the laboratory, these portals bear mentioning. Long (1951) described work with infected tissues as the most probable cause of extrapulmonary infection among laboratorians,

although still infrequent. Extrapulmonary specimens (urine, pus, fluids) may also be high-risk specimens, but again rarely causing active infection, according to Allen and Darrell (1981).

Incubation period. An incubation period of approximately 2 to 10 weeks post initial infection results as active disease lesions or inactive (latent) disease (Heymann, 2008).

Pathogenesis and host response. Infection occurs when individuals inhale droplet nuclei containing the tubercle bacilli and the bacilli bacteria begin to multiply in the small air sacs of the lung (CDC, 2011a, 2011e). After inhalation of particle sizes only 1 to 5 microns in diameter, the particles are phagocytized by aveolar macrophages in the lung, leading to a vigorous immune response (Mathema et al., 2006). According to CDC (2011b), the bacilli then enter the bloodstream and spread, and in individuals where the immune system is functioning correctly, continued spread is halted within 2 to 8 weeks post infection.   The individual is considered at this point to have LTBI. If the host's immune system cannot keep the tubercle bacilli under control, the bacteria multiplies, destroying tissue (usually in the lungs). Individuals that have reached this point in the infective process are considered to have active TB disease and may now spread the bacteria to others.

A more dynamic hypothesis by Cardona (2009) described that in LTBI, constant reinfection is occurring rather than tubercle bacilli residing in a state of dormancy. The traditional version of the static LTBI state versus Cardona's dynamic hypothesis is of current interest in the review of treatments for LTBI (Cardona, 2007).

Evidence of *Mycobacterium tuberculosis* reactivation occurring decades after initial infection has been demonstrated by Lillebaek et al. (2003). Results indicated that 1990 strains were not new, but reactivated dormant strains from those isolated in the 1960s. The rate of change of the DNA in latent infection (activated to active infection) was much longer than the rate seen during active disease.

Communicability. Heymann (2008) reported that as long as live TB organisms are discharged in sputum through coughing, singing, and like airborne routes, transmission between individuals will occur. Effective treatment usually eliminates communicability within 2-4 weeks; however, TB may still be cultured from sputum during this time (Heymann, 2008). Of note, some individuals (identified as Acid Fast Bacilli [AFB] smear-positive) may be intermittently positive and contagious for years until diagnosed and treated (Heymann, 2008). According to Heymann, the degree of communicability depends on several factors: (a) degree of intimacy, (b) duration of exposure, (c) number of AFB bacilli actively discharged, (d) infectivity of the bacilli, (e) adequacy of ventilation, (f) exposure of bacilli to sun or ultraviolet light, and (g) opportunities for aerosolization (as in coughing, singing, and talking). In addition, the degree of communicability among healthcare personnel may depend on the frequency or type of procedures performed where aerosolization or invasive contact may occur, especially when performing certain procedures in the medical laboratory (Heymann, 2008). Other characteristics associated with infectiousness (presenting a portal of exit for the bacterium) include a failure to cover mouth/nose when coughing or sneezing, and undergoing cough-inducing or aerosol-generating procedures (CDC, 2011a).

Regarding communicability, the American Thoracic Society (2005) recommends all inpatient facilities that manage persons at risk for TB have infection control policies and procedures in place to minimize the risk for nosocomial spread of infection. In addition, facilities should report persons with suspected or confirmed TB to the local health department (American Thoracic Society, 2005). Local and state statues that exist in many regions detail specifics regarding notification and treatment of diseased individuals because the communicability of these individuals poses a risk to society.

Susceptibility to infection. The risk of TB infection may depend on host's ability to fight disease (Caminero, 2010; Heymann, 2008). The HIV-infected and immunosuppressed have higher risk of infection leading to clinical disease following exposure, with the first 12-24 months post-exposure noted as a period of highest risk. Among those co-infected with HIV and latent TB, the lifetime risk of developing active TB disease is 10% to 50% (Heymann, 2008); management becomes complex and difficult when the patient has gone on to develop active TB infection (CDC, 2011e). While susceptibility to TB infection remains high in these patients, encouraging data has shown that HIV co-infection rates in persons with active TB in the U.S. fell from 15% in 1993 to 6% in 2009 (CDC, 2011a) presumably due to better disease management.

Dose and severity of infection (virulence). A low infective dose for humans has been reported to be a 50% infective dose of < 10 bacilli (CDC, 2009). Severity of infection is dependent on co-morbidity (host factors), as well as environmental factors mentioned previously. And sometimes, individuals may be infected with more than one strain, in particular, resistant strains (Cohen et al., 2011). The consequences of activation

of latent infection and possible subsequent infection with an active resistant strain are severe. Infective dose may have great bearing in the laboratory where concentrated numbers of bacilli may be present, becoming a reason for increased risk in this setting (CDC, 2009).

Prevalence and incidence of latent infection. In 2002, A Federal Tuberculosis Task Force Plan estimated prevalence of individuals in the United States with latent TB (LTBI) at 10 to 15 million (CDC, 2003a). More recent estimates have reported prevalence of LTBI in the U.S. at 9 to 14 million (CDC, 2011e); lower, but still an alarming number. The prevalence of LTBI increases with age; it is estimated that one third of world's population is infected (Heymann, 2008). There is no surveillance system in the United States for determining prevalence of LTBI; the United States depends on international calculations of prevalence by WHO in order to estimate risk (Khan, Muennig, Behta, & Zivin, 2002).

In the United States, the annual risk of new TB infection is estimated to be approximately 10 in 100,000 people overall, with some segments of the population at higher risk (Heymann, 2008). Approximately 10% of individuals diagnosed with inactive or latent tuberculosis infection (LTBI) progress to develop active TB disease, according to the CDC (2005a).

Prevalence and incidence of active disease. As mentioned earlier, many cases of active TB are the result of reactivation of inactive TB infection (LTBI). This is why it is so important to follow active TB disease cases from the standpoints that (a) these cases may have resulted from LTBI, and (b) these cases may result in new cases of LTBI, thus

promoting the cycle or chain of infection. Global cases of active TB peaked around years

2004-2005, and have since stabilized or are now decreasing (Heymann, 2008).

According to Heymann (2008), the 22 highest-burden countries account for 80% of new

cases each year, having reported a rate of 174 cases per 100,000 in 2005. In 2009, 9.4

million new TB cases were reported (WHO, 2010b).

Emergence of resistant TB, categorized as *multidrug-resistant tuberculosis (MDR*

TB) or multidrug-resistant latent tuberculosis infection (MDR LTBI) and *extensively*

drug-resistant tuberculosis (XDR TB), has come to the forefront in recent years.

Estimates of MDR TB are 4.8% of active TB cases worldwide, up to 20% of new cases in

Eastern Europe and Central Asia, and up to 60% of previously treated cases (Heymann,

2008). The countries of China, India, and Russia accounted for 57% of the overall

(estimated) incidence of MDR TB (Heymann, 2008). In China alone, 120,000 new cases

of MDR TB are identified each year and some are actually more resistant than first

thought (Tang et al., 2011). In 2009, 3.3% of all new TB cases were MDR TB, while in

some regions, MDR TB rates reached up to 28% of new TB cases in 2010 (WHO, 2010).

XDR TB incidence is about 6% of all MDR TB isolated worldwide in 2007 (Heymann,

2008), and reported to have high rates of mortality such as the 98% mortality rate

reported in one South African outbreak (Calver et al., 2010; Heymann, 2008). XDR TB,

a major public health threat, has been confirmed in 58 countries according to WHO

(2010).

Cases of active TB in the United States have been trending downward (Figure 2);

cases of active TB reported in 2009 numbered 10,893 (CDC, 2010b). Most new cases in

the United States result from reactivation of LTBI from a prior initial infection; however, in urban areas about one third of new cases of TB disease may result from recent infection or from exposure to areas where overcrowding occurs (Heymann, 2008).

*The resurgence of TB in the mid-1980s was marked by several years of increasing case counts until its peak in 1992. Case counts began decreasing again in 1993, and 2010 marks the eighteenth year of decline in the total number of TB cases reported in the U.S. since the peak of the resurgence.

Source: CDC. "Trends in Tuberculosis — United States, 2010." MMWR, March 25, 2011.

Figure 2. Reported TB cases, United States, 1982–2010. From "Key Graphics From 2010 U.S. TB Surveillance Data" (Public domain images), by Centers for Disease Control and Prevention, 2011, retrieved February 20, 2012, from http://www.cdc.gov/nchhstp/newsroom/TBSurveillanceGraphics.html

CDC has reported "no apparent trend in the number of XDR TB cases over time in the United States" (CDC, 2011a, p. 12). Ten cases were reported in 1993 in the United States, but very few since then. No cases in 2009, according to CDC (2011a). However, as more immigrants arrive in the United States, the numbers of MDR and XDR cases may increase over time. It is important to remember that medical laboratory microbiologists may be at risk of exposure to these resistant strains as they are discovered among patient populations.

Morbidity. In the United States, the rate of morbidity has fallen from 2003 through 2009 (rate of 5.1 per 100,000 to 3.9 per 100,000); morbidity in 2009 was 11,545 individuals (CDC, 2011a).

Mortality. Estimates have been made placing global deaths due to tuberculosis from years 1700 to 1900 at 1 billion individuals, and annual death rate during the time of Koch's discovery of the tubercle bacilli at about 7 million people (Nobelprize.org, 2012). In 2009, 1.7 million people died from TB (WHO, 2010b).

Risk Factors

Foreign birth. "As of 2001, TB cases in foreign-born persons now account for at least 50% of all cases reported in the United States annually" (CDC, 2002, pp. 9-10). In 2001, this was news in the United States; but by 2010, up to 65% of all active TB cases were reported in the foreign-born (CDC, 2011d). (Refer to Figure 3.) By individual U.S. states and territories, New York, Washington D.C., New Jersey, Georgia, Florida, Mississippi, Louisiana, Texas, California, Nevada, and Hawaii averaged the highest case rates in the nation (CDC, 2011a). Seven countries (Mexico, Philippines, India, Vietnam, China, Guatemala, and Haiti) accounted for 62% of foreign-born cases in United States (CDC, 2011a). Among all reported cases of MDR TB in the United States, those reported from 1993-2009 among the foreign-born rose from 25% in 1993 to 88% in 2009 (CDC, 2011e).

Proportion of TB Cases by National Origin, 2010✲✲

39.5% U.S.-born

60.5% Foreign-born
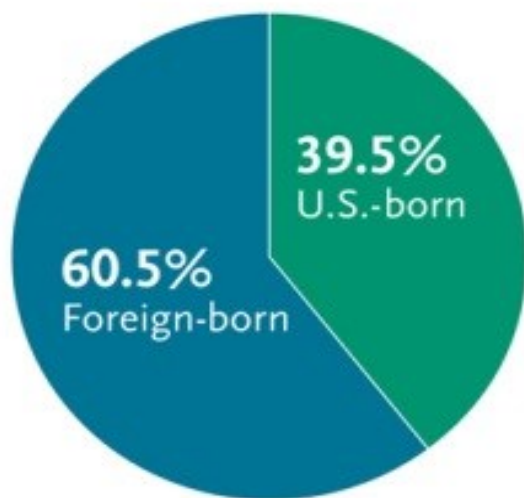
✲✲Among cases in persons with a known national origin

Source: CDC. "Trends in Tuberculosis — United States, 2010." *MMWR*, March 25, 2011.

Figure 3. Proportion of U.S. TB cases by place of birth. From "Key Graphics From 2010 U.S. TB Surveillance Data" (Public domain images), by Centers for Disease Control and Prevention, 2011, retrieved February 20, 2012, from http://www.cdc.gov/nchhstp /newsroom/TBSurveillanceGraphics.html

By number of U.S. states, the percentage of TB cases among the foreign-born rose from 13 states in 1999 to 31 states in 2009 for ≥ 50% of cases, and 2 states in 1999 to 14 states in 2009 for ≥ 70% of cases (CDC, 2011b, slide set). In addition, among all reported cases of multidrug-resistant tuberculosis (MDR TB) in the United States, from 1993 to 2009, cases among foreign-born rose from 25% in 1993 to 88% in 2009 (CDC, 2011a, 2011b).

The active TB disease rate was calculated in 2004 to be 21.5 per 100,000 among foreign-born versus 2.7 per 100,000 among U.S.-born individuals… "almost one-quarter of all TB cases in the United States occur among foreign-born persons who have resided in the United States for longer than 5 yr" (Cain et al., 2007, p. 75). Zuber, McKenna, Binkin, Onorato, and Castro (1997) have referred to this "imported" TB as preventable. In a study of 1986-1994 cases reported to the CDC, a majority of TB incident cases were in those younger than 35 years upon arrival to United States, and could have been prevented with initiation of preventive treatment (Zuber et al., 1997).

Race and ethnicity. By ethnicity in the United States, Asians and Pacific Islanders had the highest active TB case rates, while Black or African-American, and Hispanic followed in year 2010 (Figure 4). This disproportionate burden depends on (a) infection acquired in country of origin, (b) unequal distribution of TB risk factors, (c) lower socioeconomic status, and (d) overcrowding (CDC, 2011a). Medical laboratory scientists in the United States appeared representative of the diverse and ethnic makeup of the U.S. population in 2005: 12% Asian, 11% African American, and 7% Hispanic (ASCP, 2008).

TB Rates by Race/Ethnicity, 2010

Source: CDC. "Trends in Tuberculosis — United States, 2010." *MMWR*, March 25, 2011.
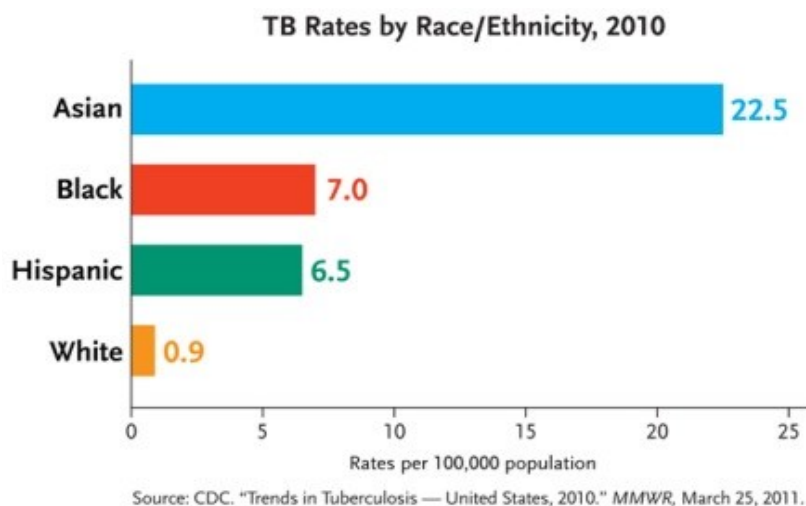
Figure 4. TB rates by race/ethnicity in the United States, 2010. From "Key Graphics From 2010 U.S. TB Surveillance Data" (Public domain images), by Centers for Disease Control and Prevention, 2011, retrieved February 20, 2012, from http://www.cdc.gov /nchhstp/newsroom/TBSurveillanceGraphics.html

To summarize, active TB infection affects racial and ethnic minorities disproportionately in the United States (CDC, 2011e).

Social determinants. The distribution and course of TB is dependent on biological factors such as co-morbidity with HIV, resistant TB strains, and social forces such as poverty, economic inequality, political violence, racism—examined thru the lens of Farmer's work in Haiti (Farmer, 1997), but also applicable to other countries where TB is moderate- or high-incidence. More and more, TB is becoming known as a social disease (Lonnroth et al., 2010; WHO, 2010a). Specific factors leading to high risk of TB transmission at the global level include overcrowding, poorly ventilated housing, poor living conditions, malnutrition, smoking, and stress (Figueroa-Munoz & Ramon-Pardo, 2008; Lonnroth, Jaramillo, Williams, Dye, & Raviglione, 2009), as well as social deprivation and poor social capital (Farmer, 1997; Figueroa-Munoz & Ramon-Pardo,

2008). Traditionally, vulnerable groups include the homeless, mobile communities, injecting drug users, and those co-infected with HIV. Development of resistant TB strains among non-adherent household contacts living in poor conditions (Velasquez et al., 2011) and among certain groups of drug abusers (Perri et al., 2011) have added concern. The impact of globalization on refugee migration patterns has been described as a risk factor where TB among migrants should be viewed and screened according to country of origin (Figueroa-Munoz & Ramon-Pardo, 2008). It has been said that the real cause of the spread of TB is not so much the microbe as socioeconomic and political factors (WHO, 2010a).

  Occupation. "Certain occupations may be associated with an elevated risk" (McKenna et al., 1996, p. 587). Among 29 U.S. states during years 1984-1985, one occupational study presented data based on information gathered on all active TB cases. Census data was used to estimate number of individuals in each occupation. This study, performed by McKenna et al. (1996), reported an overall case rate of 8.4 per 100,000 individuals, where healthcare workers carried an overall rate of 6.7 per 100,000, inhalation therapists rate of 15.6, and clinical laboratory technologists and technicians rate was reported at 6.7. The study further identified a rate of 10.5 for nursing aides, orderlies, and attendants, 22.2 for those working with animals, 8.2 for those employed in food service, 10.7 for those employees exposed to dust, licensed nurses as 6.1, registered nurses (RNs) at 5.8, and physicians at a rate of 6.6 per 100,000 individuals. McKenna et al. (1996) concluded that in low-incidence communities, healthcare workers do not appear to exhibit a risk greater than the general population. In addition, occupations tied

to low SES were associated with elevated rates. (For example, the laboratory worker category SES scores were listed as technical, faring better than farm workers, laborers, and service personnel.)

Researchers such as Baussano et al. (2011) have reported that globally, rates of newly described active TB cases (incidence) for HCP are higher than the general population, representing TB as an occupational disease. Rates of active TB infection in HCP have been DNA fingerprinted in order to determine an association with occupation (de Vries, Sebek, & Lambregts-van Weezenbeek, 2006). In the de Vries et al. (2006) research, 42% of TB cases in the Netherlands during 1995-1999 (those working in healthcare) were found to have been infected during work. While occupation alone cannot predict TST results, certain occupational factors involving contact with TB-contaminated patients or specimens remain well-known risk factors.

<div align="center">**The Healthcare Personnel (HCP) Population**</div>

Definition of Healthcare Personnel (HCP)

Throughout the literature search and review, a number of studies involved use of the terminology HCP versus HCW. It became important to note the difference while reviewing the research results. Further investigation revealed that in 2008, the general terminology *health-care worker* (HCW) was changed to *healthcare personnel* (HCP) by the U.S. Department of Health and Human Services (2008). This terminology was changed in order to broaden the definition to clarify that HCP refers to both paid and unpaid workers. This recommendation was made by the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory

Committee (HICPAC). In this recommendation, "HCP are defined as all paid and unpaid persons working in health-care settings who have the potential for exposure to case patients and/or to infectious materials, including body substances, contaminated medical supplies and equipment, contaminated environmental surfaces, or contaminated air." (U.S. Department of Health and Human Services, 2008, para. 1). While all HCP are included in this definition, the following reviewed HCP literature rarely included or operationally segregated medical laboratory microbiologists from the aggregate data.

Healthcare Personnel: By Occupation

By occupation, the percentage of active TB cases among healthcare personnel (HCP) in the United States reached 3.8%, second only to cases among unemployed and retired individuals in 2009 (CDC, 2010b). Other high-risk occupational groups such as migrant workers and correctional employees were reported at 1.2% and 0.2%, respectively (CDC, 2010b).

Tuberculin Skin Test Prevalence (Positivity) and Incidence (Conversion) Rates Among Healthcare Personnel

Globally, much work has been done to seek out prevalence and incidence rates of LTBI among HCP (Joshi et al., 2006; Menzies, Joshi, & Pai, 2007). LTBI prevalence rates ranged from 33% to 79% in low- and middle-income countries, to 5% to 55% in high-income countries (Joshi et al., 2006). Incidence of active TB infection attributable to work in health care has been cited at ranging from 1.1% in high-income countries to 5.8% in low- and middle-income countries, with rates of active TB infection consistently higher than rates in the general population in all countries (Menzies et al., 2007). Active

TB rates in low- and middle-income countries were associated with occupational exposure, while rates in high-income countries were associated with other factors (Menzies et al., 2007). One study gauged LTBI incidence based on countries with historic rates of TB incidence (not based on income), reporting that LTBI incidence in low-TB incidence countries was found to be 3.8%, intermediate-TB incidence at 6.9%, and high-TB incidence at 8.4% (Baussano et al., 2011). This latter research also reported that introduction of TB control measures (use of negative pressure rooms and N-95 masks) appears to have decreased TB annual incidence among HCP by as much as 81% in high-income countries (Baussano et al., 2011). In this literature search, several other international studies corroborated these findings (Baussano et al., 2007; Christopher et al., 2010; Drobniewski, Balabanova, Zakamova, Nikolayevskyy, & Fedorin, 2007; Roth et al., 2005). The one exception was found in a recent Malaysian study where overall prevalence of LTBI among HCP was 10.6% using a combination of the TST and the IGRA blood test (Rafiza et al., 2011). This exception may have occurred because of the better sensitivity and specificity associated with the blood test method.

This search and review of the literature also found several U.S. studies of HCP describing LTBI prevalence (TST positivity) rates ranging from 11.3% (Bailey, Fraser, Spitznagel, & Dunagan, 1995) to 32% (Cook et al., 2003). LTBI incidence (TST conversion) rates were reported at 1.2% (Larsen et al., 2002) and 1.5% (Panlilio et al., 2002), to 5.7% in high-risk settings (Cook et al., 2003). Miller et al. (2002) reported TST conversion rates of 5.8% among potentially exposed HCP, while a rate of 2.0% was determined among negative controls. These findings are again, in line with those

presented by Joshi et al. (2006) and Menzies et al. (2007). U.S. reports of higher LTBI

prevalence rates have been linked to an increase in foreign-born HCP (Cook et al.,

2003), while higher LTBI incidence rates have been reported among certain HCP

occupations (Louther, 1998).

Preventive Treatment Initiation Rates Among Healthcare Personnel

In this search, findings were limited regarding rates of preventive treatment

initiation among groups of HCP (other than laboratorians; see below). A retrospective

cohort study by Gershon et al. (2004) in Toronto described $n = 308$ HCP diagnosed with

LTBI reported to have sustained a preventive treatment initiation rate of 58% overall.

The authors surmised that the odds of HCP initiating treatment remain about one-half of

those of a non-health care worker and depended on factors of age, BCG immunization,

foreign birth, and contact with persons having TB.

Treatment Nonadherence and Barriers Among Healthcare Personnel

Preventive treatment completion rates among HCP and other high-risk groups

have been reported to range anywhere from 27% to 82% (Hirsch-Moverman et al., 2008)

when compared with the general public's completion rates approximating 60% (CDC,

2000). Overall completion rates may reach only 55% (Camins et al., 1996). In the

Camins et al. study, as many as 11.4% of those who did not complete treatment stopped

because of real or perceived drug effects. Other research has indicated that HCP

nonadherence to preventive treatment may have been due to a perception that treatment

was harmful with potential adverse drug effects (Joseph et al., 2004). While treatment

adherence is a multidimensional process including patient, treatment, environment,

disease, provider, and patient-provider characteristics (Kennedy, 2000), barriers consistently reported among HCP were those of adverse drug effects.

The Laboratorian Subpopulation

Definitions and Background

The U.S. Department of Labor Bureau of Labor Statistics (2011) has reported that May 2010 estimates of medical and clinical laboratory technologists in the United States numbered 164,430 individuals, while medical and clinical laboratory technicians numbered 156,480. Not every technologist or technician has worked in the field of medical laboratory microbiology, and not every laboratorian in the U.S. who is working with *Mycobacterium* is working as a medical or clinical laboratorian. At present, the Centers for Medicare & Medicaid Services (CMS, 2012) regulate all laboratory testing (except research) performed on humans in the United States through the 1988 Clinical Laboratory Improvement Amendments (CLIA). This overarching authority to regulate these entities began with the CLIA Subpart M, an amendment containing the personnel sections of the CLIA regulations. The Final Rule on these personnel requirements became effective on January 24, 2003. One approved U.S. registry that fits the requirements of CLIA is the American Society for Clinical Pathology, established in 1928 (ASCP, 2009).

A search of the ProQuest Dissertations & Theses and EBSCO databases revealed one study only involving American Society for Clinical Pathology (ASCP) registrants. In this study, a self-administered mail survey was performed using the ASCP mailing list. This study utilized a process where 200 randomly selected members received surveys

related to questions about job satisfaction, intent to quit, and job retention (Clark, 2008).

A 10% returned-to-sender rate was realized in this research, as was a rejection rate of

13.5%; the overall response rate was 22.5% (Clark, 2008).

Tuberculin Skin Test Prevalence (Positivity) and Incidence (Conversion) Rates

Among Laboratorians

Among HCP, medical laboratorians have been at high risk for TST positivity as

well as for developing active TB disease from a latent (inactive) form of TB. Since the

1940s and 1950s, laboratory workers exposed to sputum or post mortem samples from

tuberculosis patients have been at greater risk for incidence of active TB when compared

to the general public (Baussano et al., 2007; Harrington & Shannon, 1976; Reid, 1957).

The CDC (2005) has included laboratory workers in guidelines for TB screening

programs at the level of the health-care setting. Anyone participating in aerosol-

generating procedures or in specimen-processing procedures (including processing for

Mycobacterium tuberculosis) should take part in regular TST screening protocol

according to CDC (2005). In addition, other specific factors increasing risk in the United

States include (a) recent immigration from endemic countries, (b) working in hospitals or

other congregate healthcare facilities, and (c) microbiology staff working in the

mycobacteriology laboratory (CDC, 2000, 2005b).

Globally, high rates of LTBI prevalence have been associated with working in

laboratories, especially in low-income countries (Joshi et al., 2006). In Russia, LTBI

prevalence rates determined by a combination of TST positivity and IGRA blood test

results have been documented at 40.8% in HCP staff, but reaching 61.1% in laboratory

workers (Drobniewski et al., 2007). Roth et al. (2005) also reported high TST-positivity prevalence among Brazilian laboratorians—a rate of 61.2%. The exception to these studies was a Malaysian study using a combination of TST and blood test to determine LTBI prevalence; $n = 29$ microbiology laboratory workers, where none tested positive (Rafiza et al., 2011).

Literature was located in this search which also demonstrated high prevalence of TST positivity: a baseline of 57% among New York City laboratory workers ($n = 345$) with an accompanying incidence of LTBI determined to be 1% over a 2-year time period (Garber et al., 2003). This figure is much lower than the Canadian LTBI TST-conversion rate of 13% among laboratory workers reported by a Menzies, Fanning, Yuan, Fitzgerald, and the Canadian Collaborative Group in Nosocomial Transmission of Tuberculosis (2003) study ($n = 517$). In another U.S. study, incidence of TST-conversion was highest among laboratory technicians, as well as nurses and other subgroups of HCP (Miller et al., 2002).

Because of choice of study design used in assessing TST rates, the laboratory worker has been notably omitted from HCP subgroupings (Bailey, Fraser, Spitznagel, & Dunagan, 1995), or has been grouped into a larger conglomerate of other non-related technical services (Louther, 1998). Some studies surveyed entire laboratory entities rather than individuals (Jacobson, Orlob, & Clayton, 1985; Kao, Ashford, McNeil, Warren, & Good, 1997; Vaquero, Gomez, Romero, Casal, & Spanish Group of Mycobacteriology, 2003). All studies included in this segment of the literature review agreed that overall, work in mycobacteriology laboratories was considered "high-risk."

Preventive Treatment Initiation, Treatment Nonadherence, and Barriers Among

Laboratorians

A literature review revealed that although microbiology laboratory HCP may be offered preventive isoniazid treatment therapy for suspected LTBI, initiation rates may be as low as 20% (Garber et al., 2003); access, eligibility, and barriers were not assessed. In this review of the literature, no studies were located that described research involving LTBI treatment nonadherence or adherence barriers for the laboratorian or medical laboratory microbiologist population separate from HCP aggregate research.

Brief History of Tuberculosis Risk Among Laboratorians

The CDC has stated, "Microbiology laboratories are special, often unique work environments that may pose identifiable infectious disease risks to persons in or near them" (CDC, 2009, p. 1). Throughout the history of microbiology, published reports have described laboratory-acquired infections with TB near the top of the list. The first notable paper located in this literature search was that of Sulkin and Pike (1951), detailing the high number of suspected occupational cases of TB reported in 5,000 laboratories surveyed by the authors. At the time, laboratories kept few records of instances of laboratory infection. In 1957, Reid reported incidence of TST positivity in studies of clinical laboratory recruits to be as high as 49.2% to 88.9%, but also pointed out that cases of TB in the general public were also rampant (Reid, 1957).

Hazards of acquiring TB infection in the laboratory setting were becoming more frequent due to greater use of new culture methods, creation of aerosols in preparation of infected samples, contaminated specimen container exteriors, and general exposure to

infected patients through necropsy (Collins, & Grange, 1999; Sewell, 1995; Sulkin, 1961). A review of the literature from 1950 to 1963 demonstrated that a new focus was placed on use of protective devices and analysis of occupational hazards (Pike, Sulkin, & Schulze, 1965). Thus, after decades of debate regarding the increased incidence of active TB disease in physicians, nurses, and technical staff (laboratorians included), several states began offering workmen's compensation for tuberculosis as an occupational disease (Sepkowitz, 1994). Identification of TB risk in pathology and laboratory workers has since become important for reasons of (a) prevention, and (b) compensation practice (Seidler, Nienhaus, & Diel, 2005).

Engineering controls in laboratories. Laboratory-acquired infections like TB prompted the use of engineering controls, such as the laminar-flow biological safety cabinet (BSC) and special fit-tested respirators (such as N-95) in laboratories (Singh, 2009). In addition, the first edition of the Biosafety in Microbiological and Biomedical Laboratories (BMBL) was published in 1984 (CDC, 2009). The BMBL outlined specific recommendations and guidelines for working with microorganisms like those belonging to the *Mycobacterium tuberculosis* complex. The current version of the BMBL reported that the incidence of tuberculosis in laboratory personnel working with suspect agents has at times been three times higher than in those not working with the agent (CDC, 2009). Rates of active TB have been found to be significantly higher among laboratorians, and suspected as related to underperforming BSCs (Alonso-Echanove et al., 2001). Recommended use of another engineering control, the negative pressure room with ventilation air exchanged, was more recently reported by Menzies, Fanning, Yuan,

Fitzgerald, and the Canadian Collaborative Group in Nosocomial Transmission of TB (2000). Although laboratorians were not a part of this particular research, it is important to note that TST conversion among HCP groups was strongly associated with work in non-isolation rooms with less than 2 air exchanges per hour. Engineering controls that are not working properly, are not used properly, or are not in use at all place the medical laboratory microbiologist at risk for exposure to TB.

Occupational injury and illness classification. The current Occupational Injury and Illness Classification Manual (Version 2.0), used to code and recognize suspected occupational exposures for all U.S. workers, currently classifies tuberculosis by species of mycobacterium and characterization of clinical features, by TST positivity, by anxiety associated with exposure, and by exposure with no other manifestations (U.S. Department of Labor Bureau of Labor Statistics, 2010). Because the latent period from initial infection to TB disease is long and subject to inaccuracies in reporting of rates, TST positivity occurring among all HCP (including laboratorians) and even a census of fatalities due to TB disease as reported to Occupational Safety and Health Administration (OSHA) may be underrepresented (Sepkowitz & Eisenberg, 2005). Sepkowitz and Eisenberg reported that many HCP remain at risk today for activation of TB active disease due to TST conversions occurring in HCP during the late 1980s and 1990s, a time when nosocomial outbreaks in the United States were frequent due to resurgence of TB.

Prevention and Control in Laboratorians

Because TB is transmissible via airborne routes of infection, appropriate infection control procedures are required to protect others (including laboratorians) from infection.

While the use of these measures has not been addressed in this survey, the importance of control measures cannot be understated. Control measures have helped decrease occupational cases of TB infection over the past several decades (CDC, 2009). In healthcare facilities and congregate settings, CDC (2011e) has recommended

- prompt methods for detecting TB;

- use of airborne precautions to prevent spread of tubercle bacilli; and

- prompt and proper treatment of individuals who have suspected or confirmed disease.

Occupational concerns must also be addressed, and include the implementation and use of environmental engineering controls. Use of personal protective equipment, such as personal respirators to prevent inhalation of infectious droplet nuclei should be worn by healthcare workers (CDC, 2009, 2011e). In addition, surgical masks should be worn by the infected patients to prevent spread of droplet nuclei into the air. In the environment of the medical microbiology laboratory, use of the BSC equipped with special filters and negative pressure rooms help to prevent airborne tubercle bacilli from escaping into the work area room air (CDC, 2005b). These examples demonstrate the importance of preventing spread of TB in the occupational setting.

Importance of identifying and treating latent infection among healthcare personnel. The importance of identifying and treating LTBI among HCP is evident in an example of transmission which took place during 2003, as reported by Fitzpatrick et al. (2005). A foreign-born nurse with undiagnosed active tuberculosis exposed 32 coworkers, 613 infants, and 900 patients while employed in a New York City hospital

nursery and maternity ward. An extensive contact investigation followed; transmission was documented in four infants that had positive TST. This nurse had been diagnosed with LTBI 11 years prior, but did not initiate treatment to prevent latent TB bacteria from becoming active TB. A similar scenario was reported in 2003 when a hemodialysis technician in Nevada became ill with pulmonary TB, exposing more than 400 patients and other employees (Hickstein et al., 2004). The HCW also had a previous positive TST result but never initiated treatment. The results of a contact investigation found that the HCW had transmitted *M. tuberculosis* to 29 patients and 13 employees. In yet another case, a neonatal intensive care unit respiratory therapist with pulmonary TB exposed 180 infant patients and 248 HCP (Nania et al., 2007). These examples demonstrate the importance of identification of LTBI in health care personnel, as well as timely LTBI preventive treatment initiation and treatment adherence.

Surveillance and Healthy People 2020. Surveillance of active TB cases (as well as contacts of active cases suspect for LTBI) and associated preventive treatment is important in stopping the spread of TB in the United States. The U.S. Department of Health & Human Services (n.d.) has set specific targets related to reducing active and inactive tuberculosis (TB) rates and increasing treatment completion rates in its Healthy People 2020 (HP2020) document. What follows is a synopsis of these targets. However, please note that only one of the four objectives (IID-31) is related to LTBI.   Foreign-born persons are targeted in objective GH-2, treatment completion (adherence) rate is addressed in IID-30, and reducing active TB cases is addressed in IID-29.

First, the global HP2020 objective GH-2 decribed decreasing the TB case rate for foreign-born persons living in the United States. (A target of 14.0 cases per 100,000 population was set in relation to a baseline of 20.2 cases of active TB per 100,000 population, reported for foreign-born persons living in the United States in 2008.) Second, the Immunization and Infectious Disease objective IID-29 described reducing TB. (A target of 1.0 new case per 100,000 population was set in relation to a baseline of 4.9 confirmed new cases of TB per 100,000 population, reported to CDC by all 50 States and the District of Columbia in 2005.) Third, objective IID-30 described increasing treatment completion rate of all TB patients who are eligible to complete therapy. (The target has been set at 93% in relation to a baseline of 83.8% of persons with confirmed TB completed curative therapy in 2006.) Fourth, objective IID-31 described increasing the treatment completion rate of contacts to sputum smear-positive cases diagnosed with latent tuberculosis infection and started on LTBI treatment. (The target has been set at 79.0% in relation to a baseline of 68.1% of contacts, diagnosed with LTBI, who completed a course of treatment in 2007.)

Surveillance and molecular testing. The advent of molecular testing has become important in prevention for several reasons. To date, genotyping has assisted in public health outbreak investigations involving tuberculosis. Current methods are used to study the molecular epidemiology of TB, such as tracing the chain of TB transmission in short-term and long-term outbreaks, determine global spread, detect mixed infections in TB patients, and help in identification of new strains and resistance, as well as understand recurrent TB infections (Mathema et al., 2006). In addition, genotyping has become

important in detecting errors in handling and processing of TB isolates, such as cross-contamination in laboratories which may lead to false-positive reports of TB (American Thoracic Society, 2005; Mathema et al., 2006). The extensive topic of molecular surveillance is beyond the scope of this research.

Screening and treating immigrants to the United States. Globally, variation in TB resistance patterns makes treatment of latent or active tuberculosis difficult. Given that the TB burden is disproportionately high among the foreign-born in the United States, the importance of screening and treating immigrants to the United States from developing regions of the world for LTBI has become an important strategy in stopping progression of TB and in halting development of resistant strains. One model has predicted that if this strategy were implemented in the United States for one year, 9,000 to 10,000 cases of active TB could be avoided at a savings of $60 million to $90 million (Khan et al., 2002). Given that these benefits would accrue over the long-term, the same model predicted that half of the calculated benefit would be realized within 6 years.

Vaccination (Bacille Calmette-Guérin immunization). Bacille Calmette-Guérin (BCG) immunization was first developed in 1908 by the French scientists, Calette and Guérin, and first administered in 1921 to ward off cases of TB (WHO, 2012). BCG is no longer used in the United States because it is considered useless in preventing adult pulmonary tuberculosis (CDC, 2010b). The vaccine contains a live attenuated (weakened) strain of *Mycobacterium bovis* (WHO, 2012). BCG is an immunization used in many TB-endemic regions of the world. The World Health Organization (WHO) has recommended that BCG vaccine be administered during infancy in TB endemic

countries; however, BCG vaccination is not recommended in the United States (CDC, 2010b). As many as one-quarter of surveyed medical school graduates believe incorrectly that immunization with the BCG vaccine offers long-term protection (Salazar-Schicchi et al., 2004).

Direct observation. Public health strategies that have been used to improve LTBI and TB treatment initiation and adherence have included forms of directly observed treatment (DOT). DOT strategies have demonstrated significant improvement in treatment success when compared with control groups (Hsieh et al., 2008), although one study of cohorts followed throughout the 1990s may not be in agreement. The Bayer et al. (1998) research demonstrated minimal improvement in TB treatment completion rates where completion rates reported from 80% to 87% overall were consistent, despite a DOT rate ranging from 16.8% to 49.4%. A similar strategy was reported by Tavitian, Spakek, & Bailey (2003) and involved use of a hospital-based clinic to prescribe LTBI treatment to HCP. Treatment completion rates ranged from 90% to 100% from 1997 to 2001, demonstrating significant improvement in overall adherence and completion.

<div align="center">

Description of the Research Variables

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Risk factors associated with LTBI and active TB infection among the general population have been described previously in this chapter, as have risk factors among populations of HCP and subpopulations of laboratorians.

Independent Variables (Risk Factors)

The independent variables in this study are BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience. The use of risk assessment

questionnaires is justifiable in many studies of disease exposure. These have been used

to study occupational exposures in medical students (Koppaka, Harvey, Mertz, &

Johnson, 2003). The following section will attempt to explain why the variables have

been chosen as risk factors, as well report on research associated with them.

Bacille Calmette-Guérin (BCG) immunization. BCG immunization was

chosen as an independent variable because it has appeared in TB study literature as a

significant predictor. Two cross-sectional studies using self-administered surveys in this

review of the literature found BCG as a significant predictor of TST positivity. For

example, among U.S. laboratory HCP self-reporting TST positivity, Garber et al. (2003)

found BCG a significant predictor using both univariate and multivariate analyses. Using

multivariate analysis, an OR of 4.89 was realized when comparing TST positivity in

individuals reporting ever having had a BCG immunization and those reporting never

having received BCG. In nearby Canadian populations, Hernandez-Garduno and Elwood

(2008) reported BCG as a predictor of TST positivity prevalence (OR 19.6.), again, using

multivariate analysis in the comparison of those reporting receipt of a BCG immunization

versus those who had no recollection of BCG history. BCG was not expected to be a

significant predictor in research studies involving high-incidence TB countries, where

BCG immunization is given routinely as a preventive course. To demonstrate this, the

U.S. study of medical school students by Koppaka et al. (2003) reported no such

association between BCG and TST positivity based on birth in a high-risk country.

Although the effect of BCG vaccine on TST reactions generally wanes over time,

boosting may occur leading to false-positive TST reactions. CDC (2010a)

recommendations state that history of BCG vaccine is not a contraindication for performing or interpreting the TST. Consequently, BCG may be a significant predictor of TB infection (latent or active) because (a) its result is a true positive result, or (b) BCG has caused a false-positive TST reaction to occur, leading to confounding due to cross-reactivity (refer to Chapter 3 for more detail).

Specific effects of BCG on the TST have been noted in the literature. In a review of 24 studies where subjects were immunized as infants, 1% of subjects were TST-positive when tested more than 10 years postvaccination (Farhat et al., 2006), a low percentage when compared with recent immunization. The same review included 12 studies involving subjects vaccinated after year one; 21.2% were positive after 10 years. Reviewing 18 studies where nontuberculosis mycobacteria (NTM) was a factor, cross-reactivity was low with TST positivity ranging from 0.1% to 2.3% (Farhat et al., 2006). These researchers (Farhat et al., 2006) have concluded that BCG received in infancy is associated with minimal TST positivity, and NTM is not a big factor in TST positivity (unless the populations being tested have a high prevalence or exposure to NTM versus MTB). In addition to cross-reactivity with BCG, the TST size of zone reactivity is also varied depending on age (older adults) and number of BCG vaccinations (Farhat et al., 2006; Kazanci et al., 2010).

Place of birth. Place of birth (U.S. or foreign) was chosen as an independent variable for this study because foreign birth has been associated with increased TST positivity (LTBI) and active TB disease in the United States, reported previously in this chapter.

Among HCP working in the United States, the following statistics have been quoted directly from a 2007 report:

•In 2005, 15 percent of all US health-care workers were foreign born.

•About 44 percent of the foreign born in health-care occupations arrived in the United States in 1990 or later.

•One in four doctors (physicians and surgeons) was born abroad.

•Foreign-born health-care workers, regardless of gender, were more likely to be physicians and surgeons as well as nursing and home-care aids than their native-born colleagues.

•Women accounted for more than 70 percent of the foreign born in health-care occupations.

•Nearly 40 percent of all foreign born in health-care occupations were from Asia.

•Foreign-born health-care workers were more likely to have a college education than their native-born counterparts. (Clearfield & Batalova, 2007, p. 1)

While Clearfield and Batalova (2007) did not address HCP subgroups such as medical laboratorians, it is clear that large numbers of foreign-born healthcare workers are working in a variety of disciplines.

According to Liu et al. (2012), in the United States from 2001 thru 2008 (a) 41.6% of cases of TB occurred among immigrants and refugees, (b) 36.6% among students, exchange visitors, temporary workers, and (c) the remainder of cases occurred among tourists, business travelers, and Canadian & Mexican nonimmigrant workers. Of note, only 500,000 of the estimated 163.5 million foreign-born persons admitted annually

to the United States received TB screening (Liu et al., 2012). These figures demonstrate the importance of examining foreign birth as a predictor of TST positivity among immigrants, and especially among those destined for work in fields of health care.

In cross-sectional studies using self-administered surveys, foreign birth as a predictor of TST positivity was found to be significant as a risk factor. Garber et al. (2003) reported an OR of 3.80. One U.S. study reported TST positivity at 48.5% among foreign-born (Cook et al., 2003). Other cross-sectional studies citing place of birth as significant include Hernandez-Garduno and Elwood (2008), and Menzies et al. (2003). Li, Munsiff, and Agerton (2010) reported TST prevalence was four times higher among nonU.S.-born than U.S.-born in one large cohort study.

Years of laboratory experience. Years of laboratory experience was selected as an independent variable for this study. While the Garber et al. (2003) cross-sectional survey used type of laboratory work in its assessment, other researchers added years of work experience to survey questions. Years (or duration) of work experience have been found significant in predicting factors associated with TST positivity and/or conversion in several studies (Menzies et al., 2003; Rafiza et al., 2011) and depend on the risk group, job category, and/or workplace. Garber et al. (2003) determined that mycobacteriology type of work experience was significantly associated with predicting TST positivity. However, calculation of years by date of hire was later considered a study limitation in the Garber et al. (2003) research, resulting in years as not significant in predicting TST positivity. It is important to note that the operational definition of years of work experience should include total years in order to avoid this confusion.

Dependent Variables

The dependent variables in this study are self-reported lifetime TST positivity, preventive treatment initiation, and barriers to treatment adherence (medication side effects). The following section will attempt to explain why each dependent variable was chosen for this study, and will describe some of the related research.

Tuberculin skin test (TST) positivity. TST positivity was chosen for this study because several studies have used TST positivity as a baseline in determining LTBI prevalence. The most applicable study to this research was Garber et al. (2003); prevalence of latent TB infection was specifically defined as a positive TST result. TST positivity prevalence has been used extensively as a dependent variable in the literature, as evidenced by studies mentioned previously in this chapter.

Validity of the self-reported tuberculin skin test. At this point of the literature review, it is important to discuss literature associated with self-reported TST results. The search of the literature revealed several studies where self-reported TST data was validated using different methods now described.

Ascertainment of self-reported TST results with prior medical records of a subsample ($n = 71$) of injection drug users with HIV coinfection at a treatment program (Wolfe et al., 1995). Results found a high degree of reliability; > 90% of results were classified correctly.

Ascertainment of self-reported TST results with prior Occupational Health Services medical records of a subsample ($n = 42$) of microbiology laboratory workers in a New York City study (Garber et al., 2003). Results indicated 100% concordance.

Assessment of self-reported TST results among patients enrolled in a methadone treatment center compared with newly administered PPD booster tests. Nearly a third of patient self-reports of positive tests did not match obtained booster PPD negative results, presumably due to reversion of the PPD due to immune dysfunction (Kunins et al., 2004). (The discordance rate among HIV-infected subjects was 43%, while the discordance rate among HIV sero-negative subjects was 27% in this study.) While the phenomenon of TST reversion is currently under review (Tuberculosis Epidemiologic Studies Consortium, 2012), this study provided an example of assessment after initial survey, limited by inability to compare to prior medical records.

Research by Martin, Leff, Calonge, Garrett, and Nelson (2000) was more generic in nature, reflecting on validation of self-reported data as related to three chronic health conditions of hypertension, hypercholesterolemia, and diabetes (not specific to the TST result). Results were obtained by comparing subject survey results to medical records. Results were considered generally valid, with a high degree of validity: > 80% sensitivity, 86% to 99% overall.

Use of a self-reported TST was reported in several studies. For example, in validating the reading of actual TST zones of induration by patients and trained healthcare professionals, patients detected presence/absence of induration 99.3% of the time (Ozuah, Burton, Lerro, Rosenstock, & Mulvihill, 1999). Use of self-reported TST was also found in literature related to demographic characteristics and surveys in TB research to assist in diagnosing individuals (Bock, McGowan, Ahn, Tapia, & Blumberg, 1996; Marks et al., 2008).

Preventive treatment noninitiation. LTBI preventive treatment noninitiation rates were chosen as a dependent variable in this research because to date, very few studies have examined risk factors of TST positivity with treatment initiation. The terminology of preventive treatment was chosen for this dissertation because of a recommended change from prior terminology of preventive therapy (Cohn, 2000). Garber et al. (2003) was the only article located in this search that reported on treatment initiation rates among medical laboratorians; however, no mention was made as to the association of risk factors to initiation (or noninitiation) of preventive treatment. One U.S. study reported a high (84%) initiation rate among HCP (Camins et al., 1996). This review has already noted that CDC recommends treating TST-positive personnel working in mycobacteriology laboratories (CDC, 2005b) as well as consideration of risk groups when prioritizing LTBI treatment (Horsburgh, 2004).

LTBI treatment initiation rates of HCP are traditionally lower than those of non-healthcare personnel, reported at rates of 58% (Gershon et al., 2004). Treatment adherence and completion rates have been reported as suboptimal (Hirsch-Moverman et al., 2008), and as low as 19% (Bieberly & Ali, 2008) in some U.S. populations. Studies have demonstrated stigma barriers as associated with treatment noncompliance (Macq, Solis, & Martinez, 2006), while other studies have found that harmful, adverse effects of treatment were problematic (Joseph et al., 2004). Referring to health care workers (HCWs): "The most feasible means to improve LTBI treatment among HCWs is to address factors that impede adherence to guidelines" (Gershon et al., 2004, p. 671).

Another concern is that physician attitudes toward treatment of latent tuberculosis infection may not match recommendations set forth by CDC and WHO. International medical graduates have been surveyed and the majority was found to be less likely to treat themselves and family members, believing that BCG immunization protects long-term, LTBI treatment is ineffective, and risks of treatment are greater than benefits (Salazar-Schicchi et al., 2004). These attitudes, if present among healthcare providers, are yet another concern in initiating effective treatment. Although causes of preventive treatment noninitiation appear multidimensional, this study planned only to document whether or not the respondent (host) ever initiated treatment for a positive TST.

Treatment nonadherence (barriers). The variable of treatment nonadherence (presence of medication side-effect barriers as measured by the Brief Medication Questionnaire) was chosen for this study because to date, this search and review of the literature has not located any study related specifically to medical laboratory microbiologists. While treatment symptoms and BCG immunization have been found to be associated with nonadherence among HCP (Shukla et al., 2002) as well as in the general public (Hirsch-Moverman et al., 2008), no study has compared symptoms using a validated survey instrument among HCP. Adherence to treatment is cost-effective (Sokol, McGuigan, Verbrugge, & Epstein, 2005) but difficult to sustain for many reasons. In the case of active TB disease, treatment lasts many months and patients may stop taking medication(s) once they begin to feel better (CDC, 2011b). Treatment for LTBI is even more difficult if the individuals remain asymptomatic (Charles P. Felton National Tuberculosis Center, 2005; Joseph et al., 2004). Adherence in first month of

LTBI treatment predicts treatment completion (Menzies et al., 2005). Nonadherence can lead to treatment failure and to development of drug-resistant strains of TB (CDC, 2011e) as discussed earlier in this chapter.

It is important to note that CDC (2011e) defines treatment completion as determined by the number of doses taken over a defined period of time, and not the number of weeks or months of treatment. (Number of doses is dependent on the type of treatment regimen.) This research is not designed to gather detailed data on treatment completion; however, the question regarding completion was asked of survey respondents in order to help characterize the study cohort. Blumberg (2004) reported that the greatest strategic need in the U.S. in the fight to control TB is to find ways to improve poor LTBI treatment completion rates.

Treatment adherence is a multidimensional process including patient, treatment, environment, disease, provider, and patient-provider characteristics (Kennedy, 2000). In one qualitative study, focus groups were utilized to gauge healthcare workers' adherence to LTBI treatment in terms of barriers and perceptions (Joseph et al., 2004). The Joseph et al. study identifed several items as important barriers to treatment adherence:

- treatment is harmful with adverse effects;

- no need for medication if asymptomatic;

- misunderstanding of TB pathology;

- failure of providers to recommend treatment; and

- insufficient support by employee health, distrust or lack of confidence in employee health.

Examples of behavioral barriers and stigma associated with poor treatment adherence have been reported (Macq et al., 2006; McEwen & Boyle, 2007), as well as barriers due to differences in cultural beliefs and values (Michaels, McEwen, & McArthur, 2008). Adherence has been reported to be as low as 19% in some populations for reasons of insufficient infrastructure and social support (Bieberly & Ali, 2008). Poor past adherence was found to be the best indicator of present adherence, and avoidance coping was a strong predictor of poor adherence (hoping the disease will go away on its own) as researched by Sherbourne, Hays, Ordway, DiMatteo, and Kravitz, (1992) in chronically ill patients.

Harmful treatment with adverse effects was chosen as the type of barrier for this research, measured using the BMQ validated survey instrument. In general, LTBI treatment was most affected by medication intolerance in one study (Machado et al., 2009). In a study of U.S. HCP, one-third of employees (12 of 36) initiating but not completing LTBI preventive treatment reported barriers of adverse drug effects (Camins et al, 1996). Non-adherent HCP (26 of 51), a number approximating 51%, cited reasons of adverse drug effects, suspicions that medication was harmful or toxic, and feelings that the treatment was "overkill" (Joseph et al., 2004, p. 459) for not taking medication.

A systematic review of U.S. and Canadian studies also pointed to concerns about LTBI and TB medication side effects and toxicity (Hirsch-Moverman et al., 2008), as did a study of male veterans (Fincke, Miller, & Spiro III, 1998). The literature is in agreement: adherence decreases with an increase in duration of regimen and side effects (Charles P. Felton National Tuberculosis Center, 2005).

The CDC (2005a) reported that adverse effects of drugs used to treat LTBI cause concerns related to length of treatment and potential side effects.   Possible medications and their adverse effects include the following (CDC, 2005a):

Isoniazid (INH)

- asymptomatic elevation of serum liver enzymes (occurs in 10 % to 20 % of those taking INH);

- hepatitis in 0.1% to 0.15%, and is more common when INH is used in combination with other agents (alcohol consumption, underlying liver disease), sometimes fatal; and

- peripheral neuropathy reported in 0.2%, more likely when INH combined with diabetes, HIV, renal failure, and alcoholism.

Rifampin (RIF)

- hepatotoxicity (hyperbilirubinemia) in 0.6%;

- cutaneous reactions (pruritis with or without rash) in 6% of individuals;

- gastrointestinal symptoms (nausea, abdominal pain);

- orange discoloration of body fluids (orange staining of contact lenses);

- drug-drug interactions; and

- contraindicated in HIV patients being treated with certain anti-HIV medications.

These side effects can be debilitating. Predictors of nonadherence may include items affecting sick patients, but also things which may affect sick and well individuals alike, such as "sick from side effects of medications" (Kennedy, 2000, p. 314).

Hepatotoxicity in INH treatment of LTBI has occurred at a rate of 5.6 per 1,000 patients and appears age-related, greatest in those age 50 years and older (Fountain, Tolley, Chrisman, & Self, 2005). Healthcare personnel perceive that LTBI treatment is harmful and treatment carries a high probability of causing adverse effects (Joseph et al., 2004).

Review of measurement tools for treatment nonadherence. A review of the literature for survey tools used in assessing medication treatment adherence among individuals produced mixed results. Much of the literature was geared toward a patient population, not the relatively healthy healthcare personnel population that is the intended population of interest in this study. In addition, questionnaires specific to tuberculosis were few. The Tuberculosis Adherence Determination Questionnaire (Holstad, 2001a) and the Tuberculosis General Adherence Scale (Holstad, 2001b) first appeared in "*Antecedents of adherence to antituberculosis therapy*" (McDonnell et al., 2001), and address medication adherence based on interpersonal aspects of care, perceived utility of treatment, subject norms, intentions, and support. As mentioned, these surveys, as well as the Medication Adherence Questionnaire (Toll, McKee, Martin, Jatlow, & O'Malley, 2007) are used to assist in counseling patients regarding importance of medication adherence. Self-efficacy and health belief model form the basis for these and many of the medication adherence questionnaires. Variations of these questionnaires have appeared in literature associated with different infectious and chronic diseases such as HIV (Holstad, Foster, Dilorio, McCarty, & Teplinksy, 2010; Johnson et al., 2007). One basis for these questionnaires and scales is the work by DiMatteo et al., published in 1993, in

which cancer control regimens were assessed using a 38-item self-reported adherence questionnaire.

A review of five different adherence scales was performed by Lavsa et al. (2011) with the conclusion being that "no gold-standard medication adherence scale exists" (p. 90). One of the five under review was the Brief Medication Questionnaire (BMQ), a questionnaire developed by Svarstad et al., 1999) for use in detecting different types of nonadherence. The scale includes a two-item belief screen to "assess beliefs about drug efficacy and bothersome effects" (Lavsa et al., 2011, p. 92). The BMQ, initially validated in patients taking angiotensin-converting enzyme inhibitors, has also been used in patients with diabetes, depression, and other chronic diseases (Lavsa et al., 2011; Svarstad et al., 1999).

The BMQ instrument was chosen over several other questionnaire tools for addition to this main survey instrument tool for several reasons. The BMQ is short, already validated as a survey instrument tool, and relates directly to treatment medications. Comparison of several other survey tools (Charles P. Felton National Tuberculosis Center, 2005; Holstad, 2001a, 2001b; New Jersey Medical School National Tuberculosis Center, n.d.) revealed that most tools were not useful for surveys such as this the one used in this study. Other tools referred to active, current administration of treatment medications, or were geared toward patient populations (and not an educated HCP population). These types of items are not applicable when asking HCP respondents to self-report past TST treatment history. Specific questions pertaining to medication side effects are easily scored using the 2-item Belief Screen portion of the instrument

(Svarstad, Chewning, Sleath, & Claesson, 2003). More information on the validation and use of the BMQ will be presented in Chapter 3.

Description of the Research Variables

The research variables for use in this study were based on those used in the Garber et al. (2003), Hernandez-Garduno and Elwood (2008), Menzies et al. (2003), and Rafiza et al. (2011) cross-sectional survey formats, as well as the BMQ as it applies to medication side effects (Svarstad et al., 2003). I derived a master data set coded for the following variables of self-reported lifetime TST positivity, history of BCG immunization, place of birth, years of laboratory experience, self-reported initiation of treatment, and treatment nonadherence (medication side effect barriers) as addressed using two questions from the Brief Medication Questionnaire (Svarstad et al., 1999). The nature of each variable is described as follows (as previously discussed in Table 1, Chapter 1):

- *Self –reported lifetime history of TST positivity*: Dichotomous nominal variable, coded as either TST-negative or TST-positive.

- *History of BCG immunization*: Nominal variable. Two levels coded as no or yes.

- *Place of birth (U.S. or foreign):* Nominal variable. Two levels, coded as U.S. or foreign.

- *Years of laboratory experience*: Nominal variable. Six levels, coded as (a) 0-2 years, (b) 3-5 years, (c) 6-10 years, (d) 11-15 years, (e) 16-20 years, or (f)

over 21 years. Nominal groupings of each (no or yes) may be collapsed if

necessary.

- *Self-reported initiation of treatment* (once prescribed): Nominal variable.

   Two levels coded as no or yes. Risk factors to be assessed as related to

   noninitiation of treatment.

- *Barriers to treatment adherence (medication side effects):* Using the Brief

   Medication Questionnaire (BMQ) Belief Screen (Svarstad et al., 1999);

   questions 1(g), "How well did this medication work for you?" and 2(a), "Did

   any of your medications bother you in any way?" Combined BMQ score

   coded for three levels, (a) 0 = score of 0, (b) 1 = score of 1, or (c) 2 = score of

   2. Score will be translated to < 1 (no adherence barriers present = no); ≥ 1

   (adherence barriers present = yes). This scoring is referenced as published in

   the original validation by Svarstad et al. (1999).

These variables and the necessary inclusion criteria will be used in the study

analyses to make descriptive comparisons between all subjects in the chosen, defined

study population of medical laboratory microbiologists. Please refer to Chapter 3 for

study method detail.

Theories in Latent and Active Tuberculosis Research

Prior to discussing a comparison of the research designs, it is essential to discuss

the literature as it pertains to grounded theory in past and current LTBI and TB research.

Several different theories continued to appear throughout this review of the pertinent

literature. Louis Pasteur's germ theory, which is the basis for all research on infectious

disease, and Koch's Postulates on tuberculosis have led to the development of the present day epidemiologic triad model. Use of these principles is the basic underpinning for much of the research pertaining to TST positivity and risk factors.

Louis Pasteur's development of the germ theory of disease in writings from 1857-1858, helped form the basis for understanding of all microscopic organisms (Halsall, 1998). Koch subsequently published his discovery of tubercle bacilli in 1882 (Grimes, 2006). Koch's Postulates describing ideas about tuberculosis were formalized between 1884 and 1890 and were based on asking basic questions of (a) whether the organisms demonstrate consistency in characterization; (b) whether the organism is the cause of the illness; (c) whether the isolated organism is the cause of the disease when introduced into a health individual; and (d) if so, then the all the usual characteristics of the organism and disease are reproduced (Grimes, 2006).

These theories have formed the basis for theories and models of infectious disease, including the epidemiological triad (or triangle) model. The emphasis on the three sides of this conceptual triangle is the relationship of disease to the host, agent, and environment (Rockett, 1999; Smith, 2002). Further description of this interaction has been defined earlier in this dissertation as a framework (Williams & Nelson, 2007) of:

- agent (infecting organism or pathogen: bacteria, virus, parasite, fungi),

- host (diseased individual), and

- environment (setting where transmission occurs; factors involved).

The first evidence supporting development and use of the epidemiologic triad model has been attributed to Snieszko (1974) for research involving infectious diseases of

fish. In this research, infection occurred when susceptible fishes were "exposed to virulent pathogens under certain environmental stress conditions" (Snieszko, 1974, p. 197). More recent use of the model has involved a use of Haddon's Mattrix for assessing injury with the epidemiologic triad to understand and design programs for injury control (Lett, Kobusingye, & Sethi, 2002). In this research, injury was likened to the element of disease agent. The triad model has also been useful in infection control research of susceptible hosts, using immune status, integrity of skin membranes, agents of normal flora, and the environment of the home setting to explain acquisition of infections in home healthcare (Friedman & Rhinehart, 2000).

Research involving serious emerging infectious diseases having an animal source (such as severe acute respiratory syndrome [SARS], avian influenza, West Nile virus, monkeypox) and links between agent, host, and environment in the spread to humans have been of recent interest (Bender, Hueston, & Osterholm, 2006). Along this line of thinking, Huerta and Leventhal (2002) have used the triad model to help explain a change in vectors of disease to new and dangerous intentional vectors, intended to spread agents through the environment to susceptible hosts. An example of this concept has been in recent acts of bioterrorism using anthrax as the agent.

While the epidemiologic triad model has been useful in explaining relationships between various aspects of LTBI (TST positivity, preventive treatment noninitiation, and select treatment adherence barriers, see Chapter 1 for detail), the Health Belief Model (HBM) has also been useful in exploring behaviors associated with treatment initiation and adherence barriers.

The health belief model (HBM) was developed in the 1950s by the Public Health Service as a way to explain and predict preventive health behaviors, specifically, why individuals did not seek TB treatment (Abraham & Sheeran, 2007). One aspect of HBM is known as perceived costs or barriers to taking action. Preventive health behavior may not take place, even though an individual may believe benefits to taking action are worthwhile. Barriers to treatment, for example, may include inconvenience, expense, unpleasantness, painfulness, or upsetting characteristics (Rosenstock, 1974). Characteristics referred to as barriers may prevent the individual from adhering to desired treatment action. While HBM has not been used as a basis for this study, its relevance to other material found during the search process is great. Research by Bieberly and Ali (2008), Macq et al. (2006), McEwen and Boyle (2007), Michaels et al. (2008) and others have informed knowledge to date regarding treatment initiation and adherence, as well as adherence barriers.

One last theory that will be mentioned is the social cognitive theory. In research involving U.S. Hispanic migrant workers diagnosed with LTBI, social cognitive theory was used to ground a study that took place on several farms in the Midwestern U.S. (Wyss & Alderman, 2007). Several environmental factors were identified as barriers to diagnosis and adherence with LTBI treatment. The most significant barriers may have been feelings of lack of control over the disease process and lack of treatment options available to migrants. In addition, the researchers identified feelings of lack of control, fear of deportation, and language as barriers. In the U.S., where the majority of cases of

TB have been reported to take place in the foreign-born, these types of barriers will be important in future LTBI research.

Methods

Design Methods Used in Latent and Active Tuberculosis Research

In research on tuberculin skin test (TST) positivity, latent tuberculosis infection (LTBI) treatment initiation, and barriers to treatment adherence, methodologies and analysis methods presented in the literature review include observational (descriptive case series reports and cross-sectional surveys, as well as analytic studies including cohort and case-control designs), experimental, qualitative (ecologic and focus groups), and literature reviews. In most cases, studies were either in cross-sectional survey or cohort format, or a combination of both.

While all methods revealed useful information as presented in other sections of this literature review, only the cross-sectional survey method emerged as appropriate for this study. Examples of each method and the types of information gleaned from each are presented below.

Case series reports. Three different examples of case series were located in this search of relevant literature. First is an important example of a nurse with undiagnosed active TB (point source and the resulting contact investigation demonstrating the importance of taking prescribed treatment for LTBI (Fitzpatrick et al., 2005). Second, a case series which used Census data to estimate occupations associated with TB (McKenna et al., 1996). The last case series report focused on HCP already diagnosed with LTBI, and measured preventive treatment acceptance and adherence (Camins et al.,

1996). All three case reports were useful in identifying importance of initiating prescribed treatment, as well as in associating TB infection with certain occupations.

Cross-sectional surveys. Numerous studies located in this literature review were cross-sectional in nature. Eighteen studies determined to be cross-sectional were examined more closely. Two utilized a cross-sectional analysis of surveillance data (Cain et al., 2007; Zuber et al., 1997) to obtain data of the TB risk among the foreign-born in the United States. An anonymous survey of physicians' attitudes gathered data on physician TST-positivity prevalence and perceptions of BCG protection (Salazar-Schicchi et al., 2004), while another surveyed medical students for TST positivity, conversions, and risk factors (Wurtz et al., 1994).

The vast majority of the cross-sectional studies utilized survey questionnaires of HCP or the subpopulation of laboratorians for gathering data on prevalence or incidence of active TB (Harrington, & Shannon, 1976) or prevalence of LTBI (Alonso-Echanove et al., 2001; Drobniewski, Balabanova, Zakamova, Nikolayevskyy, & Fedorin, 2007; Garber et al., 2003; Menzies et al, 2003; Rafiza et al., 2011). One historical study (Reid, 1957) utilized a cross-sectional approach in collecting data obtained from several sources in order to determine prevalence and incidence of TB in laboratorians compared with data obtained from the general public. Two studies set out to evaluate occupational factors associated with LTBI (Menzies et al., 2000; Vaquero et al., 2003). In three studies, surveys were sent directly to U.S. laboratories to assess the prevalence of lab-acquired infections (Jacobson et al., 1985; Kao et al., 1997; Sulkin & Pike, 1951). The two remaining studies surveyed patients for active TB treatment adherence (McDonnell

et al., 2001), and TST predictors and positivity prevalence among a large group of Canadians from the general population screened for reasons other than contact investigation (Hernandez-Garduno & Elwood, 2008).

Cohort design. In all, 30 articles undergoing this literature review were determined to have used a cohort design, either prospective or retrospective cohort. In many cases a combination of the survey method and cohort design was used, most often to determine TST positivity and assess risk factors by survey, and then move on toward determination of TST-conversion over some predefined time period using cohort design. Strict use of the cohort appeared to be utilized more often when the desired study outcome was TST-conversion (LTBI incidence) or long-term treatment adherence outcome measures.

Ten study articles referred to determining rates of TST conversion (in addition to risk factor assessment) among HCP. Five took place in the United States (Bailey, Fraser, Spitznagel, & Dunagan, 1995; Cook, Maw, Munsiff, Fujiwara, & Frieden, 2003; Larsen et al., 2002; Miller et al., 2002; Panlilio et al., 2002), while another five took place outside the U.S. (Baussano et al., 2007; Christopher et al., 2010; de Vries et al., 2006; Kraut et al., 2004; Roth et al., 2005). In addition, the Koppaka et al. (2003) and Li et al. (2010) research was included in this review as pertaining to TST conversion, although performed on university students and chest center patients, respectively.

Only one retrospective cohort reported on preventive treatment initiation in HCP (Gershon et al., 2004), while one study developed a hypothetical cohort to detect and initiate LTBI treatment initiation (Khan et al., 2002). Six reported findings related to

preventive treatment adherence, related to LTBI or other general disease states (Bayer et al., 1998; Bieberly & Ali, 2008; Sherbourne et al., 1992; Shukla et al., 2002; Sokol et al., 2005; Tavitian et al., 2003), while another three reported on drug treatment adherence barriers and associated risk factors (Fincke et al., 1998; Fountain et al., 2005; Machado et al., 2009).

Of related interest to the topic at hand, three cohort studies compared use of TST with IGRA blood tests (Ferrara et al., 2005; Mazurek et al., 2001; Soberg et al., 2007), while four detected strain resistance over time (Calver et al., 2010; Cohen et al., 2011; Tang et al., 2011; Velasquez et al., 2011).

None of the cohort studies reflected in this review reporting on HCP and TST conversion specifically studied medical laboratorians or subgroups of the laboratorians in any detail. One particular study (Bailey, Fraser, Spitznagel, & Dunagan, 1995) grouped different HCP by direct patient contact and appeared to misclassify the laboratorians completely, thus missing any laboratory occupational exposures.

Case-control design. In the literature review at hand, one case-control study only was located. The study was not a true case-control, but a combination of methods. In this study, a diagnosis of LTBI using different diagnostic methods prompted placement of subjects into four different groups, one of which was a control group (Ozekinci et al., 2007). This control group contained subjects having no history of contact with TB or TB-infected individuals.

Experimental. Very few experimental studies were located that were intended to investigate outcomes of interest, such as TST positivity, preventive treatment initiation

(or noninitiation), or treatment adherence barriers. One quasi-design detailed use of DOTs in TB patients along with long-term adherence outcome as measured by treatment completion (Hsieh et al., 2008). LTBI preventive treatment adherence was studied in one example of a randomized drug trial by Menzies et al. (2005). Both examples were somewhat similar in that adherence was related and measured as completion of long-term treatment therapy. This type of experimental study protocol was also ruled out as a useful method in that no preventive treatment completion was estimated or measured as a function of adherence in this study.

Qualitative. A brief review of the literature to assess factors influencing adherence to LTBI and TB preventive treatment revealed several studies guided by behavioral models. Focus groups were used to assess resistance to assess factors influencing HCW adherence to LTBI treatment (Joseph et al., 2004). A combination of focus groups and ethnography qualitative methods assessed reasons for resistance to LTBI treatment among Mexican immigrant populations (McEwen & Boyle, 2007; Michaels et al., 2008). One study combined mixed methods and a literature review to create a stigma assessment instrument aimed at assessing stigma experiences of those with active TB (Macq et al., 2006). Only the Joseph et al. (2004) study dealt specifically with HCP and the perceived barriers in obtaining the TST, as well as the perception that LTBI treatment was harmful and may cause unwanted side effects. The other three studies dealt with the cultural and behavioral issues outside the scope of this research.

Reviews. In all, 14 review papers were included in this review of the literature. General informational reviews, meta-analysis, and systematic reviews provided data and

useful citation references. Seven of the 14 reviews were general and information, including summaries of laboratory-acquired infections (Pike et al., 1965; Sewell, 1995; Singh, 2009), summaries of TB and associated risk factors in laboratorians (Lonnroth et al., 2009; Sepkowitz, 1994), a general review of guidelines and recommendations for preventing TB in laboratories (Collins & Grange, 1999), and finally, a general review of LTBI risk estimates with the goal of creating a model for targeted LTBI treatment in the United States (Horsburgh, 2004). Three papers presented as meta-analysis of occupationally-acquired LTBI or TB in health-care settings (Baussano et al., 2011; Menzie et al., 2007; Seidler et al., 2005). The final four studies were classified as systematic reviews and dealt mainly with the topics of TB infection incidence and prevalence among HCP (Joshi et al., 2006), TB surveillance and control (Lonnroth et al., 2010), effect of BCG on TST results (Farhat et al., 2006), and adherence to LTBI treatment measures, rates, and predictors (Hirsch-Moverman et al., 2008). While these reviews covered LTBI and the TST, as well as some issues of treatment nonadherence (barriers, such as medication side effects), no one review dealt with preventive treatment initiation or associated risk factors.

Size and duration of studies. While descriptive data for healthcare personnel populations are numerous, data specific to laboratory personnel is limited. Sample sizes in cross-sectional and cohort studies referring to TST positivity and/or conversion, as well as risk factors among HCP, varied from $n = 101$ (de Vries et al., 2006) to $n = 10,795$ (Larsen et al., 2002). In the study of New York City laboratorians by Garber et al. (2003), $n = 345$. The largest studies involved data mined from other sources such as the

cross-sectional studies involving surveillance data (Hernandez-Garduno & Elwood, 2008), where *n* = 59,791 individuals. While most of the cross-sectional survey studies utilized questionnaires given at one point in time, an exception was the Garber et al. (2003) study involving measurement of TST conversion over 2 years. The time of study duration of the prospective cohort studies involving the TST among HCP was limited from a minimum of 1.5 years (Panlilio et al, 2002; Roth et al., 2005) to a maximum of 8 years (Cook et al., 2003). Pertinent LTBI prevalence, incidence, and TB statistics were collected from studies performed in the United States (Cain et al., 2007; Cook et al., 2003; Garber et al., 2003; Li et al., 2010; Panlilio et al., 2002; Shukla et al., 2002; Zuber et al., 1997), Canada (Gershon et al., 2004; Hernandez-Garduno & Elwood, 2008; Menzies et al., 2000; Menzies et al., 2003), Malaysia (Rafiza et al., 2011), and United Kingdom (Reid, 1957). The largest and most recent study of medical laboratory microbiologists was that performed by Garber et al. (2003), although a Russian study of LTBI in HCP established the laboratory as a significant entity (Drobniewski et al., 2007), as did the Malaysian research (Rafzia et al., 2011).

One prominent systematic review described low- and middle-income countries with respect to LTBI and TB prevalence and incidence among HCP (Joshi et al., 2006). Seidler et al. (2005) described occupationally acquired active TB in low-incidence areas, and Menzies et al. (2007) performed a notable systematic review with meta-analysis on active TB infection in healthcare settings by a country's mean income.

In general, the research methodologies chosen for TST positivity, treatment initiation, and treatment nonadherence (barriers) depended on study design, size of chosen study population, and length of study duration.

Analysis Methods Used in Latent and Active Tuberculosis Research

In the review of the literature, cross-sectional studies using self-administered surveys or interviews to obtain data pertaining to suspected risk factors often included calculations of outcome prevalence and survey response rates. Four such studies have been compared in order to determine useful analysis methods. LTBI (defined as TST positivity or TST conversion) and associated risk factors were compared using univariate and bivariate analysis by Garber et al. (2003), Hernandez-Garduno & Elwood (2008), Menzies et al. (2003), and Rafiza et al. (2011) against risk factors (such as age, foreign birth, BCG immunization, years and/or type of work). Multivariate analysis of the significant risk factors was then performed and depicted by use of tables. Preventive treatment initiation was also reported as a percentage by Garber et al. (2003), although no reasons were given in the Garber et al. research for individuals choosing not to initiate treatment. In the only paper to analyze treatment initiation, Rafiza et al. (2011) reported initiation as a function of whether or not the individuals received any treatment for active TB, using univariate analysis of characteristics. However, no study in this review demonstrated research performed using univariate, bivariate, or multivariate analysis of the preventive treatment initiation data.

Similar analyses appeared throughout the cohort study design literature, with the difference that instead of using TST positivity, conversion rates were used as well as

suspected risk factors. Again, in literature examples where comparison of group characteristics was made using univariate or bivariate analysis, predictors of outcome were determined by multivariate analysis (Bailey et al., 1995; Baussano et al., 2006; Kraut et al., 2004; Panlilio et al., 2002; Roth et al, 2005). Cook et al. (2003) reported only on characteristics of employees, occupation, as well as prevalence of TST positivity at baseline and TST conversion rates.

A flurry of research occurred during the mid-1990s and early 2000s because of an upsurge of U.S. TB cases, most especially associated with HIV comorbidity. A long and notable history of research involving occupational TB in laboratorians has been published, most occurring during the mid-twentieth century. An understanding of TB prevention and the advent of engineering controls have changed the face of LTBI and active TB in the United States.

These points aside, of significance is the lack of notable literature representing HCP and preventive treatment initiation (or noninitiation), as well as treatment adherence barriers (as related to treatment nonadherence). Only one pertinent study emerged demonstrating analysis of these variables. A prospective cohort study by Shukla et al. (2002) reported on rate of treatment initiation as well as on rate of treatment completion. Analysis of adherence to LTBI treatment among HCP was performed using univariate, bivariate, and multivariate analysis against BCG vaccination and disease symptoms. However, this example was limited in that the grouping 'laboratory workers' appeared to be misclassified as nonclinical, and included in the same outcome groups as clerical and custodial staff when compared against other HCP.

Confounders. Confounders were only briefly mentioned as such in the literature under review, although most of the reviewed studies did assess for them by using multivariate (logistic regression) analysis. For outcomes involving tuberculin skin test positivity, three main confounders have been identified as (a) immunization with BCG (Diel et al., 2009; Wang, Turner, Elwood, Schulzer, & FitzGerald, 2002), (b) nonoccupational exposures to active TB cases (Garber et al., 2003), and (c) unmeasured indicators of occupational exposure such as numbers and days of occupational exposures (Joshi et al., 2006). Age has been identified as a confounder because older individuals had a greater exposure prior to the advent of treatment in the 1940s and 1950s (CDC, 2010b; Nobelprize.org, 2012). One study by Farhat et al. (2006) dispelled previous issues of confounding among those infected with nontuberculosis TB in most populations, and also among those receiving BCG vaccine during infancy. But in the latter cases, the TST was tested > 10 years after the initial immunization occurred, in agreement with Wang et al. (2002) findings suggesting that BCG no longer remains a confounder if the immunization was given years prior to the TST. Work by Kunimoto et al. (2009) has also dispelled BCG as a confounder in TST research, backed by use of the newer IGRA blood test.

Gap in the Literature

In reviewing the prior sections on research and analysis methods used in determining LTBI or TST positivity, risk factors, preventive treatment initiation, and barriers to treatment adherence (medication side effects) among HCP, a gap is noted in a lack of studies among laboratorians, particularly medical laboratory microbiologists at

the national level in the United States. In addition, no one study demonstrated any type

of deep inquiry into the association between risk factors and preventive treatment

noninitiation or barriers to treatment adherence (medication side effects). Treatment

nonadherence (barriers) was noted principally in qualitative studies when compared with

this review of quantitative studies. Although research instruments have been used to

gather quantitative treatment adherence data from the general population, no one study as

represented by this literature review utilized any specific instrument in the HCP or

medical laboratory microbiologist population.

Conclusions Regarding Tuberculin Skin Test Positivity and Treatment Among U.S.

Medical Laboratory Microbiologists

The literature review provided background information on past and current TST

use in the screening of individuals for latent or active TB. In addition, this review

showed that in most cases, U.S. medical laboratory workers (especially microbiologists

and/or mycobacteriology laboratory workers) are at higher risk of LTBI and/or active TB

infection than their HCP counterparts and the general public. In the United States and

Canada, risk factors for this population include age, foreign birth, BCG immunization,

and work in the mycobacteriology laboratory (Garber et al., 2003), and years of work

experience (Menzies et al., 2003; Rafiza et al., 2011). As a subpopulation, little data are

available regarding LTBI preventive treatment initiation, treatment nonadherence

(barriers to adherence), or associated risk factors. A very low preventive treatment

initiation rate has been attributed to the laboratorian by Garber et al. (2003), but reasons

for this were not examined as in other literature pertinent to HCP in general.

Summary of the Literature Review

This research was necessary in order to identify and target this meaningful subpopulation of HCP in the United States, the medical laboratory microbiologist, for determination of self-reported lifetime history of TST positivity prevalence and risk factors, preventive treatment initiation prevalence and risk factors, and risk factors of treatment nonadherence (barriers). The elimination of TB infection in the United States is an overarching goal of the IOM (2000) and the U.S. Healthy People 2020 document (U.S. Department of Health & Human Services, n.d.). This research will add to the existing knowledge of literature by adding data assembled from a nationally known U.S. registry group of medical laboratory microbiologists registered with the American Society for Clinical Pathology (ASCP).

Research of U.S. HCP has been limited in that is has not been consistent in breaking out the subgroup having indirect contact with patients contaminated with TB microorganisms—the medical laboratorian working in the microbiology or mycobacteriology laboratory. The HCP workforce in the United States is also changing with large numbers of foreign-born employees presently working in all disciplines. The TST continues to be the primary tool for screening at-risk populations, such as the foreign-born immigrant population, and mycobacteriology laboratory personnel for LTBI. TST positivity prevalence is high in some laboratory workers, gauged to be 57% according to one small but significant study (Garber et al., 2003), and risk factors associated with LTBI prevalence and incidence included BCG immunization, foreign birth, and type or years of work experience in the United States and Canada among HCP

(Garber et al., 2003; Menzies et al., 2003). Preventive treatment initiation rates have been reported at only 20% in medical laboratorians (Garber et al., 2003), although this literature review has reported higher treatment initiation rates among other groups of HCP. Treatment nonadherence (barriers to adherence) has not been reported among medical laboratorians; but among HCP, significant barriers have involved perceptions of adverse drug effects or drug toxicity. The Brief Medication Questionnaire has been used to document these types of treatment adherence barriers in disease outcomes other than LTBI or TB.

Methods for assessing TST positivity prevalence and risk factors have been limited to cross-sectional, or a combination of cross-sectional with cohort design when seeking incidence of TST conversion. The most useful and well-designed study pertaining to this research was the Garber et al. (2003) study of microbiology laboratory workers in New York City. From this literature review, TST positivity and risk factors were most frequently assessed using survey questionnaires or interview techniques. Because the current study did not intend to assess TST conversion or over time, the cohort design was not indicated.

Validity of self-reported TST seems acceptable based on studies discussed earlier in this paper (Garber et al., 2003; Kunins et al., 2004; Martin et al., 2000; Wolfe et al., 1995). However, no true validation study was found specific to self-reported TST among any population, and only internal pilot studies were assessed during the research under review.

Although a few subgroups have been studied (physicians, nurses, non-clerical HCP, and limited data on laboratories as a whole), prevalence of LTBI among one large subgroup of HCP, U.S. medical laboratory microbiologists, is not known. New advances in blood testing have come on the market during the past decade; however, LTBI is best measured at this time using the TST. Risk factors associated with TST positivity in this study group are not well known. Preventive treatment noninitiation rates and treatment nonadherence (barriers to adherence) are not yet described among this subpopulation. In order to establish a baseline and to address the knowledge gap for this subpopulation of HCP, the data must be gathered. In addition, new and shortened preventive treatment guidelines have been published (Jereb et al., 2011), further promoting the need to determine baseline data. This data will benefit further research that may address the newly described treatment regimen.

This research is theoretically justified using the epidemiologic triad model, where the tubercle bacilli is the agent of disease, and the infected human host (medical laboratory microbiologist), presenting as TST-positive (depending on susceptibility risk factors of the host, environment, and agent), is dependent on self and environment to allow for preventive treatment initiation. Treatment nonadherence is a function of barriers in this model, where barriers in the environment (such as medication side effects) may act to prevent completion of prescribed therapy. This study will not attempt to understand behavioral reasons as they pertain to treatment initiation or barriers to treatment adherence.

This research is empirically justified for nonoccupational and occupational reasons. In past decades, lack of engineering controls in the microbiology laboratory led to increased risk of acquiring TB infection (CDC, 2009; Reid, 1957). Today, a different risk is at hand. Today, a high number of HCP working in the United States has immigrated from outside the United States (thus, considered foreign-born). The HCP subpopulation of medical laboratory microbiologists is at risk to contract and spread TB infection among patients, coworkers, and family members. To summarize the findings of the literature review regarding methodology, the cross-sectional survey method remains the best choice for collecting and assessing lifetime TST positivity and risk factor data, as well as data on preventive treatment noninitiation and treatment nonadherence (barriers). Although some biases and limitations exist when using this technique (which will be described in more detail in Chapter 3), this method design is best utilized when study funding and time limits are present. Subsequently, this research used the cross-sectional survey questionnaire method, reaching out to the largest cohort of medical laboratory microbiologist members registered with a national registry in the United States. Details are presented in Chapter 3.

Chapter 3: Research Method

Introduction

This study was conducted in an attempt to explore the relationships of independent variables of self-reported history of BCG immunization, place of birth, and years of laboratory experience against three dependent variables of (a) self-reported lifetime of TST positivity (Research Question 1), (b) preventive treatment noninitiation (Research Question 2), and (c) barriers to treatment adherence (presence of medication side effects) as measured by one portion of the Brief Medication Questionnaire (Research Question 3) in U.S. medical laboratory microbiologist members registered with the American Society for Clinical Pathology (ASCP). Methodological approaches employed in this study are now discussed in detail. Major sections of this chapter include the study design, study population, data collection, and analysis approach. An algorithm describing study population by self-reported history of TST positivity, treatment noninitiation, and barriers to treatment adherence is described, as is an explanation of how data were obtained through statistical analysis.

Tuberculin skin test (TST) positivity among healthcare personnel (HCP) has become a surrogate method for measuring prevalence of latent tuberculosis infection (CDC, 2005b). Detection of target populations for preventive treatment initiation is important in stopping the spread of tuberculosis (TB). The U.S. HCP population has become more diverse, with an increase over the years in foreign-born workers (Clearfield & Batalova, 2007). Foreign birth and associated BCG immunization may be greater risk factors in the medical laboratory microbiologist population than in the general U.S.

population. Medical laboratory microbiologists frequently work in a healthcare setting where although direct patient contact may not have occurred, exposure to patient specimens and sample containers may constitute an increased occupational exposure to TB organisms (CDC, 2005b). Years of work in the laboratory setting may therefore be a risk factor in this population (Menzies, Fanning, Yuan, Fitzgerald, & the Canadian Collaborative Group, 2003; Rafiza et al., 2011). Because no one study has focused solely on a large group of U.S. laboratorians, the ASCP national registry membership was chosen for access to this population.

A review of the literature (see Chapter 2) has revealed that many researchers have used these independent variables in cross-sectional research methods to study HCP but only a few have focused on similar data from laboratorians (Garber et al., 2003; Menzies et al., 2003; Rafiza et al., 2011). One of the most recent publications explored preventive treatment noninitiation and barriers to treatment adherence (medication side effects) in HCP (Shukla et al., 2002). Garber et al. (2003) touched only briefly on items of treatment initiation and treatment barriers among public health laboratorians in New York City. While the Chapter 2 review of the literature described U.S. HCP in terms of TST positivity prevalence and risk factors, not much is known about the U.S. medical laboratory microbiologist population as a whole. Through this survey research, I sought to answer the study's research questions, as well as describe the U.S. ASCP target population in greater detail. These items constitute the gap in the literature.

Research Design and Approach

This study was a cross-sectional quantitative study using data that were obtained from a self-administered mail survey questionnaire. These mail surveys were used to collect demographic data and self-identified tuberculin skin test history. (TST positivity was used as a surrogate for LTBI status in previous research [Garber et al., 2003]). Independent variables of self-reported history of BCG immunization, place of birth, and years of laboratory experience were compared against three dependent variables of (a) self-reported lifetime TST positivity (Research Question 1), (b) preventive treatment noninitiation (Research Question 2), and (c) barriers to treatment adherence (presence of medication side effects) as measured by one section of the BMQ (Research Question 3) using the self-administered survey questionnaire as found in Appendix A.

Justification for the Design and Approach

This cross-sectional research method was chosen because TST positivity in target populations is most often used to measure LTBI prevalence, as demonstrated throughout the Chapter 2 literature review. The purpose of the survey questionnaire was to gather data used to describe a target study population. The data collected through this survey questionnaire were categorical and descriptive in nature. The type of survey instrument chosen for this dissertation was that of a self-administered mail questionnaire. The questionnaire was built from demographic questions found on other questionnaires and reported on in other studies (Garber et al., 2003; Shukla et al., 2002; Svarsted et al., 1999). This questionnaire was used to collect demographic and medical history data (gender, age, place of birth, TB disease and nonoccupational exposure history),

tuberculin skin test and BCG history, and work history (type of work, as well as years of work experience). The basic questions used in this portion of the questionnaire have been used in other cross-sectional survey research and, more recently, in the Garber et al. (2003) study. Two closed-ended questions taken from the Brief Medication Questionnaire (BMQ) were included for the purposes of assessing medication side-effect barriers as a measure of nonadherence (Svarstad et al., 1999). (Additional information regarding validation of the BMQ and pretesting and pilot testing of this questionnaire will be discussed in latter sections of this chapter.)

Advantages of using self-administered questionnaire surveys include (a) low cost, (b) ease of obtaining data, (c) speed and relative ease of administration, (d) privacy and anonymity for the respondent, and (e) ability to cover a large geographic dispersion of respondents. In addition, no interviewer was present to bias outcome. Disadvantages of this type of research method include (a) low response rate, which can limit generalizability; (b) misunderstood or skipped questions; (c) inaccurate reporting by respondent; (d) and misinterpretation of the question(s). The greatest bias in this method involves self-reporting of past events and is termed *recall bias* (Choi & Pak, 2005).

Based on the literature review described in Chapter 2, a gap in knowledge exists regarding the relationship of self-reported lifetime history of TST positivity and treatment initiation as well as treatment nonadherence (barriers) among medical microbiology laboratorians in the United States. This study was designed to fill this gap.

Settings and Sample

Target Population

The American Society for Clinical Pathology (ASCP) is the oldest and largest certification agency for laboratory professionals in the United States (ASCP, 2011). The Board of Certification at ASCP has certified more than 450,000 individuals since its inception and has become the gold standard for the certification of clinical laboratory personnel (ASCP, 2011). The ASCP Board of Registry, accredited by the American National Standards Institute (ANSI), currently offers 30 separate certification or qualification examinations (ASCP, 2009). ANSI accreditation is considered a benchmark of excellence in standardization of certification bodies, both national and international (ASCP, 2009), making ASCP's registrant membership a valid U.S. target population for studies regarding medical laboratorians. The specific cohort with the area of responsibility known to ASCP as "Microbiology/Mycology/Parasitology/Virology" was chosen as the subpopulation for this study. This cohort was chosen because (a) a literature review revealed that this group is at risk of infection with tuberculosis (latent or active) infection due to repeated exposure to contaminated patient specimens and (b) a lack of documented research on this subgroup was apparent. This group was accessed through the only marketing firm approved by ASCP to provide registry mailing lists: INFOCUS Marketing.

The "area of responsibility" category database at ASCP is composed of data from three sources (E. Corral, ASCP Customer Service Representative, personal communication, December 15, 2011):

- SM (specialist in microbiology) and M (microbiology) category registrants.

- Updates to login information (by ASCP members, and referring to primary

  area of responsibility).

- Updates to annual (mailed) membership renewal notices (asking for primary

  area of work responsibility).

According to INFOCUS Marketing, Inc. (2011), ASCP has approximately 51,802

active members, and 13,378 (12-month) lapsed members. The number of registrants

listed with area of responsibility "Microbiology/Mycology/Parasitology/Virology" was

approximately 5,138 at the time of this study's proposal stage (INFOCUS Marketing,

Inc., 2012).

Sampling Method

The entire ASCP registrant membership cohort known as working in the area of

responsibility of "Microbiology/Mycology/Parasitology/Virology" with U.S. mailing

addresses was included in the survey research. No sampling of this group took place.

Participation was entirely voluntary; this was stated in the cover letter of the

questionnaire (Appendix A). The sampling frame for this study was the entire cohort of

registrant membership listed with ASCP area of responsibility

"Microbiology/Mycology/Parasitology/Virology," approximately 5,138 at the time of the

study proposal stage (ASCP, 2011). Therefore, randomization (selecting randomly from

the sampling frame) was not necessary. The entire cohort was selected in order to obtain

the largest representative sample for the survey response rate. Every registrant had an

equal (probable) chance of selection for this survey, as long as his or her name and

correct address appeared on the ASCP mailing list. Because only ASCP registrant members were included, results may not be generalizable to registered nonmembers of ASCP, or to other U.S. medical microbiologists (unregistered microbiologists or microbiologists registered with other groups).

Sample Size

This quantitative single stage cross-sectional study questioned eligible U.S. medical laboratory microbiologists, a cohort first estimated at approximately 5,138 registrant members of the national group known as the American Society for Clinical Pathology (ASCP). To assess adequate sample size for this study, a standard power size of .80 (80%) and an alpha level of 0.05 were chosen (Burkholder, 2010). A beginning estimate of $N = 5,138$ was used to calculate the needed sample size. This number (5,138) changed to reflect the most up-to-date number of registrants on file with ASCP upon commencement of the actual research activity. (The number of individuals was later determined to be 4,335; additional sample size calculations are presented in Chapter 4.)

Estimated sample sizes were calculated using the OpenEpi calculators for Sample Size—Proportion and Unmatched C/C Calculation (OpenEpi, 2011). The calculation was made using these two different OpenEpi methods, picking the largest required sample size estimate, and then extrapolating to the final expected sample cohort (Appendix B; Table 3).

But first, the proportion of the original cohort to achieve the final outcome (self-reported medication side effect barriers to treatment adherence) was estimated using prevalence rates obtained from the current literature. For Research Question 1, a

hypothesized prevalence rate of 33% (Joshi et al., 2006) was used. (TST positivity, also referred to as prevalence of LTBI, ranged from 57% among microbiology workers according to Garber et al. [2003] compared with rates of 36 % [Cook et al., 2003] and 33%-79% [Joshi et al., 2006] among all HCP.) Research Questions 2 and 3 were answered from the respondent reporting TST positive "yes." (It was assumed not possible for a respondent to self-report as TST-negative and be eligible to respond to treatment-initiation and treatment-barrier questions.) The estimate of the ASCP cohort expected to self-report a history of TST positivity and eligible to answer survey questions related to Research Question 2 was determined using a 20% treatment initiation prevalence rate (the lowest reported by Garber et al. [2003] in this literature search). The proportion of the entire cohort proposed eligible to answer the BMQ survey questions associated with Research Question 3 was determined using 33.3% (the prevalence rate of those reporting medication side effect barriers according to Camins et al., 1996). Thus, the proportion of the entire original estimated cohort to achieve this final outcome (medication side effect barriers to treatment adherence) was proposed to be an estimated prevalence of 2.2%.

Because 2.2% is considered a very low prevalence rate among the population under study, the highest sample size attainable was desired in this study. Sample size for the purpose of obtaining prevalence for each of the three research question outcomes was calculated using the OpenEpi (2011) software calculator for frequency in a population (95% confidence limit). Sample sizes for the treatment initiation and barriers to treatment adherence groups are much larger than those required for the TST-positive

outcome and were calculated using denominators of the at-risk population, not the overall

cohort (Table 3). Sample size for the purpose of obtaining the associations between

exposures and each of the three research outcomes was then calculated using the

OpenEpi (2011) software calculator for proportions between two groups (exposed versus

unexposed), Sample Size—Proportion and Unmatched C/C Calculation (95% confidence

limit). (Refer to Appendix B.) To assess this proportion of exposure, the literature was

again consulted. For Research Question 1 (RQ1), frequency of outcomes for BCG

immunization among cases and controls was found to be less than that of foreign birth

(Garber et al., 2003). (Corresponding years of work experience frequency data were

lacking in the literature and not estimated in this assessment.) BCG rates and odds ratios

(ORs) were thus used in the OpenEpi calculations in order to err on the side of caution.

For Research Questions 2 and 3 (RQ2 and RQ3), BCG frequency and ORs were again

used for calculations, but surrogate data among HCP noncompliance with therapy for

LTBI (Shukla et al., 2002) were used in the absence of treatment initiation or side-effect

barriers data (Table 3).

Table 3

Table Sample Size Calculations for Research Questions 1, 2, 3 (RQ1, RQ2, RQ3)

	RQ1	RQ2	RQ3
Estimated frequency (Using Open Epi calculation)	319/5,138 total cohort (6.2%)	215/1,696, or 13.0% (5,138) = 668	171/ 339, or 50.0% (5,138) = 2,569
Estimated association (Open Epi, Fleiss w/CC calculation)			
Cases (outcome)	17	30	36
Controls	33	118	72
Total	50	148	108
Summary: Minimum sample size Extrapolated requirement with an estimated 50% return of surveys (2569)	638	1,336	2,569 171(339) is 50% of total estimated cohort; n = 2,569, 36 of which must be positive for RQ3 outcome (possible, because a 2.2% frequency of 2,569 = 57 possible candidates)

To double-check sample size requirement using the Walden University tables for

Cohen's *d*, assuming alpha level .05, effect size = 0.20 (this is the most conservative, and

would lead to worst-case largest sample size requirement), and power = .80, the

corresponding sample size from the Cohen's *d* table is n = 199 respondents (Burkholder,

2010). In addition, Katz (2009) has reported that in multivariate analysis, the sample

requirement is based on having at least 10 outcomes for each independent variable in the

model. For this research having three main independent variables, n = 30 samples with

each outcome of interest (dependent variable).

In summary, using an estimated cohort of 5,138 individuals to calculate the needed sample size, different methods were used to determine adequate sample size for each research question:

- OpenEpi: A sample requirement based on eligibility of the cohort to respond "yes" to TST positivity, treatment initiation, and reported medication side-effect barriers of adherence (all three research questions) would require at least $n = 2,569$ (based on an original estimated cohort of 5,138). In summary, a return of 50% of all surveys mailed and deemed eligible to participate (originally estimated at $n = 2,569$) needed to be realized in order to adequately capture sample size needed to answer all three research questions.

- Cohen's d Table: $n = 199$, sample requirement (RQ1 frequency) is based on the smallest effect size.

- Katz (2009): $n = 30$ samples with the final outcome of interest (RQ3).

The entire cohort was surveyed, but from previous research by Clark (2008), an estimated 22.5% return rate for an ASCP population would yield 5,138 (.225) = 1,156 survey respondents. This number is lower than the anticipated 2,569 required. To increase this number of respondents over those in the Clark (2008) study, two items were added. First, an incentive using a group charity donation approach (a donation to the ASCP Scholarship Fund based on number of completed and returned surveys) was used, in part because incentives have been known to increase participation in some studies to 68% to 78% (Mangione, 1995). Second, a survey announcement card was mailed to the

prospective respondents 1 week ahead of the survey packet mailing. Neither method was used in the Clark (2008) study. INFOCUS Marketing has reported that the rate of returned mail should be much lower (no more than 1%) when compared with previous mailings involving ASCP marketing lists (S. Blake, INFOCUS Marketing Consultant, personal communication, September 17, 2012), such as the study reported by Clark (2008). It was hoped that a yield of at least 50% of the entire cohort ($n = 2569$) would be realized after implementing these tools, a number equal to the required number of returned surveys yet more conservative than the higher percentage of return as estimated by Mangione (1995).

Eligibility Criteria for Study Participants

As mentioned in Chapter 1, study participant inclusion criteria were as follows:

- Adult registrants have been certified and registered through the ASCP Board of Registry (BOR), and were included on the current ASCP member mailing list, all having U.S. mailing addresses.

- Registrant members were reported to work in the primary work responsibility of microbiology known as "Microbiology/Mycology/Parasitology/Virology" as reported by ASCP. (To address the entire ASCP registry would have proved too costly and was not necessary. As stated previously, these registrants were most likely to have had contact with TB contaminated samples.)

No study participant exclusion criteria pertain (other than to address any individuals under the age of 18 years); it was hoped that all included in the survey mailing would respond.

Characteristics of Selected Sample

Characteristics of the selected ASCP cohort were described through a combination of statistical methods used to assess the questionnaire responses. Note: This study did not include any type of treatment stage.

Instrumentation and Materials

Data Collection Tool

Data were collected using a self-administered survey questionnaire mailed through U.S. first-class mail. The full questionnaire instrument was able to be completed by a literate (able to see, read, and write in English) educated respondent. Because this target population is highly educated and all registrants have applied for registry and/or taken their ASCP board exams in the English language, they were deemed well-prepared to take this survey questionnaire. The mail questionnaire was short, two to three pages total in length. No concurrent email questionnaires were sent because current email lists represented approximately one-third to one-half of this cohort only (INFOCUS Marketing, 2011), and because older adult ASCP registrants may not have access to computer email. Completion of questionnaire was strictly on a voluntary basis. No exit or debriefing strategies were required. (The individual completed and submitted the survey anonymously, or opted out completely. An announcement postcard preceded the survey mailing, but no follow-up occurred after this point.) Complexity of the

questionnaire structure was considered low- to moderately-complex, with most questions as demographic or asking the participant to recall health history. No calculations or difficult questions were asked. The reading level, instructions, and questionnaire items were considered appropriate for this college level target population; many of the same questions were asked in the Garber et al. (2003) study. The time required to take the survey was estimated at approximately 10 minutes.

The name of the survey questionnaire for this study is, "*Tuberculin Skin Test Questionnaire for ASCP Medical Laboratory Microbiologists—2013*." The type of instrument was a self-administered, mailed questionnaire using closed-ended questions; this one-time survey questionnaire was intended to measure outcome prevalence. This may be considered a period prevalence study in which the outcome (dependent variables) that existed during lifetime history were reported at one point in time – the time of the taking of this survey questionnaire. Prevalence studies are valuable for investigating risk factors associated with progressive diseases having no clear point of onset as in latent tuberculosis infection (Checkoway, Pearce, & Kriebel, 2004). The end product of this survey is lifetime prevalence involving any self-reported TST positivity outcome, risk factors of self-reported TST positivity, preventive TB treatment noninitiation, and any barriers to treatment adherence (medication side effects) from an individual's past or present (lifetime) history. Of note, the actual survey questions were asked at only one point in time, using one mailing of the questionnaire.

The self-administered questionnaire was administered to all ASCP registrant members listed on the ASCP mailing list for the target group. This survey questionnaire (Appendix A) included items such as

- gender;

- current age;

- type of laboratory work experience;

- years of laboratory experience;

- place of birth (U.S. or foreign);

- tuberculin skin test history and status;

- any history of interferon gamma-releasing assay (blood test);

- BCG immunization history;

- history of active TB;

- history of nonoccupational exposure;

- history of preventive treatment prescription, treatment initiation, treatment refusal, and treatment completion; and

- BMQ medication side effects treatment adherence questions.

The questionnaire contained a combination of "yes" or "no" response type questions and several multiple choice. The category of "don't know" or "don't remember" was included in only the history of TST, history of IGRA testing, and BCG immunization history sections for several reasons. First, the questions are not knowledge questions, but rather questions of self-reported history. Mangione (1995) has recommended not offering a "don't know" category unless knowledge (scale-type)

questions are introduced. Second, in this literature review other researcher survey and

analysis methods did not contain the "don't know" category. Because this study was

interested mainly in those responding as TST-positive, the "don't know" category was

used only to assist the respondent by offering a third response choice for several history

questions.

All demographic and self-reported history questions (except for age) were tallied

and coded as dichotomous responses (see Appendix E for codebook). The final group of

questions referring to medication treatment completion and perceived side effects was

derived from the Brief Medication Questionnaire (Belief screen; see below for BMQ

instrument detail). The sections of the actual survey document are represented in Table

4. (See Appendix A for survey document.)

Table 4

Sections of the Questionnaire

Section	Source of content
I. Consent Form (informed and implied, not returned with survey)	Walden University Research Center
II. Member Demographics (gender, age, type of work, years of laboratory work, place of birth)	Not validated, demographic in nature (Garber et al., 2003; Rafiza et al., 2011)
III. Medical History (lifetime history of tuberculin skin test, IGRA blood test, BCG immunization, active TB, contact, exposure)	Not validated, medical history (Garber et al., 2003) (Regarding IGRA blood test history: this information is informational only, and is not known to exist on any medical history questionnaire to date)
IV. Positive Skin Test—Medical History (prescribed INH, initiation of treatment, completion of medications)	Not validated, medical history (Garber et al., 2003)
V. BMQ Belief Screen (questions 14 and 15 a, b)	Validated section, medication side effects screen indicating adherence or nonadherence (Svarstad et al., 1999)

Reliability. The reliability of this survey instrument as a whole has been addressed through use of the following items, intended to decrease sources of measurement error:

- Questionnaire design: Consistency within the questionnaire has been addressed through the flow and order of questions (arranged to make sense to respondent).

- Questionnaire design: Consistency within the questionnaire has been addressed through comparison of specific question answers to be certain the answers make sense (one cannot answer "no" to having a history of a positive TST, yet answer all the questions referring to treatment initiation and

treatment barriers). This aspect was addressed by this researcher as data were input to the analysis software.

- Processing of the questionnaire occurred through several questionnaire handling stages. Quality controls by the researcher (use of spell check when composing the questionnaire, printer proofs, and professional appearance of questionnaire) were added to enhance reliability of this survey instrument. Quality control in the stuffing of the envelopes was out of the control of this researcher; the approved marketing group was solely responsible for this duty and was held accountable. Abstracting and coding of items was controlled by numbering each completed questionnaire upon receipt by the researcher and then double-checking each numbered questionnaire with the corresponding data number in the software base in order to verify correct data entry.

- The BMQ questions were written and validated in the English language, as are other examples of demographic questions as used in routine occupational TST and TB medical history questionnaires (no translation needs to take place). In addition, all ASCP registrants have taken ASCP board exams in English and are familiar with the processes of reading questionnaires and test-taking.

- The instrument was administered to ASCP members under self-administered conditions during pretest and pilot testing processes.

Test-retest reliability is not applicable to this study.

Validity. The validity of this survey instrument as a whole has been addressed through use of the following:

- Pretesting the questions and questionnaire (Walden University, n.d.) with culturally diverse ASCP registrants to assure cultural competency (as suggested by Fink, 2009). Pretesting was informal, designed as a participating pretest to take place among three to five participants (Converse& Presser, 1986).

- Pilot testing the questionnaire with educated, professional ASCP registrants working in a similar (medical or clinical laboratory) work environment; those included in the pilot testing were not invited to participate in the actual study in order to avoid confusion and pretest bias. At least 10 to 30 participants were sought for inclusion in the pilot test (25 participants were recommended by Converse and Presser, 1986). A more thorough discussion of pretesting and pilot testing will follow in the corresponding chapter section.

- Expert review by the dissertation committee members to review construct and face validity structure (Walden University, n.d.); the dissertation committee performed reviews of this study's proposal and dissertation findings.

- Construct validity has been addressed through a thorough literature review as noted in Chapter 2, revealing the best method for this research as well as examples of specific measures of the constructs (Walden University, n.d.). In this dissertation, the best method for assessing tuberculin skin test positivity (prevalence) was determined to be cross-sectional survey research. Specific measures of constructs in this dissertation have been identified as the independent and dependent variables.

- Use of a previously validated survey questionnaire, the BMQ (Part A) for inclusion of several important survey questions in the treatment nonadherence (medication side effect barriers) component of this questionnaire; see the BMQ section below for information related to the criterion related validity of the BMQ instrument. Each section of the BMQ was previously validated (independently, and as an entire instrument). The section known as the "Belief Screen" was included as a part of this questionnaire.

Survey response rate. Efforts made by the researcher to enhance survey response rate included the following:

- An incentive (contribution to the ASCP Scholarship Fund charity) in the form of a $250 donation made to the ASCP Scholarship Fund for every 1000 completed surveys received by survey deadline (within the accepted time limit of 8 weeks).

- Voluntary participation, confidential, and anonymous.

- Mail survey (chosen because the method provided respondents privacy and choice in responding to questions with no interviewer bias).

- Mail versus email for the survey, because the email list represented approximately one-third to one-half only of this cohort (INFOCUS Marketing, 2011), and because older adult ASCP registrants may not have had access to computer email.

- Advance mailing of a survey announcement postcard (Appendix C) to the entire cohort about one week prior to mailing of survey packet, as recommended by Fink (2009).

- Cover letter and questionnaire were composed of two to three pages (short in length) as recommended by Bourque and Fielder (2003) and Mangione (1995).

- Questionnaire paper was prepared using a color other than white (easy on the eyes); light green colored paper was used as suggested (Mangione, 1995).

- Researcher contact name and information were added to enhance authenticity as suggested by Mangione (1995).

- Self-addressed stamped return envelope was included for return of the questionnaire to researcher as suggested by Mangione (1995).

- All survey packets were mailed out at the same point in time.

Recall bias. Efforts made to decrease questionnaire recall bias (respondent error as a source of measurement error) included the following:

- Respondents were college educated, literate, professional laboratory worker with knowledge of tuberculosis and preventive laboratory measures to protect against infection (including receipt of TSTs on a regular basis). Respondents were considered able to accurately interpret meaning of these questions, and honestly report personal recollections.

- Questionnaire questions were considered clear and concise; the order of the questions built upon prior questions (once the respondent answered the TST

history question). The questionnaire length was held to two to three pages in

order to hold the attention of the respondent.

Brief Medication Questionnaire instrument. As mentioned earlier, one portion

of the self-administered mail questionnaire consisted of two questions reproduced from

the Brief Medication Questionnaire (BMQ). The BMQ instrument was chosen over

several other questionnaire tools for addition to the main survey instrument for several

reasons. The BMQ sections were short, previously validated as survey instrument tools

and related directly to treatment medications. Comparison of several other survey tools

(Charles P. Felton National Tuberculosis Center, 2005; Holstad, 2001a, 2001b; New

Jersey Medical School National Tuberculosis Center, n.d.) revealed that most tools were

not useful for surveys such as this proposed survey. Other tools referred to active,

current administration of treatment medications or were geared toward specific patient

populations (and not toward an educated HCP population). These types of items were

not considered as applicable when asking HCP respondents to self-report past TST

treatment history.

The Brief Medication Questionnaire (BMQ) was first described by Svarstad et al.

in 1999; the complete questionnaire instrument and scoring instruction was published in

Redman (2003). The BMQ is a self-report tool intended for use in screening adherence

to many types of treatment medications and in identification of barriers to treatment

adherence. The tool was initially validated in patients taking angiotensin-converting

enzyme inhibitors, and has also been used in patients with diabetes, depression, and other

chronic diseases (Lavsa et al., 2011; Svarstad et al., 1999). The BMQ is composed of

several sections (a) Regimen, (b) Belief, and (c) Recall screens. The Belief screen was utilized in this questionnaire and will be discussed below. The BMQ's sensitivity was measured and validated by comparing responses to actual data obtained using the Medication Events Monitoring System (MEMS), a medication measuring system which uses a microprocessor in the cap of a patient's medication bottle. The microprocessor records date and time of bottle opening and has been termed a "gold standard" for measuring treatment adherence, according to Svarstad et al. (1999). The Regimen screen portion of the BMQ provides a place for recording the number and times pills are taken or missed in the past week. The Recall screen portion of the BMQ assesses two items referring to ability to remember taking the prescribed pills. Neither of these screens is applicable to this study. However, the Belief Screen portion of the BMQ is applicable to this study and refers to the reporting of actual or perceived adverse medication effects. Because these adverse effects have been measured as past barriers to treatment adherence in HCP (Camins et al., 1996; Joseph et al., 2004), the BMQ Belief Screen questions were included in this survey research.

Concepts and specific questions in the BMQ Belief Screen as measured by the instrument are listed in Appendix D. Scores were calculated by converting the answers to scores of 1 = yes, and 0 = no (see Appendix D). With a scoring range of 0–2 possible, a score of ≥ 1 indicates a positive screen for belief barriers (Svarstad et al., 1999).

Each of the three screens in the BMQ was analyzed against MEMS results for sensitivity (ability to detect true nonadherence), sensitivity, specificity, positive predictive value, and overall accuracy using Fisher's exact test for categorical measures

and Pearson correlation for continues measures (Svarstad et al., 1999). The three screens performed well independent of one another. Specifically, for patients with repeat nonadherence, the Belief Screen results indicated (a) 100% sensitivity, (b) 80% specificity, (c) 62% positive predictive value, and (d) overall accuracy rate of 85%. However, "the belief screen failed to identify sporadic nonadherence" (Svarstad et al., 1999, p. 119) at a sensitivity of only 10%. The instrument authors suggested portions of this instrument, including the Belief Screen, may be useful in resolving different types of medication adherence barriers. For the purposes of this study, barriers to treatment adherence refers to barriers of medication side effects as measured using the above Belief Screen portion (Part A) of the Brief Medication Questionnaire (Svarstad et al., 1999).

Permission to use portions of the BMQ survey instrument was given to this researcher via electronic email correspondence on October 25, 2011 by the first author, Dr. Svarstad. In addition, permission (see Appendix F) was granted (Dr. Svarstad, personal communication, May 6, 2012) to publish the sample questions and scoring instructions in this dissertation (see Appendix D).

Variables and Codebook

Dependent and independent variables are listed and described in the Codebook (Appendix E) as a function of the questions from the survey questionnaire (Appendix A). Data as related to the variables have been listed and described under subheadings as noted in the Codebook (Appendix E). One independent variable in particular, BCG immunization, may also act as a confounder in this study. Data were collected on other potential confounders in this study, although these may not be applicable to the specific

research questions at hand. Additional data collected from the survey questionnaires were analyzed and reported as part of the overarching summary contingency table. The variables included in the additional data analysis (by order as asked in the survey questionnaire) are as follows:

- gender;

- age;

- prevalence of respondents who have ever received the new IGRA blood test, and number reporting a positive IGRA result (the importance of which was addressed in Chapter 2);

- prevalence of respondents prescribed and completing anti-TB medications;

- prevalence of respondents prescribed but refusing the treatment; and

- reports of specific adverse drug (medication) side effects (frequency if drugs are named).

In addition, data regarding survey response rate, bad address return rate, rate of late returns, and number of incomplete surveys were compiled and reported.

Pretesting and Pilot Test

An informal pretest of this survey questionnaire took place using a "participating pretest" method whereby at least three (to five) ASCP registrants known by this researcher were told they would be participating in a practice run, reading the survey aloud and allowing for this researcher to record any issues that might aid revision. The participating pretest method, suggested by Converse and Presser (1986), is important in gauging the order of questions and general flow of the questionnaire. These participants

were asked to explain their reactions and answers in a written debriefing. The

participants were asked if any questions made them feel uncomfortable, if they had

difficulty understanding any of the questions, and if any sections seemed to drag or were

confusing (recommended by Converse and Presser, 1986). After appropriate adjustments

were made to the questionnaire instrument, the questionnaire was pilot tested among at

least 10 with a maximum of 30 (with a goal of 25, as suggested by Converse and Presser,

1986) consenting adult individuals having similar collegiate education, ASCP registry

certification, and work experience in the medical/clinical laboratory work environment.

These individuals were accessed through the ASCP member mailing list of *Generalist*

laboratorians (*Medical Laboratory Scientists*) with U.S. postal addresses in the State of

Georgia (Appendix J). Test laboratorians were also invited to participate based on

diversity in place of birth, to assess wording of the questionnaire and ability to

understand the flow of questions. The questionnaires were not mailed, but rather, handed

out in sealed envelopes for anonymous return by USPS mail to this researcher. The pilot

test was used in order to test the questionnaire for clarity of language, and for looking for

(a) failure to answer questions, (b) giving several answers to the same question, and (c)

the writing of comments in questionnaire margins (as suggested by Fink, 2009).

The pilot test data were evaluated based on the number of unanswered or

misinterpreted questions. Error rates of 15% have been used in past research to flag

questions that warrant further investigation (CDC, 2003b). The pilot test errors were

coded onto a table for evaluation (see Appendix G) in order to assess error rate. If a

question was found to have a > 15% error rate, it was reworded; a repeat of the pilot test

among a new group was acknowledged as a possibility. Once the final adjustments were

made in the questionnaire and approved by the Walden University Institutional Review

Board (IRB), the survey packet was ready for printing and mailing by INFOCUS

Marketing, Inc.

Survey Packet

The survey packet included a (a) cover letter with reason for study, incentive

information, and informed consent statement; (b) survey questionnaire with closing

instructions; and a (c) a postage paid return reply envelope. A postcard announcing the

survey questionnaire (Appendix C) was mailed approximately 1 week prior to the mailing

of the survey packet.

Operationalization

Definitions for each variable in this study were addressed in Chapter 1. In

addition, the term *lifetime prevalence* (period prevalence) was used in this study to

describe the proportion of the target population with self-reported outcomes as related to

the dependent variables (given conditions) over a specified time period (past and present

lifetime of the individual study participant). Specific operationalization of definitions

follows.

Target population. *Medical laboratory microbiologists*: For the purposes of this

study, this terminology refers to the group registered with and designated by ASCP as

primarily working in the area of the laboratory known as

"Microbiology/Mycology/Parasitology/Virology" and having U.S. mailing addresses.

Independent variables. *Bacille Calmette-Guérin immunization (BCG):* For the purposes of this study, BCG immunization refers to the self-reported lifetime history of ever receiving an immunization with the BCG vaccine.

Place of birth: In TB surveillance, a U.S.-born person is defined as someone born in the United States or its associated jurisdictions (U.S. territories include: American Samoa, C.N.M.I. [Commonwealth of Northern Mariana Islands], Guam, Puerto Rico, U.S. Virgin Islands), or someone born in a foreign country but having at least one U.S.-citizen parent (CDC, 2012). For purposes of this study, foreign-born persons are not U.S.-born. Place of birth was denoted as U.S. birth or foreign birth.

Laboratory work: For the purposes of this study, years of laboratory work refers to clinical or medical laboratory experience and includes training, as well as paid and unpaid work in areas where testing was performed on clinical specimens, control organisms, or isolates. Years were signified as strata of (a) 0-2, (b) 3-5, (c) 6-10, (d) 11-15, (e) 16-20, and (f) over 21 years.

Dependent variables. *Tuberculin skin test (TST) positivity*: For the purposes of this study, TST status refers to a self-reported lifetime history of ever demonstrating a positive TST, as recalled by the survey participant. The respondent was asked if he or she was ever told by a health department employee, occupational health department employee, or other provider (doctor) that his or her TST was positive. The term *status* may refer to a history of either a positive TST or a negative TST.

Preventive treatment noninitiation: For the purposes of this study, treatment initiation refers to starting or beginning prescribed anti-TB medication treatment, even if

treatment was not completed. Noninitiation refers to the act of never beginning the prescribed treatment.

Barriers to treatment adherence (medication side effects): For the purposes of this study, terminology of barriers to treatment adherence refers to barriers of medication side effects as measured using the Belief Screen portion of the Brief Medication Questionnaire (Svarstad et al., 1999).

Each variable was measured by responses indicated on the self-administered mail questionnaire. Each variable (except for age) was manipulated in order to create nominal level measurements. Example items may be found in the codebook located in Appendix E.

Data Collection and Analysis

Research Questions

Research questions explored in this study and their hypotheses are as follows:

Research Question 1.   What is the relationship of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience with self-reported lifetime tuberculin skin test (TST) positivity?

HO: There is no statistical association between self-reported individual independent variables of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and the dependent variable of self-reported lifetime TST positivity.

HA: There is a statistical association between self-reported individual independent variables of history of BCG immunization, place of birth (U.S. or foreign),

and years of laboratory experience, and the dependent variable of self-reported lifetime TST positivity.

Research Question 2. What is the relationship of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience with preventive treatment noninitiation among those individuals prescribed treatment for a positive TST?

HO: There is no statistical association between self-reported individual independent variables of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and the dependent variable of preventive treatment noninitiation.

HA: There is a statistical association between self-reported individual independent variables of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and the dependent variable of preventive treatment noninitiation.

Research Question 3. What is the relationship of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience with barriers to treatment adherence (medication side effects) among those initiating preventive treatment for a positive TST?

HO: There is no statistical association between self-reported individual independent variables of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and the dependent variable of barriers to treatment adherence (medication side effects) as identified using the Brief Medication Questionnaire (BMQ) in those respondents ever having initiated preventive TB treatment.

HA: There is a statistical association between self-reported individual independent variables of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and the dependent variable of barriers to treatment adherence (medication side effects) as identified using the Brief Medication Questionnaire (BMQ) in those respondents ever having initiated preventive TB treatment.

Explanation of Descriptive Analysis Used in This Study

Each dependent and independent variable was described as nominal scale measurements (see Appendix E for Codebook details).

Description of Data Analysis

All statistical procedures were performed using Epi Info™ Version 3.5.3 (CDC, 2011c). Epi Info™ provides open-access, free, and flexible software obtainable online from the Centers for Disease Control and Prevention. It has been used by healthcare and public health workers for rapid creation of data collection instruments and advanced statistical analysis of data. Epi Info™ software, accessible worldwide, has provided a useful platform for epidemiology techniques (CDC, 2011c).

Completed questionnaires were numbered with a record number upon receipt by the researcher. Data obtained from the completed questionnaires were cleaned and compiled into data sets within the Epi Info™ software. Verification of data in the data set was performed by double-checking each numbered questionnaire with the corresponding data number in the software base. Raw data are available as a separate Microsoft Excel (Microsoft Corporation, 2012) file accessible to this dissertation committee in conjunction with the dissertation, and available via special request (in

conjunction with the approval of ASCP and the Walden University Institutional Review Board).

All variables (independent and dependent) were transformed into categorical (nominal scale) measurements for statistical analysis. Data were cleaned; of note, the initiation data were transformed at this point to noninitiation as an outcome. The data, set into dichotomous variables, underwent analysis via contingency tables and logistic regression. (Note that some of the data categories, such as age and years of laboratory experience were collapsed into appropriate dichotomous variables.) A codebook was used to guide categorical placement of all data into dichotomous variables (see Appendix E).

Statistical methodologies, including univariate, bivariate, and multivariate statistics were used in the data analysis. Univariate statistics were used to describe some study population sample characteristics as related to Research Questions 1, 2 and 3, among those self-reporting as TST positive. Univariate and bivariate statistics consist of frequency and percentage. Bivariate analysis was used to examine the association between each of the independent (potential predictor) variables against each dependent (outcome) variable. Non-parametric statistics such as chi-square were utilized because no assumption regarding distribution of the variables resides in the target population (Munro, 2005). This use of the chi-square assumes that four assumptions will be met: (a) data has been categorized and frequencies can be obtained, (b) adequate sample size has been met, (c) the measures are independent of each other (mutually exclusive), and (d)

research questions and theory have been established (Munro, 2005). Chi-square analysis resulted in R statistics: X-squared, degrees of freedom (*df-*), and *p*-values.

Multivariate statistics were used to build a model with all the important and statistically significant predictors. Because this study utilized dichotomous dependent and independent variables, multiple logistic regression analysis statistics were selected for use. Logistic regression analysis allowed for the investigation of one independent variable as a risk factor while controlling for the effect of the other independent variables and potential confounders (Pallant, 2007).

Other covariates based on the survey data as collected were added to adequately assess for the presence of confounding among known variables. In addition, a broader descriptive analysis was performed among these covariates.

Variables were selected using preference (research questions were chosen from variables as they appeared throughout the literature review process). Multicollinearity among the variables (highly correlated independent variables) was detected using chi-square and bivariate analysis, as well as logistic regression analysis. Collinearity was found, and it has been addressed in the post-hoc analyses section below. Variables were not automatically discarded in initial models, as those variables that are theoretically important should be retained (Katz, 2009). As recommended by Katz, if any pair of independent variables are "correlated at > 0.90...decide which one to keep and which one to exclude If any pair of variables are correlated at 0.89 to 0.90 consider dropping one" (Katz, 2009, p. 197).

The variable selection criteria chosen were the Yates corrected chi-square with two-tailed *p* (or Fisher exact *p*-values if cell sizes are < 5 [Gregg, 2008]); 0.15 was used as *p*-value cut-off for inclusion into models. (Katz [2009] recommended including any variable that is associated with an outcome at *P* value of < 0.20 or .25 in order to avoid missing important confounders.) Even if the variables do not meet criteria, those which are reported in literature as theoretically important should still be included in the initial model (Katz, 2009).

For multiple logistic regression analysis in Epi Info™, outcomes were coded as "1" for "yes", presence of the outcome (for example, TST—positive was coded as "1", treatment initiation—no was coded as "1", BMQ adherence barriers present—yes was coded as "1"), and "0" for the referent value or absence of the outcome (for example, TST—negative was coded as "0", treatment initiation—yes was coded as "0", BMQ adherence barriers present—no was coded as "0", and so on for covariates).

Independent variables were tested as potential confounders in a backward stepwise logistic regression approach. Those not associated with an outcome at *P* value of ≤ 0.05 were excluded from the model, in association with and depending on the result of the odds ratio and Wald statistic (Munro, 2005).

The odds ratio (maximum likelihood estimation or MLE, Mid-*P* exact) was assessed for each variable, along with confidence intervals (CI) to assess the probability of occurrence (Dean, Sullivan, & Soe, 2010). The level of significance for the nominal variables in 2x2 Epi Info™ tables was determined by chi-square. The Wald statistic (expressed as *Z*-statistic in Epi Info™) was reviewed in regression analysis for each

variable in order to compare each estimated coefficient with the univariate model in assessment of significance (Munro, 2005).

The final, most parsimonious model includes main risk factors, as well as describes any potential confounders. To test assumptions on the final model, this researcher checked data for outliers or unusual patterns. Conclusions from the final model were assessed for answers to the three proposed research questions in this study.

Missing Values

Assuming missing value counts for a small portion of the total observations, analysis included the non-missing data for questions Q4, Q5, Q6, Q8, Q12, Q14, and Q15, as these questions are essential and applied directly to the research questions. If any of these essential questions were left unanswered, the respondent's entire survey was coded as a non-response (NR) in the raw data table. In other words, no partial answers for this specific group of questions were allowed. No imputation of missing values was performed, meaning that no estimated values were coded in place of missing values. All other survey questions should have been answered as part of the informational portion of this survey. When any one of the unessential questions was left unanswered, each specific question was then coded as a non-response (NR) or left blank in the coded data file, but the remainder of the survey questions and responses were entered into the database for statistical analysis. No large numbers of data were missing, and so no variables were dropped (rather than subjects), as suggested by Katz (2009).

Because INFOCUS Marketing, Inc. printed and mailed the surveys on behalf of this researcher (and is the sole access point to this ASCP population), numbering of

individual surveys for tracing of individual responses was not possible. It was expected

as highly unlikely that multiple entries would be made by the same person and so this

concern was not addressed. The surveys returned to this researcher will forever remain

anonymous. No follow-up of the target population was attempted after survey

announcements and questionnaire packets were mailed.

Study Algorithm

This study followed the algorithm as presented in Appendix H. The algorithm

was used to demonstrate relationship of the dependent variables.

Use of Tables

Tables were used to represent data obtained and compiled in the course of this

research (see Tables 5-27 in Chapter 4). To search for any statistical interaction (and

confounding) between the independent variables, stratified analyses were performed as

appropriate. Tables continued in the same manner for the remaining combinations of

independent variables (covariables).

Multivariate analysis: Multiple logistic regression was used to assess inter-

relationships of the covariates (as well as the variables analyzed in the bivariate analysis)

in order to assess interrelationships and relative strengths and probabilities of variables.

This process was used to identify individual contributions as related to the dependent

variables. Initially, all covariates (already known to have suspect or established

associations) were entered along with the dependent variables. At this point in the data

analysis, type of laboratory work was collapsed into nominal bivariate groups based on

each lab work section compared to all other combined sections.   Years of laboratory

experience groups were collapsed into nominal bivariate groups based on the mean of the respondent data. Gradual elimination of the nonsignificant variables using a backwards step approach was used to lead to a final model. These findings were compared with the bivariate analyses to check for possible interactions. When suspected, additional stratified analyses followed, and logistic regression analysis was repeated (while eliminating the probable interaction covariate by creating interaction terms in Epi Info™).

The same tables were repeated to assess initial full model logistic regression all variables, for treatment noninitiation and again for barriers to treatment adherence (medication side effects) as measured by the BMQ. Tables were then repeated to assess stepwise model logistic regression for each covariate/independent variable (removing one at a time), for treatment noninitiation and again for barriers to treatment adherence (medication side effects as measured by the BMQ).

The final, most parsimonious model for each dependent variable (research question variable) is composed of the statistically significant independent variables identified through multiple logistic regression. Confounding (a presence of > 15% relative change of the odds ratio of the independent variable [exposure] with and without the confounder) has been addressed in Chapter 4. Based on results of the Chapter 2 literature review, BCG immunization and its relationship to foreign birth was confirmed as one of several potential confounders.

Measures Taken for Protection of Participants' Rights

This study was based on self-administered questionnaires performed on a specific ASCP study population. ASCP provided preliminary basis approval to this researcher for use of a questionnaire in survey research of this target population (S. Blake, personal communication, May 10, 2012). Final ASCP approval for use of the IRB-approved questionnaire was provided on January 24, 2013. The Letter of Cooperation—Permission Letter (Appendix I) was addressed with ASCP through INFOCUS Marketing, Inc. (provided by INFOCUS Marketing, Inc. at time of contract assignment). Final approval for conducting the pilot study was also granted by ASCP, and the Letter of Cooperation (Permission—Pilot Test) has been added to this dissertation (Appendix J). The pilot test was conducted on respondents' off-duty work time, and anonymous pilot test questionnaires were handled in the same manner as the approved survey questionnaires (see below). Final approval to include the previously selected BMQ questionnaire questions in the completed proposal and subsequent dissertation documents was given by BMQ first author, Dr. Bonnie Svarstad, on May 6, 2012 (and restated to this researcher via email correspondence on July 4, 2013). (See Appendix K.)

All data arrived via U.S. mail in a de-identified state, because no survey numbers, names, or respondent return address information were included on the questionnaire. Therefore, all returned questionnaires contained no personal identifiers making them anonymous. Informed consent was addressed by using a cover letter that explained the study promised confidentiality, and that informed consent was implied by completing and returning the survey. Instructions (explaining that the completion and return mailing of

the questionnaire signified an individual's informed consent has been obtained) were stated as, "By returning a completed questionnaire, I consent." In addition, survey respondents were instructed not to use name or personal information on the return questionnaire.

This research is valid to this population and to other health care professionals, and not socially harmful. No state or federal reporting requirements as they apply to reportable diseases apply in this study, because the respondent was asked only about recollection of past events. A positive TST or active TB disease would have already been reported by the provider to the appropriate public health entity. This researcher was the only researcher handling questionnaire data and so the training of other research assistants was not necessary. This research questionnaire did not pose any unnecessary risk, such as a physical or mental strain. Because responses were anonymous, no respondent should have felt hesitant to answer questions in an honest manner, or felt at risk of losing employment because of their answers. These survey recipients are highly educated college graduates and professional adults (18 years of age or older), accustomed to working in the medical laboratory field. No special population was at risk.

Issues of confidentiality were addressed by the following:

- No names or addresses were used on any of the paper questionnaires.
- No conflict of interest existed with respect to the choice of ASCP Scholarship Fund as the incentive for donation on behalf of the ASCP survey respondents. The donation did not include respondent names, but rather was paid as a group

donation. The ASCP Scholarship Fund provides scholarships to medical laboratory students in the U.S.

- Completed paper questionnaires returned to the researcher have been secured in a locked file cabinet (and will continue to be locked in this state) for a period of at least five years. Return envelopes were not retained, but rather shredded when any personal information (such as a return address) was present. All de-identified data sets used for computer analysis were transferred to a separate hard drive (from the only computer used for this research) for locked storage. This hard drive will remain in storage for a period of at least five years.

- I have not, nor will I share or disclose any individual responses with any friends or family members.

- I have not, nor will I publish any data that will allow readers to determine the identification of the survey respondents.

No participants were contacted and no data were collected until I received approval from the Walden University Institutional Review Board (IRB). Once Walden University granted IRB approval, the corresponding IRB approval number was listed on the survey cover letter. The survey packet was not mailed until after this IRB approval number was added. Walden University's approval number for this study is 01-16-13-0046714.

Summary

To summarize, cross-sectional quantitative research was performed by accessing the U.S. mailing addresses of the ASCP registry membership target population, area of work responsibility known as Microbiology/Mycology/Parasitology/Virology. A self-administered mailed survey questionnaire using a combination of previously recognized TST history questions and a portion of the validated BMQ instrument (Svarstad et al., 1999) was mailed at one point in time, following the mailing of an announcement postcard. (A pretest and pilot test preceded these mailings.) Data obtained were analyzed using Epi Info™ software provided free of charge by the CDC. Bivariate and multivariate analysis methods were used to predict the most parsimonious models and answer the three research questions posed previously in this chapter.

Chapter 4 describes the process that was followed and provides results from actual statistical analysis of data.   The research results have been presented in the form of tables.

Chapter 4: Results

Introduction and Purpose of the Study

The purpose of this cross-sectional quantitative survey was to gather data to describe the American Society of Clinical Pathology (ASCP) medical laboratory microbiologist target study population in terms of three outcomes: (a) self-reported lifetime history of tuberculin skin test (TST) positivity (prevalence), (b) preventive TB treatment noninitiation, and (c) barriers to treatment adherence (presence of medication side effects as measured by the BMQ) using a written questionnaire. In addition, independent variables of BCG immunization, place of birth, and years of laboratory work experience were assessed as potential risk factors in the occurrence of all three of the above outcomes. An evaluation of how each outcome varied across demographic and work-related factors such as gender, age, type of work, history of TB disease, and exposure to TB was also performed.

Data collected in this survey questionnaire are categorical and descriptive in nature. The type of survey instrument chosen for this study was a self-administered mail questionnaire: *Tuberculin Skin Test Questionnaire for ASCP Medical Laboratory Microbiologists—2013* (see Appendix A). The questionnaire was composed of basic demographic and medical history questions commonly encountered in the public domain. Two closed-ended questions borrowed from the Brief Medication Questionnaire (BMQ) were approved for inclusion by the first author for the purposes of assessing medication side-effect barriers as a measure of nonadherence (Svarstad et al., 1999). (Additional

information regarding validation of the BMQ and pretesting and pilot testing of this questionnaire will be discussed in latter sections of this chapter.)

The three null hypotheses for this study predicted that self-reported lifetime history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience would not contribute to (a) self-reported lifetime tuberculin skin test positivity, (b) preventive treatment noninitiation, or (c) barriers to treatment adherence (medication side effects) among those ever initiating preventive treatment for a positive TST. Chapter 4 describes the results of this research study.

Chapter 4 describes the process that was followed and provides actual results from the statistical analysis of data using Epi Info™ Version 3.5.3 (CDC, 2011c), an epidemiology software obtained through public domain.   As described in Chapter 3, a pretest and pilot test were performed. As a result, minor adjustments were made to the questionnaire prior to commencement of the actual survey study. The procedures for performing pretest, pilot test, and survey are described, and results of statistical analyses are presented in this chapter in the form of tables.

Pretest and Pilot Study

As described in Chapter 3, the validity of this study's survey instrument as a whole was addressed through two phases of testing. These two phases of testing were performed prior to actual mailing of the study announcement postcard and survey packet and are described as pretest and pilot test phases. Both the pretest and pilot test were used to provide feedback on demographic and health history question flow only (CDC, 2003b; Converse & Presser, 1986; Mangione, 1995). Because this study was not a

clinical trial, this pretest and pilot test were not used for the purpose of instrument scale development, or to gauge prevalence or sample size. (If they had been designated for these purposes, a larger sample size would have been required for each phase [Hertzog, 2008; Johanson & Brooks, 2010; Julious, 2005; Lancaster, Dodd, & Williamson, 2004]).

Pretesting was informal, designed to take place among several ASCP member participants who volunteered to participate. After making two minor changes requiring correction of question numbers (typos), pilot testing the questionnaire was performed using educated, professional ASCP registrants working in a similar (medical laboratory) work environment. Those included in the pilot testing were not invited to participate in the actual study in order to avoid confusion and pretest bias.

Pretest Phase

In the first phase, the informal pretest, four ASCP members who volunteered were questioned about the question order and flow after having an opportunity to read and answer the written survey questions. This number of participants was chosen based on prior literature recommendations to obtain a few individuals for the purpose of obtaining feedback (Converse & Presser, 1986; Mangione, 1995; Suskie, 1996; Tools4dev.org, 2013). The informal pretest of this survey questionnaire took place in early March 2013 using a "participating pretest" method (as suggested by Converse & Presser [1986]) whereby the four ASCP members were told they would be participating in a practice run. The participants were instructed to read the survey aloud and then answer the survey questions in writing. I documented all suggestions and comments in an effort to record any issues that might aid revision. All four participants reported that the questions did

not make them feel uncomfortable in any way. All reported not having any difficulty understanding questions or the order of the questions. One respondent reported confusion on page 2 of the questionnaire due to two simple typographical errors involving numbering of questions. The typos were corrected with permission of the Walden University IRB prior to the pilot test. All questions were answered completely as anticipated, except in the case of Pretest Respondent 4, who left "AGE" as a blank field; it was assumed that this respondent did not respond to the prompt because the pretest was voluntary but not anonymous. (Respondent 4 may not have desired for me to know his/her age.) This nonresponse did not adversely affect the outcome of the pretest. As a result, age was not removed from the questionnaire at this stage. A decision was made to evaluate again after the pilot test.

Pilot Test

In the second phase, the formal pilot test, 30 ASCP members were invited to participate; 20 consented, but I received only 13 completed survey packets via USPS mail. Again, for the purpose of obtaining feedback on the questionnaire itself, this number was accepted based on prior recommendations to include at least 10 to 12 individuals similar to those in the study sample (Bourgue & Felder, 2003; Fink, 2009; Suskie, 1996). Fewer individuals are required to pilot test a short mail questionnaire than would be required for a long questionnaire (Fink, 2009).

After appropriate typographical corrections were made to the questionnaire instrument, the questionnaire was pilot tested among the 20 adult individuals having similar collegiate education, ASCP registry certification, and work experience in the

medical laboratory work environment. These individuals were accessed through the ASCP member mailing list for *Generalist* laboratorians (Medical Laboratory Scientists) with U.S. addresses in the State of Georgia. Atlanta metropolitan addresses were selected for use in the pilot test. I chose the Atlanta subgroup in order to facilitate the dispersal of invitations by me in order that these ASCP members might participate in the pilot test. These individuals received all necessary instructions, a consent letter, and the full survey packet in person. (Because these individuals might have been confused by a mailed survey referencing a professional affiliation as a U.S.-based microbiologist, they were invited to attend an informal gathering where the questionnaires were handed out in sealed envelopes for anonymous return to me via USPS mail.)

The pilot test took place during mid-March 2013. The pilot test data were evaluated based on the number of unanswered or misinterpreted questions. (No analysis of actual responses was performed.) Thirty individuals were invited to participate. Of 20 individuals who agreed to participate, 13 completed surveys were received via USPS mail, indicating a 65% response rate and surpassing the minimum number of 10 individuals required for this pilot test (as set forth in the proposal stage). The original goal of reaching 25 participants (CDC, 2003b; Converse & Presser 1986) was not met, suggesting that more individuals should have been invited to participate in the pilot test.

Upon return receipt via USPS mail, questionnaires were marked with a "P" for pilot and numbered to designate order received. Pilot test errors were coded onto a table for evaluation (see Appendix G) in order to assess question-error rate. Error rates of 15% have been used to flag questions that warrant further investigation (CDC, 2003b). No

errors (0% error rate) were noted on question (Q)1-Q10, or Q13-15(b), although a 7.7%

error rate was discovered on Q11 and on Q12. In one case, the respondent ignored

instructions to "stop here." No corrective action was warranted because respondent error

rates were less than 15% per question. A determination was made that in the future

study, I would not record any responses found after the "stop here" instruction noted in

the survey questionnaire, noting that these additional responses might lead to a spurious

finding. In addition, no problems were noted with the reporting of age in the pilot test

responses, as was mentioned in the section on pretest findings. Age remained on the final

survey questionnaire.

At this point, a discussion of Cronbach's alpha in relationship to this

questionnaire survey instrument is warranted. Cronbach's alpha is not a statistical test,

but rather a measure of internal consistency where a scale measurement is analyzed. The

two questions in this survey questionnaire that are considered scale measurements are

those borrowed from Part A (Belief Screen) of the BMQ. The Belief Screen was

previously validated by Svarstad et al. (1999) for patients with medication nonadherence.

While Svarstad et al. (1999) did not report a Cronbach's alpha, a recent comparison of

several medication adherence scales performed by Lavsa et al. (2011) did note that the

reliability in BMQ reflected 95% overall accuracy, and for the Belief Screen, a sensitivity

of 1.0 and specificity of 0.8 for identifying nonadherence. These values were compared

against Cronbach's alphas of other nonadherence screens, where reliability ranged from

0.61–0.89. (Any alpha over $\alpha = 0.7$ is considered as having a high internal consistency

reliability.) Thus, according to Svarstad et al. (1999) and Lavsa et al. (2011), the two

BMQ Belief Screen questions are considered to reflect high internal consistency.

<div align="center">**Data Collection**</div>

Recruitment

The chosen target population consisted of adult medical laboratory

microbiologists registered with and designated by ASCP as members primarily working

in the area of the laboratory known as Microbiology/Mycology/Parasitology/Virology

and having U.S. mailing addresses. This group was accessed through the only marketing

firm approved by ASCP to provide registry mailing lists: INFOCUS Marketing, Inc.

After pretesting and pilot testing, the actual study was conducted over a period of 8

weeks, taking place from March 25 through May 20, 2013. Of note, no treatment or

intervention took place among this study group.

Time Frame

The survey announcement postcard and packet were printed and mailed by

INFOCUS Marketing, Inc. Survey announcement postcards were mailed to the target

population ($N = 4,335$) in mid-March. It should be noted that the entire cohort was

originally estimated to be $N = 5,138$ at time of the study proposal; however, the final

ASCP membership number of the target cohort was not known to me until INFOCUS

Marketing, Inc. actually printed and mailed the announcement postcards. (The number

was not released to me until initial payment for printing and mailing services was

received by this marketing firm, and first postal delivery was sent out to the postal

service.) During this time, the USPS route worker responsible for the postal box was

informed to expect large deliveries of mail over the course of the next 2 months.   Survey

packet mailings to the same target population addresses ($N = 4{,}335$) occurred 1 week

later. As a result, the official cut-off for receipt of completed surveys for inclusion in

statistical analysis was then determined as May 20, 2013. Twice during May, I double-

checked each numbered survey questionnaire with the corresponding Excel file entry in

order to confirm accuracy in coding. The $250 incentive donation (for receipt of the first

1,000 completed surveys) was paid during the first week of May 2013 to the ASCP

Scholarship Fund. (No additional incentive was paid because the final number of

completed surveys received, $n = 1{,}693$, did not surpass the next payout tier of $n = 2{,}000$.)

Response Rates

INFOCUS Marketing mailed a total of $N = 4{,}335$ survey packets to individuals

who encompassed the entire ASCP target cohort, the same group that received

announcement postcards 1 week prior. (As mentioned previously, the original estimated

cohort of $N = 5{,}138$ dropped to $N = 4{,}335$ at the time of mailing. Please refer to the

sample size section below for more detail.) Twelve surveys were returned to me by

USPS as address unknown. This equated to a bad address return rate of 0.3%, in line

with the expected less than 1% previously predicted by INFOCUS Marketing. The

number of completed questionnaires returned by the 8-week deadline was $n = 1{,}693$,

realizing a 39.1% overall response rate. Incomplete surveys (previously designated

"critical questions" related to independent and dependent study variables were left blank)

that it was not possible to analyze numbered three in all. (In reality, these three

respondents failed to complete page 2 of the questionnaire.) Usable (coded and cleaned)

questionnaires returned to me by the deadline numbered $n = 1,628$, an eligible respondent

return rate of 37.6%. This response rate is much higher than the 22.5% realized by Clark

(2008) in research involving a different ASCP questionnaire mailing. Of note, 45

completed questionnaires were received well after the predetermined cut-off date and

thus were not analyzed.

A review of the literature was previously performed in order to assess estimated

sample size. Calculation of sample size justified use of the entire ASCP target cohort in

order to statistically satisfy all research questions as posed. The target sample size

required to reach enough individuals capable of answering Research Question (RQ) 1

(referencing individuals with positive TSTs) was originally estimated as $n = 638$ (based

on an estimated cohort of $N = 5,138$). The total estimated target sample size required to

obtain enough individuals capable of responding to questions about treatment

initiation/noninitiation and therefore treatment side effects and possible adherence

barriers (RQ2 and RQ3) was $n = 2,569$. In this study, the $n = 2,569$ was not met. A

thorough discussion of sample size and generalizability of results follows in a subsequent

Sample Size section of this chapter.

Coding and Missing Data

Responses were coded as nominal variables (see Codebook, Appendix E) in Excel

format. Missing value counts accounted for only a small portion of the total

observations. Analysis was not performed on any respondent questionnaire that was

missing data for Q4, Q5, Q6, Q8, Q12, Q14, or Q15, as these questions were essential

and applied directly to the research questions. In these cases, responses were left blank in

the Excel file, indicating nonresponse (NR). (Out of all the essential questions, only Q8 regarding BCG immunization was determined as missing three critical responses, a NR rate of 0.2%). No partial answers for this specific group of questions were allowed. I did not substitute imputed (calculated or estimated) values for any missing values based on other responses. During the coding process, the following situations resulted in deletion from the $n = 1{,}693$ survey group prior to final statistical analysis (these surveys were excluded from analysis):

- Nonresponse (NR) for critical survey questions (Q8: BCG, where $n = 3$).

- Respondents who responded "no" or "don't know" to Q6: Ever had a TST? ($n = 58$).

- Respondents who responded "don't know" to Q6a: Ever been told that the TST was positive? ($n = 5$).

After removal of the above individual survey results from the coded Excel file, the final number of surveys eligible for processing was calculated as $n = 1{,}628$. (Note: One respondent's survey results overlapped two of the above deletion situation groups.)

Discrepancies in Data Collection

Coding of the independent variable "years of laboratory experience" occurred by strata. Prior to analysis, I noted that that the highest two strata categories (majority of responses) were "16 to 20 years" and "> 21 years," where a response of exactly 21 years was not allowed. For purposes of data analysis, the category of "> 21" years has been altered to "≥ 21 years."

Coding of Q8 (self-reported lifetime history of BCG immunization) revealed a high number ($n = 151$) of "don't know" responses. This presented a challenge in the way data were coded from the plan presented in Chapter 3. Rather than remove all 151 surveys from further analysis, the literature was consulted. The 151 questionnaire responses were cleaned and recoded as "no" responses, per the precedent set forth by Passalent et al. (2007), where a self-reported BCG vaccination status of "unknown" or "uncertain" was recoded as "no" for designating a "nonrecipient" of BCG.

Sample Size and Generalizability

In 2012, the initial ASCP target population cohort of interest (reportedly working in area of responsibility referred to as "Microbiology/Mycology/Parasitology/Virology" and having U.S. mailing addresses) was estimated to be $N = 5,138$ (ASCP, 2011). The actual ASCP target population cohort membership in spring 2013 was found to be composed of $N = 4,335$ individuals, rather than $N = 5,138$ individuals according to INFOCUS Marketing, Inc. Survey packets were thus mailed to the entire cohort (individuals having current membership and addresses on file with ASCP) with the expectation of receiving the minimum sample size required in order to generalize findings to this population. The entire cohort was selected in order to obtain the largest representative sample for survey response rate. (Randomization was not necessary.) After coding and cleaning, eligible survey responses numbered $n = 1,628$ individuals, a number much lower than the original estimated target response of $n = 2,569$.

This discrepancy is in part due to the change in ASCP cohort membership from $N = 5,138$ to $N = 4,335$ members over the course of the year. A recalculation involved

extrapolation of the initial estimated sample size calculations for $N = 5{,}138$ to reflect

corresponding sample size calculations for the actual ASCP membership of $N = 4{,}335$

individuals. This was necessary because the original sample sizes were calculated using

Open Epi software (available in the public domain); the original estimated population

size of $N = 5{,}138$ was utilized in these software calculations. The results of this

extrapolation follow in the post-hoc analyses section.

Analysis and Results

All survey responses (serving as independent and dependent variables) were

transformed by coding into nominal scale measurements for statistical analysis, with the

exception of age. (Data on age were collected, coded, and analyzed as a continuous

variable.) After coding data, basic univariate and bivariate statistics consisting of

frequency and percentage were performed using Epi Info™ software, Version 3.5.3

(CDC, 2011c). I analyzed for frequencies (FREQ) to get an indication of the respondent

data characteristics as a whole, and then to examine by TST status. Frequency data from

Epi Info™ were depicted in percentages with 95% confidence intervals (CI). Data were

then cleaned in an effort to determine which surveys were eligible for full analysis

according to a priori decisions (no TST status, TST status unknown, or missing data). In

addition, at this point the treatment initiation data were transformed to reflect

noninitiation as the final (dependent variable) outcome described in Research Question 2.

Using Epi Info™, "TABLES" (or "Single Table Analysis") provided information

on 2x2 tables, such as odds ratios (OR) maximum likelihood ratio (MLE) with a 95%

confidence interval (CI) using mid-P method, chi-square (corrected Yates) calculations

(with 2-tailed *p* value), and Fisher exact 1-tailed *p* value (if less than 5 observations were

present in a cell). These values were then double-checked against original frequency

calculations to ensure accuracy and direction of data. Bivariate analysis was used to

examine the association between each of the dichotomous independent (potential

predictor) variables against each dependent (outcome) variable. Odds ratios (MLE) using

mid-*P* were reported according to preferred prior public health Epi Info™ statistical

models (Dean et al., 2010). The Yates corrected chi square (χ^2) with two-tailed *p*, or

Fisher exact test *p*-values (if cell sizes were < 5), were selected as per recommendation of

Gregg (2008); chi-square results were summarized and included in contingency tables.

(Exception: Age study outcomes were examined using ANOVA and *t* test because age

was the only continuous variable in the study.) Of the several choices of chi-square

available in the Epi Info™ printout, the Yates corrected chi-square was selected because

it gives the largest *P* value. According to Gregg (2008), Yates is preferred by

epidemiologists because this large *P* minimizes the likelihood of making a type I error

(although a limitation is that it increases the likelihood of making a type II error).

The initial simple regression model for each outcome was composed of the three

main independent variables (forced into the final model by a priori decision, literature

based), and any independent variable or covariates (including suspected confounders) in

the models that were bivariately associated with the outcomes at $p \leq .15$. Unconditional

logistic regression was selected in order to assess interrelationships of the covariates in

order to determine relative strengths and probabilities of variables. Sequential

elimination of the nonsignificant variables (where variables with the highest *P*-values

leave first) using a backward selection step approach led to a final model. This final

model included only those variables statistically associated with the dependent variable

(outcome) at a $p < .05$.

Multicollinearity among the variables (highly correlated independent variables)

was detected using chi-square and logistic regression analysis. Assessment for

confounders and statistical interaction for suspect confounders (a) place of birth, and (b)

BCG immunization were tested individually against independent variables of BCG

immunization, history of TB, and nonoccupational exposure to TB for dependent

outcome variable of self-reported lifetime TST positivity. The detail and findings of this

analysis is presented later in the post-hoc analyses section of this dissertation.

Descriptive Statistics

Characteristics of All Survey Respondents

Of the total number of survey packets mailed to individuals comprising the entire

target cohort ($N = 4{,}335$), descriptive and demographic characteristics of all survey

respondents ($n = 1{,}693$) were determined. This determination took into account that

some questions were left unanswered. Females ($n = 1{,}450$, 85.6%) outnumbered males

($n = 243$, 14.4%). Ages of respondents ranged from 24 to 82 years, with a mean age of

55 years and mode of 58 years. The majority of respondents reported working in more

than one type of microbiology laboratory setting. Of the total, 1,237 (73.1%) individuals

reported to have worked more than 21 years in the microbiology setting, outnumbering

the other "years of laboratory experience" categories 3 to 1, and creating a cut-point for

nominal variable recoding in all future analyses. Among all respondents, a large majority

($n = 1,564$, 92.4%) reported to have been born in the U.S., a U.S. territory, or of one U.S. citizen parent. Of the $n = 1,564$ individuals reporting U.S.-birth, $n = 39$ individuals (2.49%) were not born in a U.S. territory, but were born of a U.S. citizen parent. This was determined by hand count of those surveys indicating a "no" response to written survey questionnaire Q5, and "yes" response to Q5(a). Table 5 represents univariate summary characteristics of the entire respondent group.

Table 5

Univariate Analysis: Characteristics of ASCP Medical Laboratory Microbiologists (All Survey Respondents, n = 1,693)

Characteristic	No. (% of total)	CI$_{95}$	Total Reponses
Gender			1,693
Male	243 (14.4%)	12.7%, 16.1%	
Female	1,450 (85.6%)	83.9%, 87.3%	
Mean Age (±SD, years)	54.7 ±10.1		1,685
Type of Work*			1,693
Mycobacteriology			
Yes	1,198 (70.8%)	68.5%, 72.9%	
No	495 (29.2%)	27.1%, 31.5%	
Virology			
Yes	606 (35.8%)	33.5%, 38.1%	
No	1,087 (64.2%)	61.9%, 66.5%	
Bacteriology			
Yes	1,633 (96.5%)	95.4%, 97.3%	
No	60 (3.5%)	2.7%, 4.6%	
Parasitology			
Yes	1,262 (74.5%)	72.4%, 76.6%	
No	431 (25.5%)	23.4%, 27.6%	
Mycology			
Yes	1,151 (68.0%)	65.7%, 70.2%	
No	542 (32.0%)	29.8%, 34.3%	
Serology			
Yes	1,026 (60.6%)	58.2%, 62.9%	
No	667 (39.4%)	37.1%, 41.8%	
Molecular			
Yes	681 (40.2%)	37.9%, 42.6%	
No	1,012 (59.8%)	57.4%, 62.1%	
Other			
Yes	474 (28.0%)	25.9%, 30.2%	
No	1,219 (72%)	69.8%, 74.1%)	
Years worked in lab setting			1,693
0-2			
3-5	8 (0.5%)	0.2%, 1.0%	
6-10	58 (3.4%)	2.6%, 4.4%	
11-15	134 (7.9%)	6.7%, 9.3%	
16-20	118 (7.0%)	5.8%, 8.3%	
over 21	138 (8.2%)	6.9%, 9.6%	
	1,237 (73.1%)	70.9%, 75.2%	
Place of Birth			1,693
Foreign†	129 (7.6%)	6.4%, 9.0%	
U.S.	1,564 (92.4%)	91.0%, 93.6%	
TST Test (ever had one)			1,693
Yes	1,635 (96.6%)	95.6%, 97.4%	
No	57 (3.4%)	2.6%, 4.4%	
Don't know/don't remember	1 (0.1%)	0.0%, 0.4%	
TST Positive			1,635
Yes	276 (16.9%)	15.1%, 18.8%	
No	1,354 (82.8%)	80.9%, 84.6%	
Don't know/don't remember	5 (0.3%)	0.1%, 0.8%	

(*table continues*)

Characteristic	No. (% of total)	CI$_{95}$	Total Reponses
IFN-γ blood test			1,690
Yes	172 (10.2%)	8.8%, 11.7%	
No	1,481 (87.6%)	85.9%, 89.1%	
Don't know/don't remember	37 (21.51%)	1.6%, 3.0%	
BCG immunization			1,690
Yes	110 (6.5%)	5.4%, 7.8%	
No	1,429 (84.6%)	82.7%, 86.2%)	
Don't know/don't remember	151 (8.9%)	7.6%, 10.4%	
History of active TB			1,691
Yes	12 (0.7%)	0.4%, 1.3%	
No	1,679 (99.3%)	98.7%, 99.6%	
Nonoccupational contact/Exposure			1,691
Yes	110 (6.5%)	5.4%, 7.8%	
No	1,581 (93.5%)	92.2%, 94.6%	

Note. No. refers to number of individuals; Frequency is reported in percent (%); Mean Age refers to age in years as a continuous variable, while SD refers to standard deviation; TST = tuberculin skin test; IFN-γ blood test refers to interferon gamma blood test for latent tuberculosis infection; BCG = bacille Calmette-Guérin immunization.
*For type of work: Respondents reportedly worked in more than one category.
†Foreign birth refers to those born outside U.S. or one of the U.S. territories, unless one parent at time of birth was a U.S. citizen (CDC, 2012)

From Table 5, it becomes apparent that $n = 58$ survey respondents self-reported "no" or "don't know/don't remember" to the question referring to ever having had a TST. In addition, $n = 151$ respondents reported "don't know/don't remember" to the question referring to ever having had a BCG immunization. These two items were surprising results given the level of education and work experience of this target population. In addition, given the very high mean age in this population as noted in Table 5, age distribution is discussed further and broken down by TST status (listed later in Table 9.) Increased age may have a possible effect on recall bias. However, Coughlin reported no consistent relationship between accuracy of recall and demographic factors (such as age), stating that recall may be influenced by "differences in the study populations, the questions being asked, or the nature of the exposure" (Coughlin, 1990, p. 88). In this

ASCP reseach, respondents have already been deemed highly educated health care

personnel, many of whom are required to document an annual (or recent) TST history in

the workplace. Additional characteristics as related to age among the cleaned data set are

presented later in Tables 7 and 9.

Characteristics of Eligible Survey Respondents

The cleaned data set was composed of $n = 1,628$ individual respondent records,

representative of the entire ASCP target cohort, $N = 4,335$ individuals. Descriptive

characteristics of the individuals comprising the cleaned data set ($n = 1,628$) were similar

to that of the original (raw) data set ($n = 1,693$). The cleaned data set was then utilized

for chi-square and logistic regression analyses. Table 6 represents univariate summary

characteristics of the eligible survey respondent group, $n = 1,628$ individuals.

Table 6

Univariate Analysis: Characteristics of ASCP Medical Laboratory Microbiologists (Eligible Survey Respondents, Cleaned Data Set)

Characteristic	No. (% of total)	CI$_{95}$	Total Reponses
Gender			1,628
Male	235 (14.4%)	12.8%, 16.3%	
Female	1,393 (85.6%)	83.7%, 87.2%	
Mean Age	54.7 ± 10.1		1,620
(±SD, years)			
Type of Work *			1,628
Mycobacteriology			
Yes	1,151(70.7%)	68.4%, 72.9%	
No	477 (29.3%)	27.1%, 31.6%	
Virology			
Yes	586 (36.0%)	33.7%, 38.4%	
No	1,042 (64.0%)	61.6%, 66.3%	
Bacteriology			
Yes	1,572 (96.6%)	95.5%, 97.4%	
No	56 (3.4%)	2.6%, 4.5%	
Parasitology			
Yes	1,214 (74.6%)	72.4%, 76.7%	
No	414 (25.4%)	23.3%, 27.6%	
Mycology			
Yes	1,109 (68.1%)	65.8%, 70.4%	
No	519 (31.9%)	29.6%, 34.2%	
Serology			
Yes	987(60.6%)	58.2%, 63.0%	
No	641 (39.4%)	37.0%, 41.8%	
Molecular			
Yes	654 (40.2%)	37.8%, 42.6%	
No	974 (59.8%)	57.4%, 62.2%	
Other			
Yes	458 (28.1%)	26.0%, 30.4%	
No	1,170 (71.9%)	69.6%, 74.0%	
Years worked in lab setting			
0-2			1,628
3-5	7 (0.4%)	0.2%, 0.9%	
6-10	52 (3.2%)	2.4%, 4.2%	
11-15	129 (7.9%)	6.7%, 9.4%	
16-20	115 (7.1%)	5.9%, 8.4%	
over 21	136 (8.4%)	7.1%, 9.8%	
	1,189 (73.0%)	70.8%,75.2%	
Years experience			1,628
Cut-point			
≥ 21 years	1,189 (73.0%)	70.8%, 75.2%	
≤ 20 years	439 (27.0%)	24.8%, 29.2%	
Place of Birth			1,628
Foreign †	121 (7.4%)	6.2%, 8.8%	
U.S.	1,507 (92.6%)	91.2%,93.8%	
TST Positive			1,628
Yes	276 (17.0%)	15.2%, 18.9%	
No	1,352 (83.0%)	81.1%, 84.8%	

(*table continues*)

Characteristic	No. (% of total)	CI$_{95}$	Total Reponses
IFN-γ blood test			1,626
(ever had one)	168 (10.3%)	8.9%, 11.9%	
Yes	1,421 (87.4%)	85.7%, 88.9%	
No	37 (2.3%)	1.6%, 3.2%	
Don't know/don't remember			
BCG immunization			1,628
Yes	105 (6.4%)	5.3%, 7.8%	
No	1,523 (93.6%)	92.2%, 94.7%	
History of active TB			1,628
Yes	12 (0.7%)	0.4%, 1.3%	
No	1,616 (99.3%)	98.7%, 99.6%	
Nonoccupational contact/Exposure			1,628
Yes	106 (6.5%)	5.4%, 7.8%	
No	1,522 (93.5%)	92.2%, 94.6%	

Note. No. refers to number of individuals; Frequency is reported in percent (%); Mean Age refers to age in years as a continuous variable, while SD refers to standard deviation; TST = tuberculin skin test; IFN-γ blood test refers to interferon gamma blood test for latent tuberculosis infection; BCG = bacille Calmette-Guérin immunization.
*For type of work: Respondents reportedly worked in more than one category.
†Foreign birth refers to those born outside U.S. or one of the U.S. territories, unless one parent at time of birth was a U.S. citizen (CDC, 2012)

As can be seen in Table 6, 17% of the eligible respondents self-reported a lifetime history for a positive TST. Several other findings were of interest, and determined by hand count of the data: (a) only five respondents reported to have worked solely in the area of mycobacteriology; (b) 38 of 1,507 individuals reporting "no" to being born in the U.S. or a U.S. territory (Q5), reported "yes" to having at least one U.S. citizen birth parent (Q5a); and (c) 14 positive IGRAs were reported (of the *n* = 168 total respondents in the group reported ever having had an IGRA blood test for LTBI).

To further describe age in this target population, the following Table 7 is used to explore an age cut-off of 35 years (as suggested by Shukla et al., 2002) to differentiate characteristcs of young versus old among the cleaned data set.

Table 7

Characteristics of Young Versus Old in ASCP Medical Laboratory Microbiologists (n = 1,620, Cleaned Data Set)

Characteristics	Young (≤ 35 yrs) $n = 115$ No. (%)	Old (≥ 36 yrs) $n = 1,505$ No. (%)
BCG immunization	7 (6.1%)	98 (6.5%)
Foreign birth	12 (10.4%)	109 (7.2%)
History of active TB	0 (0.0%)	11 (0.73%)
TST positivity	8 (7.0%)	267 (17.7%)

Note. TST = tuberculin skin test; BCG = bacille Calmette-Guérin immunization status, and No. refers to number of individuals.

From Table 7, prevalence of self-reported BCG immunization was about the same in each age group while prevalence of foreign birth was higher in the ≤ 35 year age division. History of active TB was present among the older (≥ 36 year) group, and not present at all among the younger group. Self-reported TST positivity was more than double among the older population.

The survey results respresenting the $n = 276$ individuals self-reporting "yes" to TST positivity status in Table 6 were segregated from the cleaned data set for additional analyses. These results are listed in Table 8. Eighteen individuals reported noncompletion of prescribed treatment. From hand calculation of this cleaned data, 15 of the $n = 18$ individuals reported positive BMQ scores of "1" or "2" (83.33%), and 12 cited specific medication side effects (detailed in responses to Q15a), a 66.67% rate of non-completion due to specifically named medication side effects in the individuals

prescribed treatment. Characteristics of those individuals self-reporting a lifetime history

of TST positivity are depicted in Table 8.

Table 8

Univariate Analysis: ASCP Medical Laboratory Microbiologists With Self-Reported
History of Lifetime TST-Positive Status (Cleaned Data Set)

Characteristic	No. (% of Total)	CI$_{95}$ (%)	Total
Prescribed anti-TB medication			275*
Yes	143 (52.0%)	45.9%, 58.0%	
No	132 (48.0%)	42.0%, 54.1%	
Initiated taking medication			143
Yes	129 (90.2%)	84.1%, 94.5%	
No	14 (9.8%)	5.5%, 15.9%	
Complete entire course			129
Yes	111 (86.0)	78.8%, 91.5%	
No	18 (14.0)	8.5%, 21.2%	
BMQ Score†			129
0	85 (65.9%)	57.0%, 74.0%	
1	28 (21.7%)	14.9%, 29.8%	
2	16 (12.4%)	7.3%, 19.4%	

Note. No. refers to number of individuals; CI95 = 95% confidence interval
* One nonresponse (NR)
†Permission for use of these questions granted by primary owner of the Brief Medication
Questionnaire (BMQ) survey instrument (Svarstad et al., 1999) on October 25, 2011, and
permission to reprint selected questions for Appendix D received on May 6, 2012 via
electronic correspondence. (See Appendix F.) BMQ scores of 1 and 2 are graded as
"positive" for barriers to treatment adherence.

Of the *n* = 14 individuals who did not initiate treatment (see Table 8), 13 refused anti-TB

medication treatment (9.1% of the *n* = 143 prescribed treatment), and one did not respond

(0.7% of the *n* = 143 prescribed treatment). Conversely, 129 of the *n* = 143 individuals

prescribed treatment self-reported as initiating anti-TB medication treatment, a 90.2%

treatment initiation rate, and a 9.8% noninitiation rate.

Bivariate Analysis

At this point in the data analysis, age was analyzed as a continuous variable (mean in years), not as a nominal dichotomous variable, which is consistent with TST status analyses in prior literature. Years of laboratory experience was collapsed into two groups based on the mean of the respondent data. Effect sizes were measured as OR. Summary results of the bivariate analysis involving an outcome of self-reported TST status among ASCP medical laboratory microbiologists *(*cleaned data set *n* = 1,628 of the original *N* = 4,335 cohort) may be viewed in the corresponding table (Table 9). For all remaining bivariate and multivariate tables, decimals have been rounded to two places, three places for *P*-values.

Table 9

Bivariate Analysis: Self-Reported TST Status Among ASCP Medical Laboratory Microbiologists (Cleaned Data Set)

Characteristic	TST Positive n = 276 (17.0%) No. (%)	TST Negative n = 1,352 (83.0%) No. (%)	Total	OR	CI$_{95}$	χ^2,p
Gender						
Male	52 (18.8%)	183 (13.5%)	235	1.48	1.05-2.07	4.80, .028
Female	224 (81.2%)	1,169 (86.5%)	1,393	REF		
Mean Age						ANOVA t-test p
(±SD, years)	57.67 ±9.59	54.11±10.01	1,620			<.001
Age groups (years):						
Age (24-33)	5 (1.8)	84 (6.2)				
Age (34-43)	20 (7.3)	115 (8.6)				
Age (44-53)	53 (19.3)	300 (22.3)				
Age (54-63)	124 (45.1)	668 (49.7)				
Age (64-73)	61 (22.2)	168 (12.5)				
Age (74-82)	12 (4.4)	10 (0.7)				
Type of Work*						
Mycobacteriology						
Yes	215 (77.9%)	936 (69.2%)	1,151	1.57	1.16-2.14	7.90, .005
No	61 (22.1%)	416 (30.8%)	477	REF		
Virology						
Yes	103 (37.3%)	483 (35.7%)	586	1.07	0.82-1.40	0.19, .664
No	173 (62.7%)	869 (64.3%)	1,042	REF		
Bacteriology						
Yes	264 (95.7%)	1,308 (96.7%)	1,572	0.74	0.39-1.48	0.53, .467
No	12 (4.3%)	44 (3.3%)	56	REF		
Parasitology						
Yes	220 (79.7%)	994 (73.5%)	1,214	1.41	1.03-1.96	4.31, .038
No	56 (20.3%)	358 (26.5%)	414	REF		
Mycology						
Yes	198 (71.7%)	911 (67.4%)	1,109	1.23	0.93-1.64	1.81, .179
No	78 (28.3%)	441 (32.6%)	519	REF		
Serology						
Yes	168 (60.9%)	819 (60.6%)	987	1.01	0.78-1.32	<0.01, .982
No	108 (39.1%)	533 (39.4%)	641	REF		
Molecular						
Yes	105 (38.0%)	549 (40.6%)	654	0.90	0.69-1.17	0.52, .469
No	171 (62.0%)	803 (59.4%)	974	REF		
Other						
Yes	91 (33.0%)	367 (27.1%)	458	1.32	1.00-1.74	3.57, .059
No	185 (67.0%)	985 (72.9%)	1,170	REF		
Years worked in lab setting						
0-2	0 (0.00%)	7 (0.5%)	7		(Collapsed; see below)	
3-5	6 (2.2%)	46 (3.4%)	52			
6-10	18 (6.5%)	111 (8.2%)	129			
11-15	15 (5.4%)	100 (7.4%)	115			
16-20	26 (9.4%)	110 (8.1%)	136			
over 21	211 (76.4%)	978 (72.3%)	1,189			

(*table continues*)

Characteristic	TST Positive n = 276 (17.0%) No. (%)	TST Negative n = 1,352 (83.0%) No. (%)	Total	OR	CI$_{95}$	χ^2,p
Years worked in lab setting (collapsed)						
≥ 21 years	211 (76.4%)	978 (72.3%)	1,189	1.24	0.92-1.69	1.76, .184
≤ 20 years	65 (23.6%)	374 (27.7%)	439	REF		
Place of Birth						
Foreign ‡	69 (25.0%)	52 (3.8%)	121	8.32	5.64-12.31	146.02, < .001
U.S.	207 (75.0%)	1,300(96.2%)	1,507	REF		
BCG immunization						
Yes	71 (25.7%)	34 (2.5%)	105	13.39	8.71-20.87	200.81, < .001
No	205 (74.3%)	1,318 (97.5%)	1,523	REF		
History of TB						
Yes	11 (4.0%)	1 (0.1%)	12	55.89	9.48-1,218.72	42.73, < .001†
No	265 (96.0%)	1,351(99.9%)	1,616	REF		
Nonoccupational contact/Exposure						
Yes	35 (12.7%)	71 (5.3%)	106	2.62	1.69-4.00	19.58, < .001
No	241 (87.3%)	1,281 (94.7%)	1,522	REF		

Note. TST = tuberculin skin test; No. refers to number of individuals; OR = MLE odds ratio; CI95 = 95% confidence interval; $\chi2$ = Yates corrected with 2-tailed p chi-square test; Mean Age refers to age in years as a continuous variable (note that age was broken out by groups strictly for the purpose of obtaining distribution), while SD refers to standard deviation; BCG = bacille Calmette-Guérin; REF refers to referent group.
*For type of work: Respondents reportedly worked in more than one category
†Fisher Exact Test
‡Foreign birth refers to those born outside U.S. or one of the U.S. territories, unless one parent at time of birth was a U.S. citizen (CDC, 2012)

Bivariate analysis was performed to assess several factors on the likelihood that survey respondents would report ever having had a positive TST (Table 9). Eight of the independent variables emerged as statistically significant predictors of a positive TST (male gender, age, work in mycobacteriology, work in parasitology, place of birth: foreign, history of BCG immunization, history of TB, and nonoccupational contact/exposure to TB). The strongest predictor of self-reporting a positive tuberculin

skin test was a history of TB, with an OR of 55.89, indicating that respondents who reported prior history of TB were almost 55 times more likely to report a positive TST than those who reported a negative TST.

For the outcome of treatment noninitiation among respondents numbering $n =$ 143, $n = 14$ did not initiate preventive treatment. Table 10 depicts the characteristics of this subgroup, as well as those initiating prescribed preventive treatment.

Table 10

Bivariate Analysis: Self-Reported Treatment Initiation Status Among TST-Positive ASCP Medical Laboratory Microbiologists (Cleaned Data Set)

Characteristic	Noninitiate No. (% of n = 14)	Initiate No. (% of n = 129)	Total	OR	CI$_{95}$	χ^2, p
Gender						
Male	3 (21.4%)	28 (21.7%)	31	0.98	0.21-3.59	0.10, .623†
Female	11 (78.6%)	101 (78.3%)	112	REF		
Mean age* ±SD, years	56.00±7.75	57.16±8.12	142			ANOVA t-test p=.610
Type of Work‡						
Mycobacteriology						
Yes	11 (78.6%)	107 (82.9%)	118	0.76	0.20-3.62	<0.01, .458†
No	3 (21.4%)	22 (17.1%)	25	REF		
Virology						
Yes	8 (57.1%)	47 (36.4%)	55	2.31	0.74-7.54	1.50, .221
No	6 (42.9%)	82 (63.6%)	88	REF		
Bacteriology						
Yes	14 (100.0%)	123 (95.3%)	137	undef	0.16-undef	0.02, .533†
No	0 (0.0%)	6 (4.7%)	6	REF		
Parasitology						
Yes	12 (85.7%)	105 (81.4%)	117	1.37	0.32-9.53	<0.01, .513†
No	2 (14.3%)	24 (18.6%)	26	REF		
Mycology						
Yes	12 (85.7%)	95 (73.6%)	107	2.14	0.51-14.71	0.44, .263†
No	2 (14.3%)	34 (26.4%)	36	REF		
Serology						
Yes	10 (71.4%)	77 (59.7%)	87	1.68	0.51-6.48	0.32, .571
No	4 (28.6%)	52 (40.3%)	56	REF		
Molecular						
Yes	8 (57.1%)	51 (39.5%)	59	2.03	0.65-6.60	0.97, .324
No	6 (42.9%)	78 (60.5%)	84	REF		
Other						
Yes	5 (35.7%)	42 (32.6%)	47	1.15	0.33-3.66	<0.01, .513†
No	9 (64.3%)	87 (67.4%)	96	REF		
Years worked in lab setting						
0-2	0	0	0			(Collapsed. See below.)
3-5	0	3 (2.3%)	3			
6-10	0	6 (4.7%)	6			
11-15	0	7 (5.4%)	7			
16-20	4 (28.6%)	13 (10.1%)	17			
over 21	10 (71.4%)	100 (77.5%)	110			
Years worked in lab setting (collapsed)						
≥ 21 years	10 (71.4%)	100 (77.5%)	110	0.73	0.22-2.85	0.03, .410†
≤ 20 years	4 (28.6%)	29 (22.5%)	33	REF		
Place of Birth						
Foreign ∑	6 (42.9%)	18 (14.0%)	24	4.55	1.33-15.05	5.63, .014†
U.S.	8 (57.1%)	111 (86.0%)	119	REF		

(*table continues*)

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Characteristic	Noninitiate No. (% of n = 14)	Initiate No. (% of n = 129)	Total	OR	CI$_{95}$	χ^2, p
BCG immunization						
Yes	5 (35.7%)	15 (11.6%)	20	4.16	1.13-14.23	4.25, .028†
No	9 (64.3%)	114 (88.4%)	123	REF		
History of TB						
Yes	0 (0.0%)	11 (8.5%)	11	0.00	0.00-2.93	0.37, .308†
No	14 (100.0%)	118 (91.5%)	132	REF		
Nonoccupational contact/ Exposure						
Yes	0 (0.0%)	20 (15.5%)	20	0.00	0.00-1.41	1.40, .109†
No	14 (100.0%)	109 (84.5%)	123	REF		

Note. No. refers to number of individuals; TST = tuberculin skin test; No. refers to number of individuals; OR = MLE odds ratio; CI$_{95}$ = 95% confidence interval; χ^2 = Yates corrected with 2-tailed p chi-square test; undef = undefined, zeroes in cells; Mean Age refers to age in years as a continuous variable, while SD refers to standard deviation; BCG = bacille Calmette-Guérin; REF refers to referent group.

*n = 142

†Fisher Exact Test

‡For type of work, respondents reportedly worked in more than one category

ΣForeign birth refers to those born outside United States or one of the U.S. territories, unless one parent at time of birth was a U.S. citizen (CDC, 2012).

Bivariate analysis was performed to assess several factors on the likelihood that survey respondents would report never having initiated preventive treatment (Table 10). Two of the independent variables emerged as statistically significant predictors (place of birth: foreign, and history of BCG immunization) for treatment noninitiation. Both of these predictors had similar ORs, indicating that respondents who did not initiate treatment were 4 times more likely to report treatment noninitiation than those who reported treatment initiation.

Table 11 depicts characteristics of the subgroup initiating preventive TB treatment (*n* = 129), and reporting treatment adherence barriers as measured by a positive BMQ

score versus an outcome of no treatment adherence barriers as measured by a negative

BMQ score.

Table 11

Bivariate Analysis: Barriers to Treatment Adherence (by BMQ Score) Among TST-Positive ASCP Medical Laboratory Microbiologists Initiating Treatment (Cleaned Data Set)

Characteristic	BMQ positive score No. (% of n = 44)	BMQ negative score No. (% of n = 85)	Total	OR	CI$_{95}$	χ^2, p
Gender						
Male	6 (13.6%)	22 (25.9%)	28	0.45	0.16-1.19	1.89, .169
Female	38 (86.4%)	63 (74.1%)	101	REF		
Mean age* ±SD, years	56.9 ±8.7	57.3±7.9	128		ANOVA t-test p= .781	
	n=44	n=84				
Type of Work†						
Mycobacteriology						
Yes	34 (77.3%)	73 (85.9%)	107	0.56	0.22-1.47	0.97, .324
No	10 (22.7%)	12 (14.1%)	22	REF		
Virology						
Yes	17 (38.6%)	30 (35.3%)	47	1.15	0.54-2.46	0.03, .856
No	27 (61.4%)	55 (64.7%)	82	REF		
Bacteriology						
Yes	42 (95.5%)	81 (95.3%)	123	1.04	0.18-8.37	0.16, .667‡
No	2 (4.5%)	4 (4.7%)	6	REF		
Parasitology						
Yes	38 (86.4%)	67 (78.8%)	105	1.69	0.63-5.02	0.65, .421
No	6 (13.6%)	18 (21.2%)	24	REF		
Mycology						
Yes	34 (77.3%)	61 (71.8%)	95	1.33	0.58-3.24	0.21, .644
No	10 (22.7%)	24 (28.2%)	34	REF		
Serology						
Yes	29 (65.9%)	48 (56.5%)	77	1.49	0.70-3.23	0.72, .397
No	15 (34.1%)	37 (43.5%)	52	REF		
Molecular						
Yes	19 (43.2%)	32 (37.6%)	51	1.26	0.59-2.65	0.18, .675
No	25 (56.8%)	53 (62.4%)	78	REF		
Other						
Yes	12 (27.3%)	30 (35.3%)	42	0.69	0.30-1.53	0.52, .469
No	32 (72.7%)	55 (64.7%)	87	REF		
Years worked in lab setting (collapsed)						
≥ 21 years	34 (77.3%)	66 (77.6%)	100	0.98	0.41-2.42	0.03, .862
≤ 20 years	10 (22.7%)	19 (22.4%)	29	REF		
Place of Birth						
Foreign ∑	6 (13.6%)	12 (14.1%)	18	0.96	0.31-2.75	0.04, .847
U.S.	38 (86.4%)	73 (85.9%)	111	REF		
BCG immunization						
Yes	4 (9.1%)	11 (12.9%)	15	0.67	0.18-2.20	0.13, .721
No	40 (90.9%)	74 (87.1%)	114	REF		

(*table continues*)

Characteristic	BMQ positive score No. (% of n = 44)	BMQ negative score No. (% of n =85)	Total	OR	CI$_{95}$	χ^2, p
History of TB						
Yes	1 (2.3%)	10 (11.8%)	11	0.18	0.01-1.10	2.24, .060‡
No	43 (97.7%)	75 (88.2%)	118	REF		
Nonoccupational Contact/ Exposure						
Yes	6 (13.6%)	14 (16.5%)	20	0.80	0.26-2.23	0.03, .869
No	38 (86.4%)	71 (83.5%)	109	REF		

Note. No. refers to number of individuals; OR = MLE odds ratio; CI$_{95}$ = 95% confidence interval; χ^2 = Yates corrected with 2-tailed p chi-square test; Mean Age refers to age in years as a continuous variable; BCG = bacille Calmette-Guérin; REF refers to referent group. BMQ = Brief Medication Questionnaire; permission for use of these questions granted by primary owner of the Brief Medication Questionnaire survey instrument (Svarstad et al., 1999) on October 25, 2011, and permission to reprint selected questions for Appendix D received on May 6, 2012 via electronic correspondence. (See Appendix F.) BMQ scores of 1 and 2 are graded as "positive" for barriers to treatment adherence.
*n = 128
†For type of work, respondents reportedly worked in more than one category
‡Fisher exact test
ƩForeign birth refers to those born outside the United States or one of the U.S. territories, unless one parent at time of birth was a U.S. citizen (CDC, 2012)

From Table 11, it is apparent that no one variable (as evident in the bivariate analysis) demonstrated a statistically significant association of p < .05 for outcome of a positive BMQ score.

Statistical Assumptions

For nominal data and use of chi-square, the following four assumptions were met: (a) data were categorized (with the exception of age) and frequencies obtained, (b) adequate sample size was met, (c) the measures were mutually exclusive, and (d) research questions and theory were previously established by a thorough review of the literature. Goodness-of-fit, or dispersion, was assessed to see if the models fulfilled the

original assumptions. In this study, the chi-square result and degrees of freedom (df = 1

for 2x2 tables) were compared. (If chi-square value = 1, then the model perfectly fit the

data.) The following assumptions for use of unconditional logistic regression were met:

(a) the logarithm of the odds of the outcome (logit) is being modeled, (b) this logit of the

outcome changes linearly with multiple independent variables, (c) outcome variables

(with the exception of age) are distributed in binomial manner, and (d) the variance of the

outcome variable depends only on the mean (Katz, 2006). In addition, any outliers were

removed during the data cleaning stage.

Research Questions: Bivariate Analysis and Logistic Regression

     Research Question 1: TST positivity. The first null hypothesis predicted that

there would be no statistical association between self-reported individual independent

variables of history of BCG immunization, place of birth (U.S. or foreign), and years of

laboratory experience, and the dependent variable of self-reported lifetime TST

positivity. This hypothesis was tested using odds ratios (ORs) obtained using Epi Info™

TABLES analysis; resulting chi-square has been reported. Tables 12, 13, and 14 provide

2-by-2 table summaries as obtained from Epi Info™ TABLE analyses for the

independent variables.

Table 12

2x2 Table BCG Immunization vs. Self-Reported History of Lifetime TST Positivity

BCG Immunization	TST positive	TST negative	Total
BCG yes	71 (25.7%)	34 (2.5%)	105
BCG no	205 (74.3%)	1,318 (97.5%)	1,523
Total	276	1,352	1,628

Note. TST = tuberculin skin test; OR = MLE odds ratio; CI95 = 95% confidence interval; $\chi2$ = Yates corrected with 2-tailed *p* chi-square test; BCG = bacille Calmette-Guérin.

For BCG immunization "Yes":

Odds ratio (OR) = 13.39 (95% confidence interval [CI_{95}], 8.71 -20.87)

Chi-square ($\chi2$) = 200.81

p < .001

Table 12 shows that a self-reported history of BCG immunization is a statistically significant predictor of a self-reported history of lifetime TST positivity. In addition, the OR of 13.39 indicates that survey respondents who reported a history of BCG immunization were more than 13 times more likely to report a positive TST than those who reported a negative TST.

Table 13

2x2 Table Place of Birth (U.S. or Foreign) vs. Self-reported History of Lifetime TST Positivity

Place of birth	TST positive	TST negative	Total
Foreign	69 (25.0%)	52 (3.8%)	121
U.S.	207 (75.0%)	1,300 (96.2%)	1,507
Total	276	1,352	1,628

Note. TST = tuberculin skin test; OR = MLE odds ratio; CI95 = 95% confidence interval; $\chi 2$ = Yates corrected with 2-tailed p chi-square test; Foreign birth refers to those born outside the United States or one of the U.S. territories, unless one parent at time of birth was a U.S. citizen (CDC, 2012)

For foreign birth "Yes":

Odds ratio (OR) = 8.32 (95% confidence interval [CI_{95}], 5.64 -12.31)

Chi-square ($\chi 2$) = 146.02

p < .001

Table 13 shows that a history of foreign birth is a statistically significant predictor of a self-reported history of lifetime TST positivity. In addition, the OR of 8.32 indicates that survey respondents who reported a history of foreign birth were more than 8 times more likely to report a positive TST than those who reported a negative TST.

Table 14

2x2 Table Years of Laboratory Experience vs. Self-reported History of Lifetime TST Positivity

Years of Experience	TST positive	TST negative	Total
≥ 21 years	211 (76.4%)	978 (72.3%)	1,189
≤ 20 years	65 (23.6%)	374 (27.7%)	439
Total	276	1,352	1,628

Note. TST = tuberculin skin test; OR = MLE odds ratio; CI95 = 95% confidence interval; $\chi2$ = Yates corrected with 2-tailed *p* chi-square test; ≥ 21 years refers to years of laboratory experience.

For ≥ 21 years of laboratory experience group: "Yes":

Odds ratio (OR) = 1.24 (95% confidence interval [CI_{95}], 0.92 -1.69)

Chi-square ($\chi2$) = 1.76

p = .184

Table 14 shows that a history of ≥ 21 years of laboratory work experience is not a statistically significant predictor of a self-reported history of lifetime TST positivity. In addition, the OR of 1.24 indicates that survey respondents who reported a history of ≥ 21 years of laboratory work experience were no more than likely to report a positive TST than those who reported a negative TST.

For all following multivariate analyses, attributes were designated as coding of "1" (for "yes", the attribute is present) in the Epi Info™ software ANALYZE DATA view. (Referent attributes remained the same as previously listed in bivariate Tables 9, 10, and 11.) As previously stated, the age variable was the only variable in this analysis calculated by continuous variable by age per year.

- Gender: Male

- Age in years (continuous variable): Age

- Self-reported type of work; current or prior work experience (by laboratory section):

  - Mycobacteriology

  - Virology

  - Bacteriology

  - Parasitology

  - Mycology

  - Serology

  - Molecular

  - Other areas

- Self-reported lifetime history of TST positivity: TST positivity

- Treatment noninitiation

- BMQ score of ≥ 1 indicating a positive screen for medication barriers, drug effects, bothersome features as related to treatment nonadherence: Positive BMQ score

- Self-reported history of obtaining a BCG immunization: BCG immunization

- Place of birth: Foreign

- ≥ 21 Years of lab experience

- History of TB

- Nonoccupational exposure

For logistic regression (a) all pertinent variables were included in the model, and (b) then, stepwise (backward) removal of statistically nonsignificant variables (removed one at a time based on highest *P* values) was performed. Overall model significance for the logistic regression was determined by the effect of the independent variable(s) and was represented with the OR. The individual predictors were assessed by the *Z*-statistic. The final logistic regression model included only those variable(s) that were statistically associated with the dependent (outcome) variable. An evaluation for confounders and assessment for statistical interaction also took place and has been detailed later in the post-hoc analyses section.

Table 15 represents the initial logistic regression model for respondents self-reporting a lifetime history of positive TST among the cleaned data set of $n = 1,628$. All variables previously identified in the bivariate analyses as individually associated with a *P* value < .15 were included in the initial regression model.

Table 15

Initial Logistic Regression Analysis for Self-Reported History of Lifetime TST Positivity (n = 1,620*)

Characteristic	Odds Ratio	95%	C.I.	Z-Statistic	P-Value
Age	1.06	1.04	1.08	5.7211	< .001
BCG Immunization	9.10	5.18	15.99	7.6746	< .001
Foreign Birth	3.28	1.92	5.62	4.3298	< .001
Nonoccupational exposure	1.79	1.08	2.98	2.2474	.025
History of TB	30.32	3.63	253.21	3.1505	.002
Mycobacteriology Work	1.47	0.96	2.26	1.7796	.075
Mycology Work	1.10	0.72	1.67	0.4337	.665
Work in Other Areas of Laboratory	1.47	1.08	2.02	2.4152	.016
Parasitology Work	1.08	0.71	1.65	0.3740	.708
Gender: Male	1.14	0.77	1.71	0.6601	.509
$\geq$ 21 Years of Lab Experience	0.78	0.53	1.16	-1.21	.225
CONSTANT	*	*	*	-10.27	< .001

Note. TST = tuberculin skin test. Using Epi Info™ Version 3.5.3 (CDC, 2011c), CI refers to confidence interval; the *Z*-statistic has been calculated from the Wald statistic. The initial regression model for each outcome was composed of the three main independent variables ($\geq$ final model by a priori decision. Age was input as a continuous variable. Foreign birth refers to those born outside the United States or one of the U.S. territories, unless one parent at time of birth was a U.S. citizen (CDC, 2012); BCG = receipt of a bacille Calmette-Guérin immunization.
*Cases included *n* = 1,620 as restricted by AGE.

In the initial model represented in Table 15, age, BCG immunization, foreign birth, exposure to nonoccupational TB, history of active TB, and work in areas other than microbiology are statistically associated with the outcome of self-reported history of lifetime TST positivity, significant at *p* < .05. ORs are greater than 1.0, indicating a potential (and positive direction) association with TST positivity. Table 16 represents the

final regression model after all backward stepwise eliminations occurred, based on

removal of highest P values at each step.

Table 16

Final Logistic Regression Analysis for Self-Reported History of Lifetime TST Positivity (n = 1,620*)

Characteristic	Odds Ratio	95%	C.I.	Z-Statistic	P-Value
AGE	1.05	1.03	1.07	5.80	< .001
BCG Immunization	9.21	5.26	16.13	7.77	< .001
Foreign Birth	3.35	1.97	5.72	4.45	< .001
Nonoccupational Exposure	1.80	1.08	3.00	2.26	.024
History of TB	31.21	3.75	259.67	3.44	.002
Mycobacteriology Work	1.59	1.12	2.24	2.62	.009
Work in Other Areas of the Laboratory	1.45	1.06	1.99	2.34	.019
CONSTANT	*	*	*	-10.28	< .001

Note. TST = tuberculin skin test. Using Epi Info™ Version 3.5.3 (CDC, 2011c), CI refers to confidence interval; the Z-statistic has been calculated from the Wald statistic. The initial regression model for each outcome was composed of the three main independent variables (forced into the final model by a priori decision. Age was input as a continuous variable. Foreign birth refers to those born outside the United States or one of the U.S. territories, unless one parent at time of birth was a U.S. citizen (CDC, 2012); BCG = receipt of a bacille Calmette-Guérin immunization.
*Cases included n=1620 as restricted by AGE.

According to Table 16, as age increases by year, odds of TST positivity increase (OR=1.05). The odds of TST positivity increase more than nine times for the BCG immunized, more than three times for the foreign-born (over U.S.-born individuals). In the multivariate analysis, age, foreign birth, BCG immunization, nonoccupational exposure, history of TB, work in a mycobacteriology laboratory, and work in laboratory sections outside microbiology remained statistically significant and associated with a self-reported lifetime history of a positive TST (*n* = 1,620); thus, these variables remain predictors of self-reported TST positivity among the target population.

Conclusion: I am able to reject portions of the first null hypothesis which predicted there would be no statistical association between self-reported individual independent variables of history of BCG immunization ("yes") and place of birth ("foreign"), and unable to reject years of laboratory experience, as these independent variables act on the dependent (outcome) variable of self-reported lifetime TST positivity. Thus, the null hypothesis remains valid for independent variable of years of laboratory experience, while the alternate hypothesis is valid for independent variables of BCG immunization and foreign birth with respect to a self-report of lifetime TST positivity.

Research Question 2: Preventive treatment noninitiation. The second null hypothesis predicted that there would be no statistical association between self-reported individual independent variables of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and the dependent variable of preventive treatment noninitiation. This hypothesis was tested using odds ratios (ORs) obtained using Epi Info™ TABLES analysis; resulting chi-square has been reported. Tables 17, 18, and 19 provide 2-by-2 table summaries as obtained from Epi Info™ TABLE analyses for the independent variables.

Table 17

2x2 Table BCG Immunization vs. Treatment Noninitiation

BCG immunization	Treatment initiation NO	Treatment initiation YES	Total
BCG yes	5 (35.7%)	15 (11.6%)	20
BCG no	9 (64.3%)	114 (88.4%)	123
Total	14	129	143

Note. OR = MLE odds ratio; CI95 = 95% confidence interval; $\chi2$ = Yates corrected with 2-tailed *p* chi-square test; BCG = bacille Calmette-Guérin.
* Refers to Fisher Exact Test

For BCG immunization "Yes":

Odds ratio (OR) = 4.16 (95% confidence interval [CI_{95}], 1.13- 14.23)

Chi-square ($\chi2$) = 4.25

p = .028*

      Table 17 shows that a self-reported history of history of BCG immunization is a statistically significant predictor of a self-reported history of not initiating preventive treatment. In addition, the OR of 4.16 indicates that survey respondents who reported a history of BCG immunization were over 4 times more likely to report treatment nonitiation than those who reported treatment initiation.

Table 18

2x2 Table Place of Birth (U.S. or foreign) vs. Treatment Noninitiation

Place of birth	Treatment initiation NO	Treatment initiation YES	Total
Foreign	6 (42.9%)	18 (14.0%)	24
U.S.	8 (57.1%)	111 (86.0%)	119
Total	14	129	143

Note. OR = MLE odds ratio; CI95 = 95% confidence interval; $\chi2$ = Yates corrected with 2-tailed *p* chi-square test; foreign birth refers to those born outside the United States or one of the U.S. territories, unless one parent at time of birth was a U.S. citizen (CDC, 2012)
* Refers to Fisher Exact Test

For foreign birth "Yes":

Odds ratio (OR) = 4.55 (95% confidence interval [CI_{95}], 1.33 – 15.05)

Chi-square ($\chi2$) = 5.63

p = .014*

Table 18 shows that a history of foreign birth is a statistically significant predictor of a self-reported history of not initiating preventive treatment. In addition, the OR of 4.55 indicates that survey respondents who reported a history of treatment noninitiation were over 4 times more likely to report treatment noninitiation than those who reported treatment initiation.

Table 19

2x2 Table Years of Laboratory Experience vs. Treatment Noninitiation

Years of experience	Treatment initiation NO	Treatment initiation YES	Total
≥ 21 years	10 (71.4%)	100 (77.5%)	110
≤ 20 years	4 (28.6%)	29 (22.5%)	33
Total	14	129	143

Note. OR = MLE odds ratio; CI95 = 95% confidence interval; $\chi 2$ = Yates corrected with 2-tailed *p* chi-square test.
* Fisher Exact Test

For the ≥ 21 years of laboratory experience group "Yes":

Odds ratio (OR) = 0.73 (95% confidence interval [CI_{95}], 0.22 – 2.85)

Chi-square ($\chi 2$) = 0.03

p = .410*

Table 19 shows that a history of ≥ 21 years of laboratory work experience is not a statistically significant predictor of a self-reported history of preventive treatment noninitiation. In addition, the OR of 0.73 indicates that survey respondents who reported a history of ≥ 21 years of laboratory work experience were no more likely to report treatment noninitiation than those who reported a treatment initiation.

To summarize, BCG immunization and foreign birth are individually statistically significant predictors according to 2x2 Tables 17 and 18, while ≥ 21 years of laboratory experience is not significantly associated with the outcome of treatment noninitiation (Table 19). The initial multiple regression analysis is represented in Table 20, and includes all variables found to be statistically significant and *p* < .15 as determined in the

bivariate analysis (Table 10). Independent variables associated with the research

questions have been forced into the initial model based on a priori decision.

Table 20

Initial Logistic Regression Analysis for Preventive Treatment Noninitiation (n = 143)

Characteristic	Odds Ratio	95%	C.I.	Z-Statistic	P-Value
BCG Immunization	3.57	0.61	20.96	1.41	.159
Foreign Birth	3.19	0.58	17.61	1.33	.183
Nonoccupational Exposure	0.00	0.00	>1.00	-0.04	.970
Virology Work	1.95	0.57	6.70	1.06	.291
≥ 21 Years of Lab Work Experience	1.89	0.34	10.67	0.72	.470
CONSTANT	*	*	*	-3.663	≤ .001

Note. Using Epi Info™ Version 3.5.3 (CDC, 2011c), CI refers to confidence interval; the
Z-statistic has been calculated from the Wald statistic. The initial regression model for
each outcome was composed of the three main independent variables (forced into the
final model by a priori decision. Foreign birth refers to those born outside the United
States. or one of the U.S. territories, unless one parent at time of birth was a U.S. citizen
(CDC, 2012); BCG = receipt of a bacille Calmette-Guérin immunization.

No *P*-values are statistically significant for preventive treatment noninitiation as

represented in the initial logistic regression model (Table 20). After stepwise (backward)

deletion of each nonsignificant variable one at a time (where the highest *P* value is

removed, and regression is repeated), the final regression analysis model (Table 21)

remains.

Table 21

Final Logistic Regression Analysis for Preventive Treatment Noninitiation (n = 143)

Characteristic	Odds Ratio	95%	C.I.	Z-Statistic	P-Value
Foreign Birth	4.63	1.44	14.90	2.57	.010
CONSTANT	*	*	*	-7.18	< .001

Note. Using Epi Info™ Version 3.5.3 (CDC, 2011c), CI refers to confidence interval; the *Z*-statistic has been calculated from the Wald statistic. The initial regression model for each outcome was composed of the three main independent variables (forced into the final model by a priori decision. Foreign birth refers to those born outside the United States. or one of the U.S. territories, unless one parent at time of birth was a U.S. citizen (CDC, 2012); BCG = receipt of a bacille Calmette-Guérin immunization.

In the final multivariate analysis (Table 21), only the place of birth: foreign variable remained statistically significant when tested against an outcome of treatment noninitiation.

Therefore, I am unable to reject the second null hypothesis regarding independent variables of history of BCG immunization, and years of laboratory experience with respect to a self-report of lifetime preventive treatment noninitiation. I am able to accept the alternate hypothesis regarding independent variable of place of birth (foreign) with respect to a self-report of lifetime preventive treatment noninitiation.

Research Question 3: Positive BMQ score. The third null hypothesis predicted that there would be no statistical association between self-reported individual independent variables of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and the dependent variable of barriers to treatment adherence (medication side effects) as identified using the Brief Medication

Questionnaire (BMQ) in those respondents ever having initiated preventive TB treatment.

This hypothesis was tested using odds ratios (ORs) obtained using Epi Info™ TABLES

analysis; resulting chi-square has been reported. Tables 22, 23, and 24 provide 2-by-2

table summaries as obtained from Epi Info™ TABLE analyses for the independent

variables.

Table 22

2x2 Table BCG Immunization vs. Treatment Nonadherence (by BMQ Score)

BCG immunization	BMQ score of ≥ 1	BMQ score of < 1	Total
BCG yes	4 (9.1%)	11 (12.9%)	15
BCG no	40 (90.9%)	74 (87.1%)	114
Total	44	85	129

Note. BMQ = Brief Medication Questionnaire (where a score ≥1 indicates barriers to treatment adherence may be present); OR = MLE odds ratio; CI95 = 95% confidence interval; $\chi2$ = Yates corrected with 2-tailed *p* chi-square test; BCG = bacille Calmette-Guérin.

For BCG immunization "Yes":

Odds ratio (OR) = 0.67 (95% confidence interval [CI$_{95}$], 0.18- 2.20)

Chi-square ($\chi2$) = 0.13

p = .721

Table 22 shows that a self-reported history of BCG immunization is not a

statistically significant predictor of a self-reported history of treatment nonadherence as

measured by a positive BMQ score. In addition, the OR of 0.67 indicates that survey

respondents who reported a history of BCG immunization were no more likely to report a

positive BMQ score than those who reported a negative BMQ score.

Table 23

2x2 Table Place of Birth (U.S. or Foreign) vs. Treatment Nonadherence (by BMQ Score)

Place of birth	BMQ score of ≥ 1	BMQ Score or < 1	Total
Foreign	6 (13.6%)	12 (14.1%)	18
U.S.	38 (86.4%)	73 (85.9%)	111
Total	44	85	129

Note. BMQ = Brief Medication Questionnaire (where a score ≥ 1 indicates barriers to treatment adherence may be present); OR = MLE odds ratio; CI95 = 95% confidence interval; $\chi 2$ = Yates corrected with 2-tailed *p* chi-square test; foreign birth refers to those born outside the United States or one of the U.S. territories, unless one parent at time of birth was a U.S. citizen (CDC, 2012)

For foreign birth "Yes":

Odds ratio (OR) = 0.96 (95% confidence interval [CI_{95}], 0.31 – 2.75)

Chi-square ($\chi 2$) = 0.04

p = .847

     Table 23 shows that a history of foreign birth is not a statistically significant predictor of a self-reported history of treatment nonadherence as measured by a positive BMQ score. In addition, the OR of 0.96 indicates that survey respondents who reported foeign birth were no more likely to report a positive BMQ score than those who reported a negative BMQ score.

Table 24

2x2 Table Years of Laboratory Experience vs. Treatment Nonadherence (by BMQ Score)

Laboratory experience	BMQ score of ≥ 1	BMQ score of < 1	Total
≥ 21 years	34 (77.3%)	66 (77.6%)	100
≤ 20 years	10 (22.7%)	19 (22.4%)	29
Total	44	85	129

Note. BMQ = Brief Medication Questionnaire (where a score ≥ 1 indicates barriers to treatment adherence may be present); OR = MLE odds ratio; CI95 = 95% confidence interval; $\chi2$ = Yates corrected with 2-tailed *p* chi-square test.

For the ≥ 21 years of laboratory experience group "Yes":

Odds ratio (OR) = 0.98 (95% confidence interval [CI$_{95}$], 0.41 – 2.42)

Chi-square ($\chi2$) = 0.03

p = .862

Table 24 shows that a history of ≥ 21 years of laboratory work experience is not a statistically significant predictor of a self-reported history of treatment nonadherence as measured by a positive BMQ score. In addition, the OR of 0.98 indicates that survey respondents who reported a history of ≥ 21 years of laboratory work experience were no more likely to report a positive BMQ score than those who reported a negative BMQ score.

To summarize, Tables 22, 23, and 24 demonstrate that no variables are statistically significant as predictor variables in the 2x2 tables involving the three independent variables addressed in Research Question 3. The same three variables were included in assessment of stepwise model logistic regression (based on a priori decision) for each covariate / independent variable (removing one at a time), for barriers to

treatment adherence (medication side effects) as measured by BMQ scores. Positive

BMQ scores were coded as "1" in the regression analysis (Epi Info™) software; Table 25

depicts the initial regression model which includes the independent variables represented

in Research Question 3, as well as those variables found in the previous bivariate analysis

(Table 11) where *P* value was found to be < .15.

Table 25

*Initial Logistic Regression Analysis for Self-Reported Treatment Adherence Barriers as
Measured by Positive BMQ Score (n = 129)*

Characteristic	Odds Ratio	95%	C.I.	*Z*-Statistic	*P*-Value
BCG Immunization	0.39	0.07	2.30	-1.03	.301
Foreign Birth	2.59	0.51	13.15	1.14	.252
History of TB	0.14	0.01	1.24	-1.77	.077
Gender: Male	0.43	0.15	1.19	-1.63	.103
≥ 21 Years of Lab Experience	1.16	0.46	2.95	0.31	.757
CONSTANT	*	*	*	-1.19	.234

Note. BMQ = Brief Medication Questionnaire (where a score ≥ 1 indicates barriers to
treatment adherence may be present); Using Epi Info™ Version 3.5.3 (CDC, 2011c), CI
refers to confidence interval; the *Z*-statistic has been calculated from the Wald statistic.
The initial regression model for each outcome was composed of the three main
independent variables (forced into the final model by a priori decision. Foreign birth
refers to those born outside the United States or one of the U.S. territories, unless one
parent at time of birth was a U.S. citizen (CDC, 2012); BCG = receipt of a bacille
Calmette-Guérin immunization.

Table 25 represents the initial logistic regression analysis for self-reported

treatment adherence barriers as measured by a positive BMQ Score. No independent

variables are statistically significant for a positive BMQ score in this initial model. Table

26 represents the final regression model after stepwise (backward) removal of variables

having the highest P values.

Table 26

Final Logistic Regression Analysis for Self-Reported Treatment Adherence Barriers as Measured by a Positive BMQ Score (n = 129)

Characteristic	Odds Ratio	95%	C.I.	Z-Statistic	P-Value
History of TB	0.17	0.01	1.41	-1.64	.101
CONSTANT	*	*	*	-2.91	.004

Note. BMQ = Brief Medication Questionnaire (where a score ≥ 1 indicates barriers to treatment adherence may be present). Using Epi Info™ Version 3.5.3 (CDC, 2011c), CI refers to confidence interval; the *Z*-statistic has been calculated from the Wald statistic.

In Table 26, no variables are retained in the final model. After logistic regression, no *P*-values were found statistically significant or associated with the outcome of a positive BMQ score (representative of barriers to treatment adherence).

Conclusion: The third null hypothesis predicted that there would be no statistical association between self-reported individual independent variables of history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory experience, and the dependent variable of barriers to treatment adherence (medication side effects) as identified using the Brief Medication Questionnaire (BMQ) in those respondents ever having initiated preventive TB treatment. I am unable to reject the null hypothesis for Research Question 3.

Post-Hoc Analyses

Several post-hoc analyses were performed and will be described in detail in this section. First, sample size of entire ASCP cohort changed from *N* = 5,138 to *N* = 4,335 at exact time of survey (postcard announcement) mailing. The ASCP membership number changed from the time of initial proposal sample size calculations. Second, exploratory

analyses included an evaluation of covariables for assessment of statistical interaction

and confounding. Third, exploratory analyses describing several additional findings have

been discussed.

The original estimated sample size requirement changed at the precise time of

initial survey announcement postcard mailing. This discrepancy is in part due to the

change in ASCP cohort membership over the course of the year from 5,138 to 4,335

members. A recalculation of estimated, required sample size involved extrapolation of

the initial estimated sample size calculations for $N = 5,138$ to reflect corresponding

sample size calculations for the actual ASCP membership of $N = 4,335$. This was

necessary because the original sample sizes were calculated using Open Epi software

(available in the public domain); the original estimated population size of $N = 5,138$ was

actually utilized in these software calculations (Appendix B).

Referring to Table 3 (Chapter 3), the required sample sizes corresponding to each

of the three research question (RQ) response requirements were thus extrapolated to

reflect the actual $N = 4,335$ cohort and associated minimum sample sizes.

- RQ1: 638 of 5,138 = 12.42%; for $N = 4,335$, the new minimum sample size

    became 538 individual respondents.

- RQ2: 1,336 of 5,138 = 26.00%; for $N = 4,335$, the new minimum sample size

    became 1,127 individual respondents.

- RQ3: 2,569 of 5,138 = 50.00%; for $N = 4,335$, the new minimum sample size

    became 2,168 individual respondents. Of these, 1.40% must be positive for

    the RQ3 outcome (36 of 2,569 = 1.40% by the former estimate); therefore, out

of 2,168 individuals, the new sample size became $n = 30$ (individual

respondents that had to be positive for the RQ3 outcome of medication side

effects as measured by the BMQ).

In conclusion, the updated (actual) sample size of $n = 1,628$

- Surpassed the minimum sample size for RQ1 requirements (to reach enough

  individuals self-reporting TST positivity);

- Surpassed the minimum sample size for RQ2 requirements (to reach enough

  individuals self-reporting treatment initiation for purposes of achieving

  sample size required for RQ3 treatment adherence barriers); and

- Although minimum sample size of $n = 2,168$ was not achieved for RQ3, the

  total number of respondents reporting medication side effects, $n = 44$, was

  well above the required $n = 30$ individuals reporting the outcome as set forth

  in the original minimum sample size requirement.

Although the original estimated 50% eligible survey response rate was not achieved in

this study, minimum (adequate) sample size was achieved in order to generalize results to

all three research questions, according to original sample size estimates based on

estimates and prevalences of outcomes and case/control prevalences of independent

variables as reported in the literature. Therefore, these results may be generalized to this

ASCP target population.

Exploratory analyses were performed to assess confounding and statistical

interaction of two variables, place of birth (foreign birth) and BCG immunization for

outcome of self-reported TST positivity. This logistic regression analysis was performed

using Epi Info ™ analysis recommended by Dean et al. (2010, pp. 133-136). Foreign

birth was analyzed by itself (and not controlling for any other variables) in order to obtain

a crude OR. *P*-values were deemed statistically significant for these variables, just as for

the TABLES model obtained in the earlier bivariate analyses. Foreign birth was then

analyzed along with the BCG immunization variable, in order to control for BCG

immunization. This resulted in an adjusted OR. An interaction term was then created in

the Epi Info™ dialog box to assess whether the additional variable modified or

confounded the relationship, and run in the logistic regression analysis in order to look at

P-value only. An assessment was made to determine if the *P*-value changed from

statistically nonsignificant ($p > .05$) to statistically significant ($p < .05$). If so, statistical

interaction occurred. To assess confounding, I analyzed the resulting crude and adjusted

ORs using the equation provided by Dean et al. (2010):

% Difference = (│ CRUDE OR – ADJUSTED OR │) ∕ (ADJUSTED OR) x 100

Important confounding typically occurs when OR values differed by > 15% (Dean et al.,

2010; Gregg, 2008).

        For dependent (outcome) variable of TST positivity, Epi Info™ analysis of the

independent variable, place of birth (foreign), was carried out to investigate whether any

interaction occurred between it and each covariable of BCG immunization,

nonoccupational exposure to TB, and history of active TB. The same process was

repeated using independent variable BCG immunization. The summary results obtained

after performing each individual logistic regression analysis are summarized in Table 27.

Table 27

Summary Table: Epi Info™ Unconditional Logistic Regression Analysis, Confounding Assessment; Outcome TST Positivity (Final Analysis, n = 1,628*)

Interaction Term/Covariable	Crude OR†	Adjusted OR†	Difference	Analysis by Interaction term: *p*-value
Interaction Term Foreign Birth:				
BCG Immunization	13.43	7.07	>15%	.654
Nonoccupational Exposure	2.62	2.56	<15%	.512
History of TB	56.08	49.04	<15%	.979
Interaction Term BCG Immunization:				
Foreign Birth	8.33	3.17	>15%	.654
Nonoccupational Exposure	2.62	2.37	<15%	.272
History of TB	56.08	61.56	<15%	.980

Note. TST = tuberculin skin test. Foreign birth refers to those born outside the United States or one of the U.S. territories, unless one parent at time of birth was a U.S. citizen (CDC, 2012); BCG = receipt of a bacille Calmette-Guérin immunization.
*Cleaned data set
†OR = Odds Ratio as calculated by   Epi Info™ Version 3.5.3.

From Table 27, it is reasonable to consider covariable BCG immunization as a

confounder in the presence of foreign birth, considering the literature as a whole, where

foreign-born are more likely to receive BCG immunization. From the summary findings

presented in Table 27

- No statistically significant interaction occurred among these variables, as assessed by the *P* values obtained from analysis of interaction terms using Epi Info™ unconditional logistic regression.

- Foreign birth confounds the BCG immunization—TST positivity association in this population.

- BCG immunization confounds the foreign birth—TST positivity association in this population.

Several other post-hoc observations were made among data obtained during this study. A large number of respondents indicated they never had (or did not know if they had ever had) a TST (*n* = 58). This data set was not analyzed further in this dissertation. This outcome was unexpected, as it was thought that all medical microbiologists (previously or currently working) had experienced a TST.

As mentioned earlier in this chapter, among 276 TST-positive individuals, 19 U.S. citizens were born outside the United States, and reporting a history of BCG immunization. Among these 19, 10 individuals reported no BCG immunization (52.63%), and 9 reported a history of having had a BCG immunization (47.37%). If those 19 individuals born outside the United States (but defined by CDC as U.S.-born) were combined into the foreign birth category, the frequencies of BCG immunization among these groups would change to reflect prevalences more commonly seen in moderate- to high-risk endemic regions. The number of BCG immunized in the United States would be assessed at *n* = 9, while those immunized outside the United States would become *n* = 62. Although thought-provoking, statistical analyses were not run on these new values.

Thus, it is important to remember the definition currently in use by the CDC for the term

foreign born.

Summary of Findings

The entire cohort (N = 4,335) of the microbiologists registered with and

designated by ASCP as primarily working in the area of the laboratory known as

Microbiology/Mycology/Parasitology/Virology and having U.S. mailing addresses was

surveyed using a self-administered mail questionnaire: *Tuberculin Skin Test*

Questionnaire for ASCP Medical Laboratory Microbiologists—2013 (see Appendix A).

This final number of ASCP cohort members differed from the initial estimate of N =

5,138 because of a drop in membership over the year (from time of study proposal to

time of first survey announcement postcard mailing.)

After a pretest and pilot test phases, this study was conducted over a period of

eight weeks, from March 25 through May 20, 2013, resulting in n = 1,628 eligible

responses. (Responses initially numbered n = 1,693, but cleaning and coding of data led

to a final number of eligible responses, n = 1,628.) A summary of overall descriptive

findings may be found in the study algorithm (Appendix H).

The majority of eligible survey respondents in this study were female n = 1,393

(85.6%). The mean age of eligible respondents was reported at 58 years for those self-

reporting a history of TST positivity, 54 years for TST negativity. Most reported to have

worked in several areas of the laboratory, while only five reported to have worked solely

in the mycobacteriology section. Seventy-three percent of respondents reported working

more than 21 years in the laboratory setting. The prevalence of self-reported lifetime

TST positivity status among this cleaned data set was calculated at $n = 276$ (17.0%).

Only 121 (7.4%) individuals of the eligible data set were foreign-born (less than

that expected), and a small number, 168 (10.3%), reported ever having had the newer

IGRA blood test replacement for the TST. Twelve (0.7%) individuals reported having

had a history of active TB during their lifetime, while $n = 106$ (6.5%) reported a history

of nonoccupational contact.

Among those self-reporting a history of TST positivity ($n = 276$), $n = 143$ (52%)

reported to have been prescribed anti-TB medication; 129 (90.2%) reported initiation of

this medication, while $n = 13$ (9.1%) refused treatment. Of the 129 individuals who

began (initiated) treatment, $n = 111$ (86%) completed the entire course. Twenty-seven

(20.9%) reported that these medications bothered them; 44 of the $n = 129$ (34.1%)

reported a positive BMQ total score indicating presence of treatment adherence barriers

(medication side effects). The overall prevalence rate of a positive BMQ score among

those reporting noncompletion of prescribed treatment among the cleaned data set ($n =$

1,628) was 0.89% (less than 1%). In addition to descriptive characteristics, risk factors

were assessed by bivariate and multivariate analysis.

Risk factors for the prevalence of self-reported TST positivity were assessed. In

the bivariate analysis, male gender, age, type of work setting (mycobacteriology,

parasitology), foreign birth, BCG immunization, history of TB, and nonoccupational

exposure to TB were associated with a positive TST. Work in bacteriology, mycology,

serology, virology, molecular, and other areas of the laboratory, as well as ≥ 21 years of

laboratory experience were not significant risk factors. In the multivariate analysis, age, type of work setting (mycobacteriology and other areas of the laboratory), foreign birth, BCG immunization, history of TB, and nonoccupational exposure remained statistically associated with a self-reported lifetime positive TST status. Years of work experience ($\geq$ 21 years) were not found to be significantly associated in any of the analyses.

Risk factors for the prevalence of self-reported preventive treatment noninitiation were assessed. In the bivariate analysis, foreign birth and BCG immunization were associated with preventive treatment noninitiation. Male gender, age, type of work, history of TB, nonoccupational exposure, and ≥ 21 years of work experience were not significant risk factors. In the multivariate analysis, only foreign birth remained statistically associated with self-reported lifetime preventive treatment noninitiation after stepwise backward deletion.

Finally, risk factors for the prevalence of self-reported treatment adherence barriers (a positive BMQ score indicating perceived medication side effects) were assessed. In the bivariate and multivariate analyses, no variables were associated with a positive BMQ score.   In the multivariate analysis, male gender, age in years, type of laboratory work, history of TB, nonoccupational exposure, foreign birth, BCG immunization, and ≥ 21 years of laboratory work experience, were not statistically associated with a self-reported positive BMQ score (treatment adherence barrier of perceived medication side effects).

To summarize, after adjustment, multivariate analysis identified age (odds ratio [OR] per year, 1.05; 95% confidence interval [CI_{95}], 1.03-1.07), work in

mycobacteriology (OR, 1.59; CI_{95}, 1.12-2.24), and work outside of microbiology (OR,

1.45; CI_{95}, 1.06-1.99), foreign birth (OR, 3.35; CI_{95}, 1.97-5.72), BCG immunization (OR,

9.21; CI_{95}, 5.26-16.13), history of TB (OR, 31.21; CI_{95}, 3.75-259.67), and

nonoccupational exposure (OR, 1.80; CI_{95}, 1.08-3.00), as significant risk factors for a

self-reported positive TST. Foreign birth (OR, 4.63; CI_{95}, 1.44-14.90) was associated as

a significant risk factor for a self-reported history of treatment noninitiation. No risk

factors as tested in this study were significantly associated with treatment adherence

barriers as measured by BMQ score.

In post-hoc analyses involving TST positivity, no statistically significant

interaction was found to have occurred for place of birth (foreign) and each covariable of

BCG immunization, history of TB, and nonoccupational exposure to TB. The same

analysis of interaction terms was repeated using independent variable BCG

immunization. However, foreign birth was found to confound the BCG immunization—

TST positivity association in the target population. In addition, BCG immunization

confounded the foreign birth—TST positivity association in this population.

Other post-hoc analyses findings involved unexpected prevalence results. One

finding was that a large number of respondents indicated they never had (or did not know

if they had ever had) a TST ($n = 58$). As previously mentioned, this outcome was

unexpected as it was thought that all medical microbiologists (previously or currently

working) had experienced a TST. Also, among 276 TST-positive individuals, 19 U.S.

citizens were born outside the United States, reporting a history of BCG immunization.

Among these 19, 10 reported no BCG immunization (52.63%) and 9 reported having had

BCG immunization (47.37%). If those 19 individuals born outside the United States (but defined by CDC as US-born) had been considered as foreign-born rather than U.S.-born, frequencies of BCG immunization would change greatly to reflect prevalences more commonly found in moderate- to high-risk TB endemic regions.

Chapter 5, Discussion, Conclusions, and Recommendations, discusses the research results within the context of a discussion comparing this study's results with results obtained in other notable research. Similarities and differences are debated, as well as a discussion of how the results are interpreted with regard to theory. Study limitations, recommendations, for future research, and conclusions are provided.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this cross-sectional quantitative survey was to gather data to describe the American Society of Clinical Pathology (ASCP) medical laboratory microbiologist target study population in terms of self-reported lifetime history of tuberculin skin test positivity prevalence, preventive treatment noninitiation, and barriers to treatment adherence (medication side effects as measured by the BMQ) using a written survey questionnaire. In addition, independent variables of BCG immunization, years of laboratory work experience, and place of birth were assessed as potential risk factors in the occurrence of all three of the above outcomes. An evaluation of how each outcome varied across demographic and work-related factors was also performed. The purpose of this chapter is to interpret the data analysis. Research findings are discussed in terms of similarities and differences, as well as in terms of theoretical constructs. Study limitations, recommendations for future research, and conclusions are provided.

Data collected in this survey questionnaire are categorical and descriptive in nature. The type of survey instrument chosen for this study was a self-administered mail questionnaire: *Tuberculin Skin Test Questionnaire for ASCP Medical Laboratory Microbiologists—2013* (see Appendix A). This study represents lifetime prevalence (also termed *period prevalence*) to describe the proportion of the target population with self-reported outcomes as related to the dependent variables (given conditions) over a specified time period (past and present lifetime of the individual study participant).

Interpretation of Key Findings

This quantitative cross-sectional self-administered mail questionnaire survey took place during Spring 2013; 1,693 individuals responded within the allotted time, a 39.1% overall response rate. The total number of respondent surveys eligible for statistical analysis numbered 1,628 of the 4,335 survey packets originally mailed to the entire ASCP target cohort, an eligible respondent return rate of 37.6%. This response rate is an improvement over the 22.5% realized by Clark (2008) in research involving a different ASCP questionnaire mailing. The improvement in response rate may have been due to two items: (a) an announcement postcard that was mailed 1 week prior to the survey packet and (b) an incentive in the form of an ASCP scholarship donation that was offered on behalf of all survey respondents. (A bad address return rate of 0.3% was realized, in line with the less than 1% previously predicted by INFOCUS Marketing.) As discussed in Chapter 4, the respondent rate was high enough for all three required sample sizes to be achieved, allowing results to be generalizable to this ASCP target population of medical microbiologists.

This study represents lifetime prevalence (also termed *period prevalence*). A snapshot of the ASCP target population looks like this: The majority of eligible survey respondents were female, aged mid-50s, working more than 21 years in the laboratory setting, and most were born in the United States. The ages of all survey respondents ($n =$ 1,693) ranged from 24 to 82 years, with a mean age of 55 years, higher than the ASCP reported average mean of 50 years for medical laboratorians (ASCP, 2008). This target population was noted to be older in age, with a majority of U.S.-born members—more

than previously expected. Many survey respondents reported to have worked in several

areas of the laboratory, while only a few individuals reported to have worked solely in the

mycobacteriology section.

Seventeen percent of the eligible study respondents ($n = 1,628$) surveyed in this

study self-reported lifetime history of a positive TST. There are few published studies

describing TST positivity or preventive treatment initiation among medical laboratory

microbiologists in the United States. Although preventive treatment initiation rates were

high among those prescribed anti-TB medications, almost half of those self-reporting a

positive TST claimed not to have ever been prescribed medications in their past. A high

percentage (86%) of those prescribed treatment completed the entire course. Those who

did not complete treatment were most likely to claim medication side effects as the cause.

(The use of Part A of the BMQ in this cross-sectional survey was found to be useful in

ascertaining specifics regarding medication side effects in this target population.)

The three null hypotheses for this study predicted that self-reported lifetime

history of BCG immunization, place of birth (U.S. or foreign), and years of laboratory

experience would not contribute to (a) self-reported lifetime tuberculin skin test

positivity, (b) preventive treatment noninitiation, or (c) barriers to treatment adherence

(medication side effects) among those ever initiating preventive treatment for a positive

TST. Risk factors were assessed by bivariate and multivariate analysis.

Research Question 1: TST Positivity

The self-reported prevalence rate of TST positivity was 17.0% among this eligible

ASCP study population ($n = 1,628$), higher than the 11.3% reported among HCP by

Bailey et al. (1995), yet much lower than the 57% among microbiologists in the Garber et al. (2003) research. Findings of 17% TST positivity prevalence are low, confirming prior percent ranges determined by Joshi et al. (2006). As expected, the 17% positivity rate is much less than the 49.2% to 88.9% positivity prevalence determined by Reid (1957) during a time long past when few or no engineering controls or treatment for TB were in place. Unlike many of the cohort and case/control studies reported in Chapter 2, no incidence rates (TST conversion data) were collected in this study.

The self-reported prevalence rate of active TB history in this eligible population was reported at 0.7% ($n = 12$), lower than the 3.8% estimated in U.S. HCP as reported by CDC (2010b). The odds of reporting a history of TB among TST-positive individuals was calculated at an OR of 31.21 in the final multivariate analysis. Nonoccupational exposure was reported at an OR of 1.80 in the final model. These findings add to the existing knowledge of this U.S. subgroup of laboratorians.

For gender, males were 1.48 times more likely (OR = 1.48) than females to self-report a positive TST history. Male gender was statistically significant in bivariate analysis but was not retained as a predictor in the final multivariate model for TST positivity. This finding is consistent with the Garber et al. (2003) research where male gender was not retained in the final multivariate model as a predictor of a positive TST. In the current study, only four cases of TB disease were reported among males ($n = 1,628$), but this equates to 246 per 100,000 individuals; this is extremely high when compared with the average male rate of 11.8 per 100,000 for cases of active TB in the United States. (McKenna et al., 1996).

The mean age of those eligible respondents (n = 1,620) self-reporting a lifetime history of TST-positive status was 58 years, and 54 years for those reporting TST-negative status. Increasing age was a statistically significant continuous variable in the bivariate and multivariate analysis, $p < .001$, suggesting a connection whereby prevalence of LTBI increases with age. This finding is in agreement with the epidemiology of LTBI as reported by Heymann (2008). Age appears to be connected with "years of experience" in the microbiology laboratory, as a majority (73%) of all eligible respondents reported working $\geq$ 21 years, with an OR of 1.24, although the years of experience variable was not retained as statistically significant in any of the prediction models. This was an unexpected finding: $\geq$ 21 years of work experience was not a risk factor for a positive TST.

Type of laboratory work areas mycobacteriology, parasitology, and other (work outside microbiology) were found to be statistically significant when bivariate analysis was performed. After stepwise (backward logistic regression) multivariate analysis, the only work areas to remain statistically significant in the model used to predict TST positivity were mycobacteriology and other (work outside microbiology). The finding of mycobacteriology type of work confirms research by Garber et al. (2003), as well as reinforces the need for microbiology laboratories to follow the CDC guidelines for biosafety in mycobacteriology laboratories (CDC, 2009) and prevention of TB among healthcare workers (CDC, 2005b).

Among those self-reporting a history of TST positivity, a large number (74.6%) were foreign-born and had received BCG. Place of birth (foreign) was found

significantly associated for TST positivity, significantly associated at p < .001 in both bivariate and multivariate analyses. The bivariate OR in this study was reported at 8.32 in bivariate analysis of those self-reporting TST positivity, and adjusted OR of 3.35 obtained in multivariate analysis (final model). The number of medical microbiologists in this category reached $n = 69$ (25%) of those reporting TST positivity. Although the raw prevalence percentage of 25% is less than that reported in the Cook et al. (2003) study, it is higher than that reported in the Clearfield and Batalova (2007) study. The multivariate analysis adjusted OR of 3.35 realized in this study of ASCP medical microbiologists confirms the adjusted OR of 3.80 reported among New York City laboratorians in the Garber et al. (2003) research.

With respect to BCG immunization, self-reported history of immunization as related to self-reported TST positivity yielded an OR of 13.39 in bivariate analysis, and a $p < .001$; the adjusted OR after multivariate analysis was reported at 9.21, $p < .001$. This bivariate finding is at least 2.75 times (and multivariate finding more than double) the prior multivariate analysis reports (OR = 4.89) in HCP (Garber et al., 2003) and does not confirm the lack of association to TST positivity previously reported by Koppaka et al. (2003).

With respect to Research Question 1 posed in Chapter 1, I am able to reject portions of the first null hypothesis, which predicted that there would be no statistical association between self-reported individual independent variables of history of BCG immunization (yes) and place of birth (foreign), and unable to reject years of laboratory experience (≥ 21 years), as they act on the dependent variable of self-reported lifetime

TST positivity. Thus, the null hypothesis remains valid for the independent variable of years of laboratory experience, while the alternate hypothesis is valid for the independent variables of BCG immunization and foreign birth with respect to a self-report of lifetime TST positivity.

After adjustment, multivariate analysis identified age, work in mycobacteriology, and other work (outside microbiology), foreign birth, BCG immunization, history of TB, and nonoccupational exposure as significant risk factors for a self-reported positive TST.

Research Question 2: Preventive Treatment Noninitiation

For the dependent variable of preventive treatment noninitiation, initiation rates were first collected and analyzed prior to recoding to those of noninitiation. In this research study, the noninitiation rate was only 9.8%, meaning that the treatment initiation rate was very high, 90.2% (among the $n = 143$ who were prescribed anti-TB treatment). This confirms the Camins et al. (1996) initiation rate of 84% among HCP but is at least 1.5 times that of the initiation rate reported by Gershon et al. (2004) and 4.5 times the initiation rate noted in the Garber et al. (2003) study. Of note, the Garber et al. (2003) study findings did not state whether their reported 20% treatment initiation rate was an overall rate (including all those who were prescribed treatment in the denominator). The Garber et al. study did state that the 20% treatment with Isoniazid was calculated by dividing those treated by the total number of TST positive individuals, and that "eligibility for treatment ... was not assessed" (Garber et al., 2003, p. 806). If I had attempted to recalculate the current study's initiation rate based on the Garber et al. method, then treatment initiation prevalence of the ASCP microbiologists would become

46.7%. This new value is more than twice the Garber et al. rate. These considerations point to the importance of fully understanding prevalence definitions as set forth in the literature.

Treatment completion rates in the current study were based on the assumption that respondents were first prescribed treatment and then initiated treatment. One hundred eleven completed an entire course of prescribed treatment (86.0%). These findings are higher than the 27% to 82% ranges of completion rates among HCP as reported by Hirsh-Moverman et al. (2008), higher than the 55% reported by Camins et al. (1996), and almost one and a half times higher than the general public's completion rates, reported to be approximately 60% (CDC, 2000).

For predictors, place of birth: foreign birth (with a bivariate OR of 4.55 and a multivariate adjusted OR of 4.63) was found to be significantly associated with treatment noninitiation and was retained as the lone variable in the multivariate analysis (final model). BCG immunization and years of experience (≥ 21 years) were not retained in the final model as predictors. These findings are new information in filling the gap of knowledge on HCP known as U.S. medical laboratory microbiologists. To date, no other study has provided predictor information on this type of subpopulation of HCP.

With respect to Research Question 2 posed in Chapter 1, I am able to reject the portion of the second null hypothesis as it refers to the independent variable of place of birth (foreign) with respect to a self-report of lifetime preventive treatment noninitiation. I am unable to reject the second null hypothesis regarding the independent variables of history of BCG immunization and years of laboratory experience with respect to a self-

report of lifetime preventive treatment noninitiation. Thus, the null hypothesis remains valid for the independent variables of BCG immunization and years of laboratory experience. The alternate hypothesis is valid for the independent variable of place of birth (foreign) with respect to a self-report of lifetime preventive treatment noninitiation.

After adjustment, multivariate analysis identified only foreign birth as a significant risk factor for a self-reported preventive treatment noninitiation.

Research Question 3: Barriers to Treatment Adherence (Medication Side Effects)

Real or perceived medication side effects were measured by a positive BMQ score (barriers to treatment adherence), numbering 44 individuals out of 129 individuals who initiated preventive treatment. This equates to a 34.1% positive BMQ score rate, indicating perceived treatment adherence barriers (barriers of medication side effects). The actual number of respondents who named anti-TB medications and described specific medication side effects numbered 27 (20.9%). Twenty-two of the 27 named INH as the medication and side effects, consistent with prior reports (nausea, liver toxicity, increased liver enzymes, exhaustion, appetite adversely affected). Hepatotoxicity was reported in 11 of the 22 reporting specific side effects, a rate of 8.5%, or 85 per 1,000 individuals, much higher than the 5.6 per 1,000 rate reported by Fountain et al. (2005).

Of note, 15 of the 18 medical laboratory microbiologists in this study who did not complete treatment reported perceived medication side effects (as measured by a positive BMQ score), a rate of 11.6% of those initiating treatment. This finding is only slightly higher than the 11.4% of HCP who did not complete treatment, stopping because of real or perceived medication side effects, reported by Camins et al. (1996). Overall, in this

entire respondent data set ($n = 1,628$), the prevalence rate of a positive BMQ score is

0.89%, a very low prevalence rate.   The obtained noncompletion rate (among those

initiating treatment) of 11.6% due to side effects in this study population is one-third of

that reported by Camins et al. (1996) and almost one-fifth that reported by Joseph et al.

(2004). Current findings confirm these and the Shukla et al. (2002) studies in that

treatment symptoms of anti-TB medications are severe enough to cause treatment

nonadherence and noncompletion of regimen. No risk factors were determined by

bivariate or multivariate analysis of variables tested in this study.

With respect to Research Question 3 posed in Chapter 1, the third null hypothesis

predicted that there would be no statistical association between self-reported individual

independent variables of history of BCG immunization, place of birth (U.S. or foreign),

and years of laboratory experience and the dependent variable of barriers to treatment

adherence (medication side effects) as identified using the Brief Medication

Questionnaire (BMQ) in those respondents ever having initiated preventive TB treatment.

I am unable to reject the null hypothesis for Research Question 3.

After adjustment, multivariate analysis did not identify any of the tested

independent variables as significant risk factors for self-reported barriers to treatment

nonadherence (medication side effects).

Findings in the Context of Theory

In the context of the epidemiologic triad model as described in Chapter 1, it is

reasonable to surmise that medical laboratory microbiologists in the United States may be

at greater risk of reporting TST positivity and at risk of treatment noninitiation, and

reasonable to surmise that this subpopulation could also be at risk for experiencing these barriers. In all three scenarios, the risk of acquiring TB infection (disease outcome reflected as TST positivity) was conjectured to be associated with (a) the exposure to tubercle bacilli (agent); (b) a lack of preventive treatment (host); and (c) place of birth, years of exposure, and barriers to treatment (environment).

The findings of this study suggest an association to the tubercle bacilli (agent) through type of microbiology area of work "mycobacteriology" and "other" laboratory areas. No assertions can be made from type of work area listed as "other", because this is a general response, intended to assist those microbiologists who could not relate to the type of work areas as listed. Work in mycobacteriology areas, however, is in line with previous research as having been associated with a possible occupational exposure hazard (CDC, 2000, 2005b). History of TB and nonoccupational exposure to TB are also suggested as associated with the agent's presence in the target population. In general, these findings make it difficult to separate the actual source of agent in individuals: whether the agent's presence is due to occupational or nonoccupational exposure. In addition, older age in years has been associated with increased exposure to TB agent because of occupational (lack of engineering controls) exposure, or nonoccupational exposure during a time when TB was quite prevalent in the United States (CDC, 2009, 2010b; Heymann, 2008; Reid, 1957).

Risk factors for preventive treatment noninitiation (in the host) were neither confirmed nor unconfirmed in this study. Of the 276 individuals self-reporting a positive TST history, only 143 (52%) were prescribed anti-TB medications. (Why the others

were not prescribed was beyond the scope of this study, but does leave almost half of the TST-positive population in this study untreated.) Of the 143 individuals prescribed treatment, $n = 129$ (90.2%) did indeed report initiating treatment, and $n = 111$ (86%) completed the entire course of treatment. Only $n = 14$ (9.8%) noninitiated preventive treatment; 13 of the 14 individuals refused treatment. Only foreign birth was associated as a risk factor in treatment noninitiation in this study, perhaps because the foreign born assume a positive TST is due to BCG immunization and not due to the LTBI (agent infection).

For the environmental leg of the triad, place of birth "foreign" remained a significant predictor for presence of the TB agent. However, in this study, a lower number than expected, 121 (7.4%) of the total eligible respondents, were foreign born. Receipt of BCG immunization was strongly tied to foreign birth (as expected); 74.6% of those self-reporting TST positivity were foreign-born who received BCG. Years of experience (≥ 21 years) was not found to act as a predictor, and no risk factors were found to be associated with barriers to treatment (medication side effects).

This study's findings are relevant to the epidemiologic triad model as it pertains to the overarching problem of identifying and halting the spread of tuberculosis among U.S. HCP, specifically, medical laboratory microbiologists. A summary of survey responses indicate that several individuals reporting a positive TST and having received BCG immunization at some point in their lifetime did not report any treatment. A closer look to uncover why this is so is needed in order to address the host (and BCG immunization of the host itself). CDC (2010a) recommends that persons who have had

BCG vaccination be given the TST test (and/or the more sensitive IGRA blood test) and recommended prophylaxis. Once a positive BCG immunization status has been reported, confusion in TST interpretation and subsequent prescribing of treatment persists among many that the positive TST is due to the BCG immunization (CDC, 2010a). This misconception (and disconnect in these study results) may be the leg of the epidemiologic triad that requires intervention in order to prevent further spread of TB. The older TST-positive target population in this study should seek out additional testing to confirm or rule out any current infection with LTBI.

Limitations of the Study

Limitations which may have influenced the outcomes in this study were previously detailed in Chapter 1 as potential weaknesses. Foremost among these is the use of a survey method incorporating a self-reported questionnaire tool, which may result in recall bias as well as concerns over coverage, sampling, nonresponse, and measurement types of errors (Dillman, Smyth, & Christian, 2009). This survey was designed for the study population of U.S. ASCP professional health care personnel, and not necessarily generalizable to other groups.

Recall bias in the self-reporting of history of BCG immunization might have been problematic. BCG immunization responses of "don't know" $(n = 151$ individuals) were troublesome. Passalent et al. (2007) recommended recoding these responses to "no" (never had a BCG immunization) in order to lessen the chance of a Type I error. However, this might create an opportunity for a Type II error. Conversely, recall bias in the self-reporting of treatment adherence was most likely minimal because all

respondents reporting a positive TST ($n = 276$) drilled down through all the remaining

questions without missing any responses. The BMQ questions were completed in detail.

This completeness in the latter portion of the survey provided validation in reports of

prescribed treatment adherence and treatment completion.

Sampling error was addressed by mailing surveys to the entire cohort; although,

only a 39.1% overall response rate was realized (leaving a 60.9% nonresponse rate). Of

note, the ASCP mailing lists included only active members, not all ASCP registrants.

Selection bias may have been introduced when I found that the ASCP target

group did not include everyone in the entire registry, but rather the members who opted-

in to outside receive mailings. Results indicated older age among the target population,

as well as a number of foreign-born that was much less than expected, possibly due to

this bias. Selection bias could be addressed in future research by surveying a state

population of medical laboratorians who are required by law to have a license. (The use

of listings including all registrants, rather than a select membership, is preferable.)

Even though minimal required sample size was achieved, the majority of this

cohort was not represented in findings. Study results were based only on those

questionnaires returned within the allotted time frame. At least 45 late responses

postmarked more than one month past due date were not included, eliminating a portion

of the survey sample results.

Inaccuracy of responses was minimized through the use of pretest and pilot test

phases. However, both phases were limited in number of respondents. The pilot test

response rate was low overall, perhaps because so few individuals ($n = 30$) were invited

to participate. To improve this response rate in future research, I suggest gaining approval to perform pilot testing at a formal conference for medical microbiologists, where large numbers of the target population might gather and the pilot might be easily explained to volunteer participants. In addition, the pilot test group was composed of ASCP generalists, a group used in order to prevent test-retest bias. This group was similar, but not the same as the cohort of medical microbiologists surveyed.

Misclassification bias may have occurred. Some respondents may not be currently engaged in the workforce; they may be retired. Because of the structure of the questionnaire, there was no way to determine how many years or hours worked in each type of microbiology work area. This may have caused misclassification bias with subsequent measurement error. For example, it was thought that increased age might and should be related to years of laboratory experience. However, this was not the case. Years of laboratory experience was not found to be a risk factor associated with any of the outcomes under study. Although I worked from standardized demographic question syntax when presenting these questions in the questionnaire survey, I did not determine the extent to which years and type of experience related to actual contact with specimens harboring the TB agent. Older aged individuals reported a greater history of active TB (Table 7), but perhaps not as great an exposure to TB in the workplace occurred as was previously thought.

Limitations of the use of tuberculin skin test (TST) as a tool include possible reporting of false results due to BCG immunization interference, and misreading of skin reactions leading to false positive and false negative results. These potential problems

were outside the scope of this study. However, one item of interest was the high number of individuals reporting that they had never had a TST. Was this because they had a chest X-ray instead? Or, did these individuals refuse to have a TST performed? These questions, although not mentioned in other literature outcomes, were missing from this study survey, and may have added more information in the context of those not reporting having had a TST.

And finally, this survey was intended to collect general lifetime prevalence information. Results are not to be assessed without remembering that a history of a positive TST in an individual may not be linked to a specific treatment response. (The same individual may have had many negative TST results in the past, or even several positive outcomes.) This may help explain why individuals reporting having had a positive TST, BCG immunization, and a positive IGRA blood test were never prescribed treatment.

Recommendations for Future Research

Recommendations do not exceed study boundaries. Future research should seek to implement studies of other medical and nonmedical laboratorian groups (such as the ASCP generalist population) in order to seek out and target groups at high risk of developing a positive TST and subsequent LTBI. It is not yet known whether these other groups contain large numbers of foreign born, especially those individuals arriving to the United States from regions of endemic TB. In addition, future research should seek to incorporate new IGRA blood test findings in comparison with TST results. This study noted a small number of individuals reporting that they had indeed been offered the

IGRA test (with several reporting a positive result). The current study analyses will make for solid baseline data, useful in future TST and IGRA research.

The inclusion of all ASCP membership would further determine the need for appropriate TB interventions elsewhere in the laboratory. In addition, expanding this research would allow for comparison of prevalence data among a diverse group of medical laboratorians, including an assessment of the foreign-born, as well as the younger population of laboratorians.

For the survey tool itself, several enhancements are recommended in future use of this questionnaire. First, for "years of laboratory experience", a cut-point between years of work experience categories was chosen between 20 years and under, and > 21 years. This choice was based on the majority of respondents marking the highest category. I would suggest adding several more levels of experience above the > 21 year subgroup, due to the mean age of the current target population. I would also suggest clarifying the due date of the survey and placing it in a more conspicuous area of the questionnaire. (This action may increase response rate and decrease the amount of late responses.)

In addition, additional research questions may be added to further investigate the TST-positive group reporting no treatment, and the "never had a TST" group. These two groups will provide the information necessary to allow for understanding and development of an appropriate intervention. Theoretical implications as pertaining to the epidemiologic triad relate to the agent (individual has not been tested for the TB bacteria), and host (in the questionnaire, respondents were not instructed to answer questions regarding BCG immunization if no TST status was known). Environmental

reasons may exist as to why these respondents reported never having had a TST or no treatment for a positive TST. These implications should be investigated further. After all, one goal of public health is to identify and treat LTBI in order to prevent it from becoming active TB.

Implications

These results make an important contribution to the existing literature, enhancing social change initiatives through identifying prevalence of self-reported lifetime tuberculin skin test positivity, risk factors, and preventive treatment noninitiation and barriers to treatment adherence (medication side effects) in the U.S. medical laboratory microbiologist subpopulation of healthcare personnel. Strategies to promote improved understanding and TB prevention treatment of this high-risk subpopulation can be achieved by using knowledge obtained from this research. Positive social change at this individual and target group level may result in the improvement of human and social conditions by contributing to decreases in TB disease mortality and morbidity, and proper stewardship of ever-decreasing resources. Targeted strategies intended to reduce prevalence of positive TSTs among healthcare personnel and improve treatment initiation rates, as well as reduce barriers to treatment adherence, are important in preventing TB reactivation to active TB disease (CDC 2005a, 2005b; Charles P. Felton National Tuberculosis Center, 2005; Fitzpatrick et al., 2005).

Within the ASCP professional registry membership, educational strategies designed to target specific personnel when first certifying with ASCP or upon membership renewal may assist in promoting treatment initiation. If particular risk

factors (such as foreign birth) are associated with barriers to treatment in this same group, educational interventions may be designed which will alleviate these barriers. Additional research among other certification groups of ASCP could follow, adding to the initiative among laboratorians to halt the spread of TB.

This study differs from previous HCP studies by addressing the U.S. medical laboratory scientist population identified by ASCP as working in the area of responsibility known as "Microbiology/Mycology/Parasitology/Virology." The collection of this data and subsequent analysis supports an epidemiologic model for describing this ASCP subpopulation. The sharing of research findings with the ASCP and its membership, other healthcare professionals, and the public health community at the close of this study will assist in bringing the issue of TST positivity from an historic lifetime prevalence perspective and aspects of preventive treatment noninitiation and adherence barriers to light. In addition, findings will be shared with the owners of the BMQ survey instrument (Svarstad et al., 1999).

Although newer interferon-gamma blood tests promise more accurate identification of LTBI status, at present, the TST remains a recommended, inexpensive method for detecting LTBI among healthcare personnel (CDC, 2005a). Gauging TST positivity among a national HCP group such as this ASCP subpopulation aids public health in further understanding LTBI among U.S. medical laboratorians. New and shortened LTBI preventive treatment guidelines have been published (Jereb et al., 2011), promoting a need to determine baseline data. This data will benefit further research that may address the newly described treatment regimen.

Implications for social change do not exceed this study's boundaries. Findings of this study suggest that while a low number of the target population (17.0%) is at risk for self-reported TST positivity, those prescribed treatment actually initiated the treatment (90.2%), and the majority initiating (86%) completed the entire course of treatment. However, a large percentage (48%) were never prescribed treatment (and if they were, refused treatment). A recommendation of this study is that these individuals be targeted for the newer, more sensitive IGRA blood test to identify LTBI, and that appropriately prescribed treatment be implemented (CDC, 2010a).

Although this study fulfills the first step of many in filling the knowledge gap regarding this target population of HCP, medical laboratory microbiologists, several recommendations for action may be made. Study findings reflect the target population's overall prevalence data, and several predictors (risk factors) of TST positivity were found to be statistically significant. Results for treatment noninitiation and adherence barriers were not as noteworthy. The results of this study remain important in the knowledge base as a whole, especially because this is one of the first studies to delve deeply into the treatment history of a large cohort of medical laboratorians. Action should be taken to present study findings to local and state public health officials, as well as to occupational groups such as the Association for Professionals in Infection Control (APIC) and the American Society for Clinical Pathology (ASCP) through peer-reviewed journal articles and meeting abstracts.

This study will further assist in helping understand LTBI (prevalence as measured with TST history) among this cohort of medical laboratory microbiologists, a

subpopulation of healthcare personnel in the United States. The CDC (2002) has reported that to maintain the current decline in TB incidence in the United States, timely treatment management of TB by "prevention of transmission through infection control" (CDC, 2002, p. 6) is of great importance.

Conclusion

To conclude, the "take home" message that captures the key essence of the study is that the target population has now been described, filling the gap previously not found in the literature. This ASCP target population of U.S. medical laboratory microbiologists is at greatest risk for developing LTBI (and active TB) in those reporting positive TST histories, older in age, working (or having had previously worked) in mycobacteriology or areas outside the microbiology laboratory, and of foreign birth. In addition, BCG immunization (although a confounder associated with foreign birth) is a predictor, although years of work experience does not appear to be a significant predictor of TST positivity. As expected, history of TB and nonoccupational exposure were found to act as predictors of a positive TST. Foreign birth is now known as a predictor of treatment noninitiation, but no predictors were identified in relation to barriers to treatment adherence through adjusted multivariate analyses (possibly due to the low prevalence rate of those noninitiating prescribed treatment.)

This study represents pioneering research of the ASCP subpopulation of U.S. medical laboratory microbiologists, surveyed as an entire cohort. This research describes this target population as well as investigates potential risk factors associated with TST positivity, preventive treatment nonadherence, and barriers to treatment adherence

(medication side effects). These baseline results are generalizable to this target

population, and will be helpful to those seeking to study this group in future research.

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Appendix A: Cover Letter and Survey Instrument

**TUBERCULIN SKIN TEST QUESTIONNAIRE FOR
MEDICAL LABORATORY MICROBIOLOGISTS – 2013**

CONSENT FORM

You are invited to take part in a research study about lifetime history of tuberculin skin test results, treatment, and associated risk factors. You were selected for participation in this study because of your professional affiliation with American Society for Clinical Pathology (ASCP) as a U.S.-based microbiologist. This study aims to provide a description of the self-reported lifetime history of tuberculin skin test positivity and other associated epidemiologic risk factors for microbiologists with work responsibilities in the areas of Microbiology / Mycology / Parasitology / Virology, and a U.S. mailing address on file with ASCP. **You must be 18 years or older to participate in this study.**

This form is part of a process called "informed consent" to allow you to understand this study before deciding whether to participate in the study. This study is being conducted by a researcher named Julie Ann West, who is a doctoral student at Walden University. You may already know the researcher as a medical laboratory scientist, but this study is not affiliated with that role.

Background Information:
The purpose of this study is to describe medical laboratory scientists in terms of self-reported lifetime history of tuberculin skin test positivity and associated epidemiologic risk factors.

Procedures:
If you agree to be in this study, you will be asked to:
 • Complete a questionnaire. The questionnaire should take about 10 minutes of your time. (This is the only point in time you will be contacted for information.)
 • Answer all applicable questions to the best of your recollection.
 • Complete the front and back of the questionnaire form.
 • Do **not** place your name or any identifying information on the questionnaire.
 • Return the completed questionnaire in the self-addressed, postage prepaid envelope **within 4 weeks of receipt**.

Voluntary Nature of the Study:
Participation in this study is voluntary. Your decision to participate will in no way affect your relationship with ASCP or the researcher.

Your responses are important and will remain confidential. Your data will only be shared in aggregate, and no individual information will be connected with the data in any reports or materials.

Risks and Benefits of Being in the Study:

Being in this study would not pose risk to your safety or wellbeing. Your answers will be combined with others to learn about tuberculin skin test results, treatment, and associated risk factors in the medical laboratory microbiologist population. Aggregate results will be shared with the public health community.

Payment:

On behalf of survey respondents, a donation of $250 will be made to the ASCP Scholarship Fund for every 1000 completed surveys received by survey deadline.

Privacy:

Any information you provide will be kept anonymous. The researcher will not use your personal information for any purposes outside of this research project. Also, the researcher will not include your name or anything else that could identify you in the study reports. Data will be kept secure (under lock and key) for a period of at least 5 years, as required by the university.

Contacts and Questions:

You may ask any questions you have now. Or if you have questions later, you may contact the researcher via phone (678-471-6708) or email (Julie.west@waldenu.edu). If you want to talk privately about your rights as a participant, you can call Dr. Leilani Endicott. She is the Walden University representative who can discuss this with you. Her phone number is 1-800-925-3368, extension 1210. Walden University's approval number for this study is **01-16-13-0046714** and it expires on **January 15, 2014.**

<u>Please keep this consent form for your records</u>. Statement

of Consent: I have read the above information and I feel I understand the study well enough to make an informed decision about my involvement. By returning a completed survey, "I consent." By returning a survey, I understand that I am agreeing to the terms described above.

**TUBERCULIN SKIN TEST QUESTIONNAIRE FOR
ASCP MEDICAL LABORATORY MICROBIOLOGISTS—2013**

RETURN ONLY THIS QUESTIONNAIRE

Instructions: *Please respond to the following questions below by filling in direct answers and check marks (√) in the spaces provided. On completion, this questionnaire should be placed in the researcher's stamped return envelope.* ***Please do not place your name on any of the material.***

Member Demographics:

1. What is your **Gender**? _____ Male _____Female

2. What is your current **AGE**? _____years

Type **of Work**:

3. Laboratory Section(s) where you work or have worked in the past (**check all that apply**):
  _____ Mycobacteriology   _____ Bacteriology   _____Mycology   _____ Molecular
  _____ Virology   _____ Parasitology   _____Serology   _____ Other areas

4. **How many _years total_ have you _worked_ in a laboratory setting?** (Include training, as well as paid and unpaid work in work areas where testing was performed on clinical specimens, controls, or isolates.) **Check ONE response** to indicate an approximate total number of years:
  _____0-2 yrs   _____3-5 yrs   _____ 6-10 yrs   _____ 11-15 yrs   _____16-20 yrs   _____ over 21 yrs

5. Were you born in the USA or a U.S. Territory?   _____ Yes   _____ No

  (5a.) If "NO", was at least one birth parent a U.S.-citizen?   _____ Yes   _____ No

Lifetime History of Tuberculin Skin Test (PPD):

6. In your lifetime, have you ever had a Tuberculin Skin Test (PPD)?
  _____ Yes (Continue with question 6a., and complete reverse side of this questionnaire)
  _____ No (*Continue with questions 7, 8, 9, 10)
  _____ Don't know or Don't remember (*Continue with questions 7, 8, 9, 10)

(6a.) In your lifetime, have you ever been told that your Tuberculin Skin Test (PPD) was positive?
  _____Yes (positive)   _____No (negative)   _____Don't know or Don't remember

7. In place of the PPD skin test: Have you ever received an interferon gamma-releasing assay (IGRA) blood test to detect latent tuberculosis?

_____ Yes _____No _____Don't know or Don't remember

> **If you answered "YES" to question #7:**
> (7a.) Were you ever told that this **blood test** was positive?
> _____ Yes (positive) _____ No (negative)

Lifetime History of bacille *Calmette-Guérin (*BCG) immunization:**

8. Have you **ever** had a BCG immunization (vaccine)?

_____ Yes _____No _____Don't know or don't remember

History of active tuberculosis (T(B):

9. Have you ever been told that you had **active TB**?

_____ Yes _____ No

Contact or exposure:

10. Have you had **nonoccupational contact** with anyone that was diagnosed with active TB?

_____ Yes _____ No

*If you answered "NO" or "Don't know or don't remember" to Question 6(a), STOP HERE. RETURN this questionnaire as instructed.

The following questions refer to history of **positive SKIN TEST (PPD) only:**

> **If you answered "YES" to question #6(a):**
> 11. Were you ever **prescribed** Isoniazid (INH) or other anti-TB medications by a health department, occupational health department, or by another provider (doctor)?
> ____ Yes (Go to question 12) ____ No (End of survey. Stop here.)
>
> 12. Did you **begin taking** these medications (begin your treatment, even if you did not complete it)?
> ____ Yes (Go to questions 13 - 15)
> ____ No ⟶ Did you refuse treatment? ___Yes ___ No (End of survey. Stop here.)
>
> > 13. Did you **complete** these medications as prescribed (entire course of treatment)?
> > _____Yes _____No
> >
> > **Medications: If you ever began taking** Isoniazid (INH) or anti-TB medications for your positive Tuberculin Skin Test (PP(D):
> > 14. How well did the medication work for you?
> > ____well _____okay ____not well ____don't know
> > 15a. Did any of your medications bother you in any way? ____ Yes ____No
> > 15b. If YES, please **name** the anti-TB medication(s):
> > _____
> > In what way(s) did it bother you? _____

Thank you. Your participation is greatly appreciated. Please return your completed survey in the enclosed self-addressed postage-prepaid envelope within 4 weeks of receipt to: (Researcher Postal Address)

Note: Permission to use Part A of the BMQ survey instrument (see Questions 14, 15a, 15b) was given to this researcher via electronic email correspondence on October 25, 2011 by the first author, Dr. B. Svarstad.

Appendix B: Sample Size Calculations

Research Question 1:

Sample Size for Frequency in a Population

Population size(for finite population correction factor or fpc)(N):	5138
Hypothesized % frequency of outcome factor in the population (p):	33%+/-5
Confidence limits as % of 100(absolute +/- %)(d):	5%
Design effect (for cluster surveys-$DEFF$):	1

Sample Size(n) for Various Confidence Levels

ConfidenceLevel(%)	Sample Size
95%	319
80%	142
90%	229
97%	386
99%	527
99.9%	808
99.99%	1063

Equation
Sample size n = [DEFF*Np(1-p)]/ [(d^2/Z$^2_{1-\alpha/2}$*(N-1)+p*(1-p)]

Research Question 2:

Sample Size for Frequency in a Population

Population size(for finite population correction factor or fpc)(N):	1696
Hypothesized % frequency of outcome factor in the population (p):	20%+/-5
Confidence limits as % of 100(absolute +/- %)(d):	5%
Design effect (for cluster surveys-$DEFF$):	1

Sample Size(n) for Various Confidence Levels

ConfidenceLevel(%)	Sample Size
95%	215
80%	100
90%	158
97%	257
99%	340
99.9%	493
99.99%	617

Equation
Sample size n = [DEFF*Np(1-p)]/ [(d^2/Z$^2_{1-\alpha/2}$*(N-1)+p*(1-p)]

Research Question 3:

Sample Size for Frequency in a Population

Population size(for finite population correction factor or fpc)(N):	339
Hypothesized % frequency of outcome factor in the population (p):	33.3%+/-5
Confidence limits as % of 100(absolute +/- %)(d):	5%
Design effect (for cluster surveys-$DEFF$):	1

Sample Size(n) for Various Confidence Levels

ConfidenceLevel(%)	Sample Size
95%	171
80%	103
90%	141
97%	188
99%	216
99.9%	251
99.99%	271

Equation
Sample size n = [DEFF*Np(1-p)]/ [(d^2/Z$^2_{1-\alpha/2}$*(N-1)+p*(1-p)]

Research Question 1:

Sample Size for Unmatched Case-Control Study

For:

Two-sided confidence level(1-alpha)	95
Power(% chance of detecting)	80
Ratio of Controls to Cases	2
Hypothetical proportion of controls with exposure	27
Hypothetical proportion of cases with exposure:	72.56
Least extreme Odds Ratio to be detected:	7.15

	Kelsey	Fleiss	Fleiss with CC
Sample Size – Cases	14	14	17
Sample Size – Controls	28	27	33
Total sample size:	42	41	50

References

Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19
CC = continuity correction
Results are rounded up to the nearest integer.
Print from the browser menu or select, copy, and paste to other programs.

Research Question 2:

Sample Size for Unmatched Case-Control Study

For:

Two-sided confidence level(1-alpha)		95
Power(% chance of detecting)		80
Ratio of Controls to Cases		4
Hypothetical proportion of controls with exposure		35
Hypothetical proportion of cases with exposure:		65.33
Least extreme Odds Ratio to be detected:		3.50

	Kelsey	**Fleiss**	**Fleiss with CC**
Sample Size - Cases	26	26	30
Sample Size - Controls	104	102	118
Total sample size:	130	128	148

References

Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19
CC = continuity correction
Results are rounded up to the nearest integer.
Print from the browser menu or select, copy, and paste to other programs.

Reseach Question 3:

Sample Size for Unmatched Case-Control Study

For:

Two-sided confidence level(1-alpha)	95
Power(% chance of detecting)	80
Ratio of Controls to Cases	2
Hypothetical proportion of controls with	35

exposure

Hypothetical proportion of cases with exposure:		65.33
Least extreme Odds Ratio to be detected:		3.50

	Kelsey	Fleiss	Fleiss with CC
Sample Size – Cases	32	31	36
Sample Size – Controls	64	62	72
Total sample size:	96	93	108

References

Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19
CC = continuity correction
Results are rounded up to the nearest integer.
Print from the browser menu or select, copy, and paste to other programs.

Results from OpenEpi, Version 2, open source calculator--SSCC

http://www.openepi.com/OE2.3/SampleSize/SSCC.htm
Source file last modified on 09/20/2010 22:10:31

Appendix C: Announcement Postcard

Appendix D: Items from the Brief Medication Questionnaire (BMQ)

The following questions from the BMQ were approved for use on October 25, 2011, and approved for use in this dissertation on May 6, 2012 by:

Bonnie L. Svarstad, Ph. D.
Professor Emerita
University of Wisconsin
School of Pharmacy

BMQ ITEMS:

(Q1g) How well does the medicine work for you?
1 = well
2 = okay
3 = not well

(Q2) Do any of the medications bother you in any way? YES _____ NO_____
(Q2a) IF YES, please name the medication and check below how much it bothers you.

                              How much did it bother you?
 Medication Name   A lot Some A little Never In what way did it bother you?
_____   _____ ____ ____ ____ _____

SCORING PROCEDURES for BMQ SCREENS
Screen   Scoring
_____
Belief Screen (Questions 1g and 2-2a)
Did R report "not well" or "don't know" in response to Q 1g?   1 = yes 0 = no
Did R name the prescribed drug as a drug that bothers him/her? 1 = yes 0 = no
NOTE: Score of ≥1 indicates positive screen for belief barriers

(Svarstad, Chewning, Sleath, & Claesson, 1999)

Appendix E: Study Codebook

Tuberculin skin test questionnaire for medical laboratory microbiologists: Summary of questions (Q) and transformed data coded to be used for analysis (CODEBOOK)

Question numbers to be analyzed for informational purposes to aid in describing the population	Categorical levels	Codes
(Q1) Gender	Male/Female	SEX Male = 0 Female = 1
(Q2) Current age in years	Age in years	AGE
(Q3) Type of work (laboratory sections)	(1) Mycobacteriology (2) Virology (3) Bacteriology (4) Parasitology (5) Mycology (6) Serology (7) Molecular (8) Other	TYPE Yes = 1, No = 0 MYCOB VIRO BACTI PARA MYCOL SERO MOL OTH
(Q6) Ever had a TST?	Yes/No/DK	TSTT No = 0 Yes = 1 DK = 2
(Q7) IGRA blood test?	Yes/No/DK	IGRA No = 0 Yes = 1 DK=2
(Q7a) IGRA positive?	Yes/No/DK	IGRAPOS No = 0

Yes = 1
DK=2

(Q11) Ever prescribed Isoniazid or other anti-TB medications?	Yes/No (needed to establish flow of questions)	PRESC No = 0 Yes = 1
(Q12, "no" response): Refused treatment	Yes/No	REF No = 0 Yes = 1
(Q13) Did you complete entire course of treatment?	Yes/No	COMPL No = 0 Yes = 1

Questions analyzed in order to answer research questions #1, #2, #3: DEPENDENT VARIABLES	Categorical Levels	Codes
1a. (Q6a) Dependent variable: Lifetime self-reported history of TST positivity	Yes/No/DN	TSTPOS No = 0 Yes = 1 DN = 2
2. (Q12) Dependent variable: Treatment initiation for a positive TST	Yes/No	INTIATE No = 0 Yes = 1
3. (Q14, Q15) Dependent variable: BMQ questions regarding medication and adherence: total range = score of 0-2 (Svarstad et al., 1999)	**Total score of ≥1** indicates **positive screen for medication barriers** (drug effects and bothersome features, related to treatment nonadherence) (Q14) Not well, don't know Yes = 1 Well, okay No = 0 (Q15) Yes = 1 No = 0 Q14+Q15 = BMQ score; where: Nonadherence = Positive screen	BMQ Adherence = Negative screen for medication barriers Negative =0 Nonadherence = Positive screen for medication barriers Positive = 1 Positive = 2

Adherence = Negative screen

Questions analyzed in order to answer the research questions #1, #2, #3: INDEPENDENT VARIABLES	Categorical Levels	Codes
1. (Q8) Independent variable: BCG immunization	Yes/No/DK	BCG No = 0 Yes = 1 DK = 2
2. (Q5) Independent variable: Place of birth (a response of "yes" to either Q5 or Q5a = U.S.-born)	U.S. or Foreign birth	BIRTH U.S. = yes = 0 Foreign = no = 1
3. (Q4) Independent variable: Years of laboratory experience	(1) 0-2 yrs (2) 3-5 yrs (3) 6-10 yrs (4) 11-15 yrs (5) 16-20 yrs (6) over 21 yrs Depending on responses: The mean will determine a split of categorical responses to be used in logistic regression < the selected cutoff = No > the selected cutoff = YES	YREXP 123456 YREXPCUT No = 0 Yes = 1
Possible Confounders	**Categorical Levels**	**Codes**
(Q9) History of active TB?	Yes/No	HIST No = 0 Yes = 1
(Q10) Nonoccupational exposure to anyone diagnosed with active TB?	Yes/No	EXPOS No = 0 Yes = 1

Appendix F: Letter of Permission for Use of Selected BMQ Questions in Research

Subject : **Re: PhD student has question for you regarding Brief Medication Questionnaire instrument...**

   Date : Tue, Oct 25, 2011 02:03 AM CDT

  From : <u>**Bonnie Svarstad**</u>

     To : <u>Julie West</u>

You have permission.

Bonnie L. Svarstad, Ph. D.
Professor Emerita
University of Wisconsin
School of Pharmacy

On Oct 24, 2011, at 4:07 PM, Julie West wrote:

Hello Dr. Svarstad,
Today, I received a copy of the Redman (2003) book, "Measurement Tools in Patient Education." I now have a published version of the BMQ. However, please see attached / forwarded email dated 10/17/2011. I have not heard from you since I mailed a response to your last email. I want very much to obtain permission to use the BMQ. As noted, I will require survey instrument validation data for the BMQ (if you agree to my response - seen below).
Again, many thanks for your interest in my research. I appreciate any assistance you may be able to provide.
Sincerely,
Julie West

Julie Ann West
Walden University
PhD Public Health student, specialization: Epidemiology

Original E-mail
From: "Julie West"
Date: 10/17/2011 11:49 AM
To: Bonnie Svarstad
Subject: Re: PhD student has question for you regarding Brief Medication Questionnaire instrument...

Hello Dr. Svarstad,

The HaPI database staff claimed not to have a copy of your BMQ survey instrument. I have since ordered the Redman (2003) book, "Measurement Tools in Patient Education", in order to obtain a published version of the BMQ.

As per your instructions (noted in last email):

1. I plan to use the BMQ (part A) in my PhD dissertation project for Walden University. My research involves performing a quantitative, descriptive survey of American Society for Clinical Pathology (ASCP)-registered medical laboratory scientists. A combination demographic questionnaire plus portions of the BMQ will be used in a mail survey format to evaluate self-reported tuberculin skin test status (TST), associated risk factors for positive TST, as well as latent tuberculosis infection (LTBI) treatment initiation and barriers to treatment adherence in status-positive individuals. The results will be analyzed, reported, and published in the Walden University dissertation database.

2. I will acknowledge you and your co-authors, as well as the original 1999 article describing the BMQ. I plan to use acknowledgements in the text, in any tables or figures, and in the reference section of the dissertation.

3. I agree not to charge anyone for the results I obtain using the BMQ, now or in the future.

4. I agree not to publish the BMQ instrument itself in my dissertation, or in any future publication.

I have already consulted my committee chair to determine if I must include the BMQ instrument in the appendix of the dissertation. He approved of your requirements, and has instructed me to agree to your terms. His contact information (should you require it) is as follows:

Hadi Danawi, Ph.D.
Public Health Faculty Mentor
Walden University
College of Health Sciences

I appreciate your assistance in this matter. I look forward to sharing my results with you and your colleagues.

If possible, please attach a copy of the entire BMQ and validation data to a reply email to me.

I thank you so very much,

Sincerely,

Julie West

Julie Ann West
Walden University
PhD Public Health student, specialization: Epidemiology

Original E-mail

From: Bonnie Svarstad
Date: 10/14/2011 09:07 AM
To: Julie West
Subject: Re: PhD student has question for you regarding Brief Medication Questionnaire instrument...

As first author/owner, I handle permissions. The database folks have no role in granting permissions. You simply need to tell me what you plan to do with it. I will grant permission if you agree to acknowledge the authors and original article in which the BMQ was described and evaluated, if you agree to NOT charge anyone for the results, and if you agree not to publish the instrument itself as we retain copyright. If you send a note to me agreeing to the conditions, then I respond that it's ok to use it. BLS

Appendix G: Evaluation of Pilot Test Data

Question #	Skipped; no response when one expected (a)	Errors: more than one response (b)	No Errors (c)	Error Rate (a+b)/(a+b+c)
1.	0	0	13	0
2.	0	0	13	0
3.	0	0	13	0
4.	0	0	13	0
5.	0	0	13	0
5.a.	0	0	13	0
6.	0	0	13	0
6a.	0	0	13	0
7.	0	0	13	0
7.a	0	0	13	0
8	0	0	13	0
9.	0	0	13	0
10.	0	0	13	0
11	0	1	12	7.7%
12	0	1	12	7.7%
13	0	0	13	0
14	0	0	13	0
15.a	0	0	13	0
15.b	0	0	13	0

Appendix H: Algorithm for Questionnaire Study

ASCP Medical Microbiologist Study Population
Questionnaires mailed ($N = 4,335$); Completed/returned ($n = 1,693$)*

Non Respondents ($n = 2,642$)
(Includes $n = 12$ 'address unknown' and $n = 45$ late returns, not processed)

Cleaned data set ($n = 1,628$); Ever been told your tuberculin skin test (TST) was positive?

Yes ($n = 276$)

No ($n = 1,352$)

Was **preventive treatment prescribed?**

Yes ($n = 143$)
Preventive treatment initiated?

No ($n = 132$)

Yes ($n = 129$)

No ($n = 14$, noninitiated); 13 of 14 individuals refused treatment

Treatment completed ($n = 111$)

Barriers to Treatment Adherence as measured by the Brief Medication Questionnaire Part A score: ($n = 44$, positive score)

How well did the medication work for you? Well/Okay ($n = 96$)   Not Well/Don't Know ($n = 33$)

Did any of your medications bother you in any way? Yes ($n = 27$)   No ($n = 102$)

*Note: $n = 58$ self-reported never having had/not knowing if they had a TST

Appendix I: Letter of Cooperation, ASCP

American Society for Clinical Pathology (ASCP) American Society for Clinical Pathology (ASCP)
ASCP Headquarters
        33 West Monroe Street, Suite 1600, Chicago, IL 60603-5617
        312-541-4999 (phone); 312-541-4998 (fax)
January 24, 2013

Dear Julie Ann West (Walden University Student),

Based on my review of your research proposal, we give permission for you to mail the study survey questionnaire entitled "TUBERCULIN SKIN TEST QUESTIONNAIRE FOR MEDICAL LABORATORY MICROBIOLOGISTS—2013" As part of this study, we grant you to access ASCP's mailing list of lab professionals through InFocus Marketing, Inc., and mail the survey questionnaires to those listed as having primary 'area of work responsibility' as designated by ASCP in "Microbiology/Mycology/Parasitology/Virology." Individuals' participation will be voluntary and at their own discretion.

We understand that our organization's responsibilities include: Approval of the announcement postcard, cover letter/consent, and self-administered mail questionnaire prior to reproduction and mailing by our partner, Infocus Marketing, Inc. We reserve the right to withdraw from the study at any time if our circumstances change.

We understand that the data collected will remain entirely confidential and may not be provided to anyone outside of the research team without permission from the Walden University Institutional Review Board.. We understand that the Walden University Institutional Review Board has assigned approval number 01-16-13-0046714 to this study.

Sincerely,
Senior Marketing Analytics Manager
Contact Information: ASCP
        33 West Monroe Street, Suite 1600
        Chicago, IL 60603
        800-267-2727

Appendix J: Letter of Cooperation (Pilot Test), ASCP

Letter of Permission (Pilot Test)

American Society for Clinical Pathology (ASCP)
ASCP Headquarters
33 West Monroe Street, Suite 1600, Chicago, IL 60603-5617
312-541-4999 (phone); 312-541-4998 (fax)

February 18, 2013

Dear Julie Ann West (Walden University Student),

Based on my review of your research proposal, we give permission for you to pilot test the study survey questionnaire entitled "TUBERCULIN SKIN TEST QUESTIONNAIRE FOR MEDICAL LABORATORY MICROBIOLOGISTS—2013." As part of this study, we grant you access to ASCP's mailing list of lab professionals through InFocus Marketing, Inc., and distribution of the survey questionnaires to those listed as having primary 'area of work responsibility' as designated by ASCP in "Generalist"- "MLS/MT" category, U.S., State of Georgia mailing addresses. Individuals' participation will be voluntary and at their own discretion.

We understand that our organization's responsibilities include: Approval of the announcement postcard, cover letter/consent, and self-administered mail questionnaire prior to distribution of the pilot test survey packet. We reserve the right to withdraw from the study at any time if our circumstances change.

We understand that the data collected will remain entirely confidential and may not be provided to anyone outside of the research team without permission from the Walden University Institutional Review Board. We understand that the Walden University Institutional Review Board has assigned approval number 01-16-13-0046714 to this study.

Sincerely,
Senior Marketing Analytics Manager

Contact Information: ASCP
33 West Monroe Street, Suite 1600
Chicago, IL 60603
800-267-2727

Appendix K: Letter of Permission for Use of Select BMQ Questions in Dissertation

Subject :
Re: PhD student has question for you regarding Brief Medication Questionnaire
instrument...
Date : Thu, Jul 04, 2013 08:14 PM CDT
From : Bonnie Svarstad
To :   Julie West

That's fine.

Bonnie L. Svarstad, Ph. D.
Professor Emerita
University of Wisconsin
School of Pharmacy

On Jul 4, 2013, at 4:56 PM, Julie West wrote:

> Hello Dr. Svarstad,
>
> I hope you have been well. Some time has passed since I last requested permission to
use Part A of your Brief Medication Questionnaire as part of my Walden University
public health dissertation project... almost 2 years (discussion thread attached to this
email). Well, I am happy to report that I am writing Chapter 5 of the dissertation. The
research itself was a long process, but I acquired a great deal of data in the process. To
refresh your memory, my research involved use of a quantitative, descriptive survey of
American Society for Clinical Pathology (ASCP)-registered medical laboratory
microbiologists. A combination demographic questionnaire plus Part A of your BMQ
was used in a mail survey format to evaluate self-reported tuberculin skin test status
(TST), associated risk factors for positive TST, as well as latent tuberculosis infection
(LTBI) treatment initiation and barriers to treatment adherence in self-reported TST-
positive individuals. The results will be reported and published in the ProQuest
dissertation database before year's end, if all goes as planned.
>
> I would like your permission to include a copy of my survey instrument in my
dissertation appendix. The questionnaire document is attached. I have included this
phrase at the bottom of page 2 of this appendix document: "Note: Permission to use Part
A of the BMQ survey instrument (see Questions 14, 15a, 15b) was given to this
researcher via electronic email correspondence on October 25, 2011, by the first author,
Dr. Svarstadt."
>

>
> Thank you for your help in this matter. Once the dissertation has been completed, I will share the findings with you. (I have accrued a great deal of interesting data for this target group.)
>
> Thank you,
> Julie West
>
>
> Julie Ann West
> Walden University
> PhD Public Health student, specialization: Epidemiology

Subject :
Re: PhD student has question for you regarding Brief Medication Questionnaire instrument...
Date : Sun, May 06, 2012 04:15 PM CDT
From : Bonnie Svarstad
To :   Julie West

Yes. Best wishes. Bonnie

Bonnie L. Svarstad, Ph. D.
Professor Emerita
University of Wisconsin
School of Pharmacy

On May 6, 2012, at 7:44 AM, Julie West wrote:

> May 6, 2012
> Hello Dr. Svarstad,
>
> In October, you granted permission allowing me to use portions of the Brief Medication Questionnaire (BMQ) in my PhD dissertation. When giving permisson to me, I agreed not to publish the BMQ instrument. I am about to submit my entire proposal to the Walden University IRB, and I would like to make one last request of you:
>
> In the Appendix of my dissertation: May I cite the two specific BMQ items that I plan to use in my research survey questionnaire? The dissertation will be published in the ProQuest dissertation database only.

May I reproduce the following in the APPENDIX section of the dissertation? Something like:
>
> APPENDIX C: SAMPLE ITEMS FROM THE BRIEF MEDICATION QUESTIONNAIRE
>
> The following sample questions from the BMQ were approved to reprint in the dissertation by:
>
> Bonnie L. Svarstad, Ph. D.
> Professor Emerita
> University of Wisconsin
> School of Pharmacy
>
> SAMPLE BMQ ITEMS:
> (Q1g) How well does the medication work for you?
> 1 = well
> 2 = okay
> 3 = not well
>
> (Q2, 2a)
> Do any of the medications bother you in any way?   YES _____ NO_____
>
> a. IF YES, please name the medication and check below how much it bothers you.
> How much did it bother you?
> Medication Name   A lot   Some   A little   Never   In what way did it bother you?
> _____   _____   _____   _____   ____   ____
> SCORING PROCEDURES for BMQ Part A
>
> Screen   Scoring
> _____
> Belief Screen (Questions 1g and 2-2a)
> Did R report "not well" or "don't know" in response to Q 1g?   1 = yes   0 = no
> Did R name the prescribed drug as a drug that bothers him/her?   1 = yes   0 = no
> NOTE: Socre of >=1 indicates positive screen for belief barriers
> (Svarstad, Chewning, Sleath, & Claesson, 1999)

> Many thanks - I appreciate your time in considering this request.

> Julie Ann West
> Walden University
> PhD Public Health student, specialization: Epidemiology

Curriculum Vitae

Julie Ann West
Decatur, Georgia

EDUCATION

Lakeland Community College, Mentor, Ohio   AAS   1981
Medical Laboratory Technology, Certificate in Medical Laboratory Technology

Edison Community College, Ft. Myers, Florida   AA   1986

The University of the State of New York (Excelsior College), Albany, New York
                                                                 BS   1989
(Included combined coursework from The Ohio State University, University of South Florida, and The University of Florida)

Walden University, Baltimore, MD   PhD graduate study   2006-2013

HONORS

High School: Valedictorian, Perry High School
High School: National Honor Society

Undergraduate: Graduated with Honors, Edison Community College

EMPLOYMENT

Microbiologist, Medical Technologist
Atlanta Veterans Administration Medical Center: Decatur, Georgia   2009-present

Microbiologist, Medical Technologist
Quest Diagnostics, Tucker, Georgia   2006-2009

Laboratory Administrative Director (Supervisor and Manager)
DeSoto Memorial Hospital, Arcadia, Florida   2003-2006

Generalist, Medical Technologist
DeSoto Memorial Hospital, Arcadia, Florida   1999-2003

Microbiologist, Medical Technologist

Southwest Florida Regional Medical Center, Ft. Myers, Florida   1983-2000

Generalist, Medical Laboratory Technologist
Southwest Florida Regional Medical Center, Ft. Myers, Florida   1981-1983

PROFESSIONAL AFFILIATIONS AND OFFICES HELD

Certifications:
Medical Laboratory Technician (MLT)   since 1981
American Society for Clinical Pathology (ASCP)

Clinical Laboratory Scientist (CLS)
National Certification Agency (NCA)   1989-2004

Medical Laboratory Scientist (MLS)
American Society for Clinical Pathology (ASCP)   since 2005

Specialist in Microbiology (SM), (ASCP)   since 2006

Licensures:
State of Florida Medical Technologist and Laboratory Supervisor
(Hematology, Serology, Microbiology, Chemistry, Molecular,
Immunohematology)   1981-present

Professional Associations:
Member: American Society for Microbiology (ASM)   since 2005

Associate Member: American Society for Clinical Pathology (ASCP)   recurring

Member: (CDC) TB Education and Training Network   since 2008

Member: Council of State and Territorial Epidemiologists (CSTE)   2013

Member: Association for Professionals in Infection Control and Epidemiology (APIC)
                                                                      2013