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UNIVERSITY OF CALIFORNIA, SAN DIEGO

Latent Tuberculosis Infection in United States Military: Concordance, Conversion, and Adverse Events Associated with Treatment

A dissertation submitted in partial satisfaction of the
requirements for the degree
Doctor of Philosophy

in

Public Health (Epidemiology)

by

Janet June Tang

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2014

The dissertation of Janet June Tang is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California, San Diego

San Diego State University

2014

DEDICATION

To my family, friends, and co-workers who supported me
throughout the process.

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LIST OF ABBREVIATIONS

BCG, bacille Calmette-Guerin

CDC, Centers for Disease and Control and Prevention

CHAMPS, Career History Archival Medical Personnel System

CI, confidence interval

EMB, ethambutol

HMO, health maintenance organization

HR, hazard ratio

HCW, health care worker

ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification

IFN-g, Interferon-gamma

IGRA, interferon-gamma release assay

INH, isoniazid

LTBI, latent tuberculosis infection

MDR, Military Health System Data Repository

MTF, military treatment facilities

NPV, negative predictive value

OR, odds ratio

PDTS, Pharmacy Data Transaction Service

PPV, positive predicted value

PZA, pyrazinamide

RIF, rifampin

SD, standard deviation

TST, tuberculin skin test

TB, tuberculosis

US, United States of America

WHO, World Health Organization

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ACKNOWLEDGEMENTS

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ABSTRACT OF THE DISSERTATION

Latent Tuberculosis Infection in United States Military: Concordance, Conversion, and Adverse Events Associated with Treatment

by

Janet June Tang

Doctor of Philosophy in Public Health (Epidemiology)

University of California, San Diego, 2014

Caroline A. Macera, Chair

Military personnel are at a higher risk of tuberculosis (TB) infection through military deployments, assignments to high incidence countries, and close contact with refugees and prisoners of war. Service members are routinely tested; those with active TB or latent tuberculosis infection (LTBI) are treated. The purpose of this dissertation was to (1) propose a method for LTBI surveillance among United States military personnel using pharmacy and medical records; (2) determine LTBI conversion rates and associated risk factors in Navy health care workers (HCWs) using this method; and (3) evaluate adverse events associated with LTBI treatment in this population. These studies used data from the Military Health System Data Repository, a collection of databases on health care services (inpatient, outpatient,

and prescription information) provided to military personnel.

Using both pharmacy and medical records, among 3,089,436 military personnel, 133,365 service members were identified with LTBI; 38.9% (n = 51,943) had LTBI indicated in both sources within 180 days of each other. Moderate concordance ($\kappa = 0.55$) was observed between both sources for LTBI.

The LTBI incidence among 18,975 Navy HCWs over the study period was 1.7% (95% CI 1.5-1.9), with an incidence density of 4.6 per 1,000 person-years (95% CI 4.12-5.13). Using survival analysis, being non-white and foreign born were LTBI risk factors for HCWs, while overseas duty stations and Iraq or Afghanistan deployments were inversely associated with LTBI diagnosis.

Among 74,537 service members prescribed LTBI treatment, 96% (71,427) were dispensed isoniazid and 4% (3,110) rifampin. Treatment-associated adverse events were reported in 7.0% of service members. During the study period, the number of service members starting treatment decreased over time, but the incidence of adverse events did not change. Isoniazid was a risk factor for any adverse event compared to rifampin using logistic regression. Prescribing vitamin B6 was associated with lower odds of adverse events. For service members older than 25 years, the odds of having any adverse event increased with age.

This proposed method for TB surveillance can be beneficial for military LTBI providers and could be used in the absence of a global LTBI reporting system to monitor incidence and treatment-associated adverse events.

Chapter 1

Background and Significance/Research Objectives

1.1 Tuberculosis

1.1.1 History

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, has been known by a number of different names: *consumption* and *phthisis* in ancient Greece, *yaksma* in ancient India, *scrofula* during the Middle Ages in Europe, and the *white plague* in 19th century Europe and North America.[1–4] TB has been found in ancient early Neolithic, pre-Columbian, and Egyptian remains.[5–7] The oldest molecular evidence of TB infection was found in a 9,000 year old woman and child from a Neolithic settlement in the Eastern Mediterranean.[5] While the history of TB dates back thousands of years, it did not become a public health concern until the Industrial Revolution, where crowded living conditions were conducive to its transmission. TB caused one in four of all adult deaths in Europe in the 17th and 18th century. In 1921, the first TB vaccine, known as the bacille Calmette-Guerin (BCG) vaccine became widely used in Europe.[8] A new era of effective treatment began in 1946 with streptomycin, and in 1952 isoniazid made TB curable in most patients.[9,10] In 1953, the Centers for Disease Control and Prevention (CDC) established a national surveillance for TB. Since 1953, TB case rates had declined

every year, until the 1980s and 1990s when case rates began to increase.[11] This resurgence of TB was due to a combination of factors: the emergence of the human immunodeficiency virus (HIV) epidemic, greater immigration of people from countries where TB is endemic, TB transmission in congregate settings (i.e. jails, prisons, shelters, schools, or workplaces), the development and spread of multidrug-resistant TB strains, and the deterioration of TB control programs. In 1993, the World Health Organization (WHO) declared TB to be a global emergency, and called for all countries to make TB control a priority. In the last 10 years, the rate of new TB cases declined worldwide. While considerable progress has been made, the elimination of TB remains a challenge.

1.1.2 Mechanism of Transmission

TB is spread through airborne particles ($1\,\mu m$ to $5\,\mu m$ in diameter) that are expelled into the air by someone with pulmonary or laryngeal TB disease by coughing, sneezing, shouting, or singing.[12,13] Depending on the ventilation, these particles can remain airborne for long periods of time and can travel throughout a room or building.[14] Infection can occur when a susceptible person inhales these bacteria-containing particles, which then travel to the alveoli of the lungs. *M. tuberculosis* is moderately infectious, with approximately 20% to 30% of people exposed to an active TB case becoming infected.[15] Infectiousness and closeness of contact to the active TB case are the most important determinants of infection. Positive sputum smears, positive cultures, the degree of positivity, and coughing pattern all affect infectiousness.

1.1.3 Latent Tuberculosis Infection

After people are infected with *M. tuberculosis*, their immune response will determine if active TB develops, becomes a latent infection, or if the organism is eradicated. Approximately 5-10% of people infected will develop active TB.[4,16] An unknown proportion of the 90-95% of the infected people that do not develop actie TB will contain the organism into a latent TB infection (LTBI) in which the

microbe remains in a quiescent, yet viable state.[17] After decades of research, there is still limited information on how *M. tuberculosis* establishes a latent infection. While the exact mechanism is unknown, clinical and epidemiological research has indirectly demonstrated the presence of LTBI, and that treatment of it reduces the risk of developing active TB. Among people that develop LTBI, the organism may remain dormant for anywhere from a short period of time to decades. For 5-10% of people with LTBI that do not receive treatment, after some time their immune system may no longer be able to contain the organism, allowing it to grow again; this *reactivation* will result in developing active TB.[17]

1.1.4 Risk of Reactivation to Tuberculosis Disease

The risk of reactivation is affected by a number of risk factors. One condition is time from infection. As the time from infection increases, the risk of reactivation decreases. The greatest risk of reactivation occurs within the first two years after infection, where half of the lifetime risk occurs.[18–20] Studies performed by the United States (US) Public Health Service between 1950 and 1970 found a 0.74% active TB incidence rate among untreated TB-infected household contacts within the first two years after exposure. Three to five years after exposure the incidence rate was halved (0.31%), and halved again at six to seven years (0.16%).[18] Other risk factors for reactivation to TB include age, sex, fibrotic lesions, diabetes mellitus, enal disease, silicosis, concurrent corticosteroid therapy, gastrectomy and jejunoileostomy, neoplastic diseases, post-organ transplantation, body weight, occupation, smoking, and HIV infection and acquired immune deficiency disease syndrome (AIDS).[21,22]

1.1.5 Tuberculosis Worldwide

TB is the second leading cause of death after HIV/AIDS due to a single infectious agent. An estimated 8.6 million people developed active TB in 2012 with 1.3 million dying from the disease. The South East Asia and Africa regions account for 56% of the world's cases. India and China alone account for 38% of

the world's cases. While men account for most TB cases and deaths, TB is one of the top three killers in women. Approximately 13% (1.1 million) of the 8.6 million active TB cases were HIV positive, 75% of which are from Africa.[23] TB is the most common opportunistic infectious complication and the most common cause of death among patients with HIV.[24] It is estimated that one third of the world's population, about 2.3 billion people, are infected with LTBI.

1.1.6   Tuberculosis in the United States

TB is a recognized public health problem in the US. In many high incidence countries, active TB is an immediate public health threat; low incidence countries like the US experience a significant epidemiological burden due to LTBI.[25] Most active TB cases occur among people who were exposed in the past, developed LTBI, then later developed active TB.[26] Because of this, a key component of TB control is the identification and treatment of LTBI cases.[27] The *M. tuberculosis* infection rate in the US population is estimated to be 5-10%.[19] The rates of new cases of active TB have been decreasing over the last decade and almost 10,000 new cases of active TB were reported in 2013, with 65% occurring among foreign born people. Half of all active US TB cases occur in four states: California, Texas, New York, and Florida.[28] Similar to active TB, the prevalence rate of LTBI has dramatically decreased. In 1971-1972, the prevalence of LTBI was estimated at 14.3%, which dramatically decreased to 5.7% in 1999-2000 (estimated to be over 11 million people). Like active TB, LTBI affects foreign-born people disproportionately, with LTBI prevalence at 18.7% compared to 1.8% in people born in the US. Ethnic minorities, specifically frican Americans and Mexican Americans, have higher prevalence and increased odds for LTBI compared to whites.[29]

1.1.7   Testing for Tuberculosis

In the US, there are two tests approved by the FDA used to detect TB infection: the Mantoux tuberculin skin test (TST) and Interferon-Gamma Release Assay (IGRA). The TST is the standard method for determining if a person is

infected with *M. tuberculosis.* It is an intradermal injection of 0.1 milliliter of purified protein derivative tuberculin, containing 5 tuberculin units, into the inner surface of the forearm. The reaction of the skin at the test area is observed 48-72 hours after administration. The local reaction involves a palpable raised, hardened area or swelling, and its diameter is measured in millimeters. The interpretation of the measurement depends on the size, in millimeters, of the induration, the person's risk of being infected with TB, and risk of progression to disease if infected.[30] Conversely, the IGRA is a blood test, which measures a person's immune response to *M. tuberculosis.* Interferon-gamma (IFN-g) are released when infected white blood cells are mixed with *M. tuberculosis* antigens.[31] The test interpretation is determined by the IFN-g concentration. Neither test differentiates between active TB and LTBI. After a TST or IGRA conversion (negative to positive on either test), active TB or LTBI is diagnosed by a medical history review, physical exam, chest radiographs, or other clinical laboratory tests. It is standard practice that once a person converts from negative to positive TST result, that person should not be tested for TB again in the future using a TST or IGRA; instead future evaluations should include annual clinical evaluations and/or chest radiographs.

1.1.8   Targeted Testing

A strategic component of TB control in the US is identifying people with LTBI. Current US recommendations advise that people with higher risk for TB infection, which includes those with a recent TB infection and those with clinical conditions associated with reactivation of LTBI, be tested.[19] Testing persons at low risk is discouraged according to these recommendations. Populations considered at higher risk for TB include those recently infected with *M. tuberculosis*; persons with HIV/AIDS; persons receiving immunosuppressive therapy, persons with recent close contact with infectious TB cases; persons with abnormal chest radiographs consistent with prior TB; recent immigrants (within the last 5 years) from high prevalence countries; injection drug users; residents and employees of high risk congregate settings; health care workers (HCWs) with exposure to TB or high risk populations; mycobacteriology laboratory personnel; persons with clini-

cal conditions such as silicosis, diabetes mellitus, chronic renal failure, leukemias and lymphomas, carcinoma of the head or neck and lung; persons with weight loss of more than 10% of ideal body weight; persons with gastrectomy and jejunoileal bypass; children under 4 years of age; or infants, children, and adolescents exposed to adults in high-risk categories.[19]

1.1.9 Clinical Manifestations

Clinical manifestations differ depending on whether the person has LTBI or active TB. LTBI is asymptomatic, not infectious, and most people are not aware they are infected. Unlike LTBI, active TB usually causes people to fall ill, is infectious, and has symptoms ranging from mild to severe. Active TB usually affects the lungs and respiratory tract, but can also spread to any organ system in the body. Pulmonary TB symptoms may include productive cough, hemoptysis, chest pain, fatigue, anorexia, weight loss, fever, sweating, and chills.

1.1.10 Treatment

Isoniazid (INH) was first recommended as a treatment of LTBI in 1965.[32] The current preferred treatment for LTBI is 5 mg/kg (max 300 mg) of INH taken by mouth daily for nine months. This recommendation is based on the quality of evidence available and expert opinion. Other alternative treatment regimens include: INH at 5 mg/kg (max 300 mg) taken by mouth daily for six months or INH at 15 mg/kg taken by mouth twice weekly for nine months or six months. An alternative treatment to INH is rifampin (RIF), also recommended when INH is contraindicated, at 10 mg/kg (max 600 mg) taken by mouth daily for four months. While these alternative treatments are acceptable, limited efficacy and clinical data set the recommendations of these regimens behind the preferred treatment. Current guidelines recommend a concomitant course of vitamin B6 with LTBI treatment to prevent peripheral neuropathy and central nervous system effects for pregnant women and persons with conditions where neuropathy is common, such as diabetes, uremia, alcoholism, malnutrition, and HIV infection.[19] In the past, a

two month regimen of RIF and pyrazinamide was a short treatment option, but since August 2003 it is no longer recommended due to reports of severe liver injury and death.[33] A new 12 week LTBI treatment, which is a combination of INH and rifapentine (a similar, but different drug from RIF), was recently recommended as an alternative to nine months of INH. While this new treatment was well tolerated in clinical trials, the extent of treatment related adverse events is unknown.[34]

1.2 Tuberculosis and the Military

1.2.1 Introduction and Military Relevance

Military personnel experience a higher risk of TB infection through military deployments, assignments to high incidence countries, and close contact with refugees and displaced persons.[35,36] Environments such as ships, barracks, and other housing and working arrangements, involve close contact with others for extended periods of time, which facilitate person-to-person transmission. While active TB in the US military has been on the decline since 1992, increases in active TB infection were observed in the military in 2009 and 2012.[37] In the military, active TB is a concern due to its effect on operational readiness and potential to spread among members. With the continuing presence of military personnel around the world, the concerns over the increasing number of multi-drug resistant TB and extensive-drug resistant cases are becoming more common.

1.2.2 Tuberculosis Testing

Because tuberculosis is a heightened concern in the US military, all service members have in the past been routinely tested for TB by TST and those who tested positive were prescribed treatment.[38–41] After CDC updated their screening recommendations to implement targeted TB testing in 2000, all military branches updated their policies be aligned with CDC. The Air Force and Coast Guard updated their practices in 2005, the Army in 2008, and the Navy and Marine Corps in 2009.[42–45] It is still policy to test all new recruits for TB and treatment

is given to positive service members, if medically indicated.

1.2.3 Latent Tuberculosis Infection in the Military

Active TB (both pulmonary and extrapulmonary) is a reportable event/ medical condition to the Armed Forces Health Surveillance Center, but LTBI is not.[46] This lack of a global reporting system makes it challenging to identify and monitor LTBI cases. Generally, 1-2% of military personnel seroconverting is not considered a concern, although a reactor rate greater than 2.5% would trigger a search for an active case.[36,47–49] Some studies reported LTBI prevalence among Navy and Marine recruits ranging from 1.5%-5.1%.[50–54] Limited studies on TST conversion among non-recruits in non-outbreak situations among military personnel have reported a prevalence range of 1.0%-2.0%.[36,47,51] The information on LTBI is limited to a few specific studies which were unable to analyze potential risk factors, and no studies have assessed the use of pharmacy data to monitor the identification of LTBI. This novel approach of using medical and pharmacy data would fulfill the current gap in LTBI surveillance and would provide data in a timely basis, have low biases, and include the full capture of health services information on all military personnel.

1.2.4 Health Care Workers

TB is a known occupational hazard among HCWs and they are considered a special risk group.[55–58] The resurgence of TB in the mid-1980s, health care associated outbreaks, and emergence of multidrug-resistant TB strains prompted CDC to issue new guidelines for preventing transmission of TB in health care settings. The implementation of the infection control guidelines lead to a decrease in the number of TB outbreaks in health care settings and reduced transmission to patients and HCWs. Updated 2005 CDC guidelines reflect the changing epidemiology of TB in maintaining momentum and eliminating the risk from those with unsuspected and undiagnosed active TB. Foreign-born HCWs are observed to have higher rates of TB compared to US-born HCWs.[59–61] The risk and conversion

rate varies by type of health care setting, occupation, prevalence of TB in in the community, composition of patient population, and effectiveness of TB infection control measures. A recent study on HCWs reported a 1.2% conversion rate and a review of 15 older studies calculated a median conversion rate of 1.1% (range <0.1-12%).[56,62] In the past, specific types of health care occupations have been shown to be at higher risk of TB, particularly nurses and physicians, although two recent studies found no increased risk.[57,61,63] HCWs in the military occupy a special role that differs from civilian HCWs. Only one study on HCWs in the military has calculated occupation specific rates, which were done at military medical center in 1995-1996. Ball and Van Wey reported a 3.1% conversion rate among military HCWs, compared to a 1.3% conversion rate among civilian HCWs and 0.7% among nurses.[64] However, no other studies have reported occupation specific rates among military HCWs or calculated risk for those occupations.

1.2.5   Overseas Duty Stations and Deployments

More time spent in close contact with a high-risk population and serving in high incidence geographic areas is associated with higher cumulative incidence. Service members are frequently deployed and have overseas duty stations in TB endemic regions, such as Iraq, Afghanistan, and other parts of Asia. However, one study found Navy and Marines stationed at US shore-based facilities reported consistently higher positive TST rates compared to service members stationed aboard ships in the Atlantic and Pacific (1.00% vs. 0.78%, p<0.001).[51] Additionally, no association was found between active TB and deployments to Iraq or Afghanistan, nor was there an increase in active TB incidence, which was similar to what had been reported during World War II, the Korean War, and the Vietnam War.[65,66] Currently, there is no research on LTBI risk among HCWs in overseas duty stations or those deployed in the Middle East.

1.3 Adverse Events Related to Treatment of latent tuberculosis infection

1.3.1 Adverse Event Incidence Rates

LTBI treatment is frequently prescribed to active duty military who test positive for LTBI. The risk of developing active TB and the risk of adverse events related to the prescribed regimen are both considered when determining treatment. Some of the possible adverse events related to the treatment include hepatotoxicity, peripheral neuropathy, headache, dizziness, rash, nausea or vomiting, abdominal pain, gastrointestinal upset, thrombocytopenia, and discoloration of body fluids. The study of adverse events and risk factors for adverse events in a relatively young healthy military population is limited. Recent studies in the civilian population have reported incidence rates of adverse events ranging from 4.4%-9.4% within the general population.[67–71] Other studies found adverse event incidence rates ranging from 5.7%-11.3% in those treated with INH and 3.1%-8.3% in those treated with RIF.[67–71] No published studies have quantified the rate of adverse events or analyzed the risk of adverse events with the type of LTBI treatment and potential risk factors using pharmacy data. The complete health data available on a captured population like the military makes this type of pharmacoepidemiology research possible and needs to be explored to determine how prescribed treatment affects service members' health.

1.3.2 Hepatotoxicity

INH is very effective in treating LTBI but is associated with notable adverse events. n particular, hepatotoxicity has been reported in a number of studies.[70,72–75] In response to concerns about adverse events related to LTBI treatment, in 2004 CDC began a national project to monitor severe events and quantify and characterize these events, particularly hepatic related events.[72] Minor asymptomatic elevations in aspartate aminotransferase levels occur in 10%-20% of people receiving INH, but usually resolve while continuing therapy.[76] The main major ad-

verse event for RIF is also hepatotoxicity, and like INH minor abnormalities are also seen in liver function tests, but usually resolve even with continuation on therapy. Current literature estimates the incidence of hepatotoxicity among those treated with INH ranged from 0.1%-6.1% and 0.0%-2.0% for RIF.[67–71,77,78] The risk of hepatotoxicity is associated with advancing age, alcohol consumption, pregnancy (including postpartum), HIV/AIDS infection, viral hepatitis, chronic liver disease, cirrhosis, or other liver disorders.

1.3.3 Other Adverse Events

Another notable but rare adverse event associated with INH is peripheral neuropathy. This condition is unusual in healthy individuals (less than 0.2%) and usually prevented by a concomitant prescription of vitamin B6.[12,19] Diabetes mellitus, uremia, alcoholism, malnutrition, pregnancy, and HIV infection are conditions that may predispose those taking INH to peripheral neuropathy. Other adverse events that have been documented with INH or RIF include headache, dizziness, rash, nausea or vomiting, abdominal pain, gastrointestinal upset, thrombocytopenia, and discoloration of body fluids.[19,74,77–82]

1.4 Objectives

Using data from various comprehensive electronic US military personnel, medical, and pharmacy data sources which had not previously been used for evaluation of LTBI and their associated risk factors related to conversion and treatment, this dissertation had three main objectives:

1. Determine the concordance of LTBI in both pharmacy and medical records among active duty military personnel, describe the identified LTBI population, and assess the utility of pharmacy records as a source for LTBI surveillance.

2. Calculate conversion rates (incidence rates) among Navy HCWs and identify risk factors associated with LTBI conversion among these service members.

3. Quantify the rate of specific adverse events of interest and assess their relationship to the main exposure, LTBI treatment, and to additional risk factors among active duty service members.

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Chapter 2

Concordance of Pharmacy and Medical Records for Surveillance of Latent Tuberculosis Infection in the United States Military

2.1 Abstract

Background: A key component of active tuberculosis control and prevention is treating latent tuberculosis infection (LTBI). Because there is no standard reporting system for LTBI in the US military, the purpose of this study was to determine the utility of using pharmacy and medical records for LTBI surveillance among military personnel.

Methods: The study sample included 3,089,436 active duty military personnel with both pharmacy and medical records from October 30, 2001 through September 30, 2011. LTBI match cases were identified by the presence of LTBI-specific medications in pharmacy records plus LTBI diagnosis codes in medical records within 180 days of each other. Concordance between LTBI cases in pharmacy and medical records was calculated using the Cohen's κ statistic.

Results: Among military personnel with LTBI indicated in either pharmacy

or medical records (n = 133,365), 38.9% (n = 51,943) had LTBI indicated in both pharmacy and medical records within 180 days. We observed moderate concordance between pharmacy and medical data sources in LTBI diagnosis ($\kappa = 0.55$; 95% CI 0.54-0.55; p<0.001).

Conclusions: The results of this study suggest that pharmacy data may be useful in identifying and tracking LTBI cases in the absence of a global tracking system in a military population. Further evaluation of LTBI coding practices in hospitals and clinics could improve the value of electronic medical records.

2.2 Introduction

In the US, one of the key components of tuberculosis (TB) control is treating latent tuberculosis infection (LTBI) to prevent the development of active disease.[1] Military personnel have an increased risk of TB infection through military deployments, assignments to high-incidence countries, and close contact with refugees, displaced persons and prisoners of war.[2,3] Environments, such as ships, barracks, and other housing and working arrangements, involve close contact with others for extended periods of time, which can facilitate person-to-person transmission. Because TB is a heightened concern in the US military, service members are routinely screened and those who test positive are prescribed treatment.[4–7] Active TB incidence in the US is low and infection trends in the US and US military have declined since 1992. Nevertheless, increases in active TB infection were observed in the military in 2009 and 2012.[8,9]

In countries with low TB incidence, such as the US, most incident active TB cases occur among people who were once exposed, developed a latent infection, and later developed active TB.[10] Even when LTBI is not infectious, approximately 5-10% of infected individuals develop active TB without treatment. The highest risk of developing active TB is in the first 2 years after infection, when half of all cases will occur.[11] Thus, LTBI treatment and identification of associated risk factors are critical to the Centers for Disease Control and Prevention's goal of TB elimination.[1] In the US military, active TB is a concern because of its effect

on operational readiness and potential to spread among members. Active TB (both pulmonary and extrapulmonary) is a reportable event/medical condition by the Armed Forces Health Surveillance Center, but LTBI is not.[12] Because of this absence in reporting and because LTBI is asymptomatic, it is difficult to identify and track cases. There is no "gold standard" or universal system for reporting and tracking LTBI, and there are limited studies that evaluate trends over time.

Recommended treatment for active TB consists of four drugs: isoniazid (INH), rifampin (RIF), ethambutol, and pyrazinamide.[13] The recommended treatment for LTBI is INH, with RIF as an alternative treatment if INH is contraindicated.[14] Other than TB and LTBI, INH and RIF are rarely prescribed for other conditions, except for select mycobacterial diseases. Those treatment regimens include simultaneous co-prescription of at least two other mycobacterial agents (e.g., RIF, pyrazinamide, or ethambutol). Service members who met this pattern were excluded from our study.[15,16] Pharmacy data for active duty military personnel include records of prescriptions to treat TB. Previous studies that assessed the potential of utilizing pharmacy data in military and general managed care settings to track active TB and LTBI found mixed results.[17–21]

The objectives of this study were to determine the concordance of LTBI in both pharmacy and medical records among active duty military personnel, describe the identified LTBI population, and assess the utility of pharmacy records as a source for LTBI surveillance.

2.3   Methods

For this retrospective population-based descriptive study, we identified active duty service members through the Pharmacy Data Transaction Service system, which is part of the Military Health System Data Repository (MDR). MDR is a data warehouse containing a complete collection of health care services (covered by TRICARE insurance) provided to military service members, veterans, and their beneficiaries. This system is maintained by the Office of the Assistant Secretary of Defense (Defense Health Agency) and has been in operation since 1999. The

Pharmacy Data Transaction Service system includes all outpatient prescriptions dispensed inside and outside the US at military treatment facilities, managed care support contractors, and TRICARE mail order pharmacies, but does not include inpatient prescriptions. Information used in this study included prescription name, date dispensed, dosage, and days supplied. In MDR, medical data from outpatient visits are stored in the Standard Ambulatory Data Record for all military hospitals and clinics and the TRICARE Encounter Data - Non-Institutional for civilian care covered by TRICARE insurance. Data from inpatient visits for all military hospitals are stored in Standard Inpatient Data Record and for civilian care covered by TRICARE insurance in TRICARE Encounter Data - Institutional Data, also within MDR. All sources contain information on diagnoses and procedures. Diagnoses are recorded using the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM).

Active duty service members with pharmacy and outpatient or inpatient medical records from October 1, 2001 through September 30, 2011 were eligible for analysis. Service members less than 17 or more than 75 years old were excluded.

2.3.1   Case Definition

LTBI medical cases were defined as service members with medical records containing any one of the following ICD-9-CM diagnosis codes: 795.5 (nonspecific reaction to test for tuberculosis without active tuberculosis), 795.51 (nonspecific reaction to a tuberculin skin test without active tuberculosis) and 795.52 (nonspecific reaction to cell mediated immunity measurement of gamma interferon antigen response without active tuberculosis).

LTBI pharmacy cases were defined as service members with pharmacy records of either: 300 mg oral daily or 900 mg oral twice weekly of INH for at least 30 days; RIF with an oral daily dose of 600 mg for at least 30 days (if INH was not dispensed); or, if there was a regimen change, the sequential use of INH and RIF was also considered an LTBI case if RIF was dispensed 7 to 180 days after INH was last dispensed (Table 2.1). If INH was dispensed in combination with pyrazinamide and/or ethambutol within 30 days, or if RIF was dispensed in

combination with ethambutol within 30 days, service members were not considered an LTBI case because these combinations are prescribed for active TB.

2.3.2 Demographic Variables

We obtained demographic variables from the Career History Archival Medical Personnel System,23 including age, gender, race (white, African American, Asian, or other), ethnicity (Hispanic or non-Hispanic), education (high school diploma or equivalent, or some college or more), marital status (married, never married, or divorced/separated/other), rank (junior [E1-E3], midlevel [E4-E5], senior enlisted [E6-E9], or warrant/commissioned officer [WO/O]), service branch (Army, Air Force, Navy, Marine Corps, or Coast Guard), and occupation (infantry, health care specialist, or other).[22] We calculated age by subtracting the birth date from the first date of LTBI diagnosis or LTBI prescription. We used the Department of Defense Conversion Index to categorize occupation.[24]

2.3.3 Data Analysis

We identified a match between an LTBI medical and pharmacy case if any LTBI medical diagnosis date in outpatient or inpatient records and any LTBI pharmacy date were within 180 days of each other. Concordance between the pharmacy and medical records was measured by total percent concordance and Cohen's κ statistic. The κ statistic accounts for rates of chance agreement; a κ value of 0 indicates that agreement is no better than chance, while a κ value of 1 indicates perfect agreement. The strength of concordance was defined as poor ($\kappa \leq 0.20$), fair ($0.21 \leq \kappa \leq 0.40$), moderate ($0.41 \leq \kappa \leq 0.60$), good ($0.61 \leq \kappa \leq 0.80$), and very good ($0.81 \leq \kappa \leq 1.00$).[23] If service members had both an LTBI medical diagnosis and LTBI prescription, but the diagnosis date and pharmacy date were outside the 180 day range, they were categorized by the earliest record and data source. For example, a service member with both records 181 days apart would be an LTBI medical case if the medical diagnosis came before the LTBI prescription. Pharmacy record sensitivity, specificity, and positive and

negative predictive values were calculated using medical record diagnosis as the reference. We calculated descriptive statistics, including 95% confidence intervals (CIs), for select demographic variables for LTBI cases that matched on pharmacy and medical records. A p-value <0.05 was considered statistically significant and no adjustments were made for multiple comparisons.

All analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC). This study was conducted in accordance with the amended Declaration of Helsinki. The Naval Health Research Center Institutional Review Board approved the protocol for this study (NHRC.2012.0022).

2.4   Results

During the study period, 3,089,436 active duty military personnel had both pharmacy and medical records. There were 321,592 medical records from 114,542 service members with LTBI diagnosis documented, and 357,819 pharmacy records from 74,537 service members with LTBI prescriptions. Of those with LTBI prescriptions, 94.5% (70,446) were prescribed INH, 4.2% (3,110) were prescribed RIF, and 1.3% (981) were initially prescribed INH then later prescribed RIF.

Overall, 4.3% of service members (133,365 of 3,089,436) had LTBI indicated in either pharmacy or medical records. Of these, 38.9% (n = 51,943) had records indicating LTBI in both pharmacy and medical records within 180 days of each other (Table 2.2). There were 73,939 service members identified to have an LTBI prescription in pharmacy data, 70.3% of which had an LTBI medical diagnosis within 180 days or a pharmacy record, while 29.7% did not. From the medical records, 111,369 service members were identified, of which 46.6% had an LTBI prescription, while 53.4% did not. Of the 81,422 people that were discordant, 72.3% (58,828) had an LTBI diagnosis but no corresponding LTBI prescription, 23.1% (18,823) had an LTBI prescription, but were missing an LTBI diagnosis, and 4.6% (3,771) had both an LTBI diagnosis and LTBI prescription but the records were outside of the 180 day window. The agreement between pharmacy and medical records was 97.4% with the majority of service members having no record

of an LTBI diagnosis or prescription. Moderate concordance between the LTBI pharmacy and medical data sources was observed ($\kappa = 0.55$; 95% CI 0.54-0.55; p<0.001). The sensitivity of LTBI prescriptions using LTBI medical diagnoses as a reference was 46.6% (95% CI 46.4-46.9) and the specificity was 99.3% (95% CI 99.3-99.3). The positive and negative predictive values were 70.3% (95% CI 69.9-70.6) and 98.0% (95% CI 98.0-98. 0), respectively (Table 2.3).

Of the 51,943 service members who matched on LTBI medical and pharmacy records, most were white (47.1%), non-Hispanic (81.3%), men (83.9%), who never married (50.8%), and had a high school diploma or equivalent (80.4%; Table 2.4). The average age was 25.7 years (SD = 6.7; range, 17-66). Junior enlisted (47.6%) and Army personnel (38.6%) made up the highest percentage of LTBI match cases. The most common LTBI medication dispensed was INH (96.0%) followed by RIF (2.4%).

2.5 Discussion

TB in active duty service members is relatively uncommon, but the failure to identify and properly treat LTBI puts other service members and mission readiness at risk. The objective of this study was to determine the utility of pharmacy data as a potential mechanism of LTBI surveillance. The results of this study demonstrated moderate concordance between pharmacy and medical records, and found high agreement between the data sources. This may be explained by a high prevalence index (0.94), where the proportion of agreement of LTBI within the pharmacy and medical records greatly differed from the proportion of agreement of no LTBI in both the pharmacy and medical records. Since the prevalence index was high, the chance agreement was also high and the kappa was reduced accordingly.

Using ICD-9-CM coding alone, the prevalence for LTBI in service members was 3.6 %. The sensitivity of LTBI prescriptions among service members to LTBI diagnoses was 46.6%. The positive predictive value of 70.3% indicates that there is a 70.3% probability that the service member has an ICD-9-CM LTBI diagnosis,

given there was an LTBI prescription documented in the pharmacy data. All estimations remained stable after changing the match range from 180 days to 90, 270, and 365 days (data not shown). If pharmacy records were used to establish the LTBI prevalence rate over medical records, the rate would be 2.4%, with a sensitivity and specificity of 70.3% and 98.0%, respectively. All prevalence rates in the current study fall within the range of other published studies on the US military during this study period (0.5%-4.3%), and included a number of TB exposure events.[3,24–28] This study found LTBI diagnoses occurred frequently without any corresponding LTBI prescriptions and, to a lesser degree, LTBI prescriptions lacked corresponding LTBI diagnoses.

Several studies have reported potentially promising results in using pharmacy data to supplement traditional TB surveillance and assess active TB management.[17–21] Most studies were in a health maintenance organization populations, and the references used in these studies were not consistent. For example, one study, using 2 to 4 anti-TB drugs alone, found 84%-89% sensitivity to TB cases identified through public or health maintenance organization records.[17] Another found 80% sensitivity, using 2 or more anti- TB drugs, when using verified TB cases identified through the TB registry or pharmacy data.[18] Finally, a military study found pharmacy data sensitivity ranging from 60%-81% when using either a confirmed medical event reported to the Armed Forces Health Surveillance Center or a positive laboratory specimen, with the highest sensitivity in 2 to 4 anti-TB drugs alone (70%-81%).[19] The most commonly used TB test in the US military, the tuberculin skin test, has high sensitivity (89%) and specificity (86%) in people with normal immune responsiveness.[29] Administering it in a low prevalence population, such as the US, could result in a higher number of false positives than true positives, which could be attributed to less than 100% specificity and cross-reactivity with the test (i.e., bacille Calmette-Gurin vaccination or exposure to non-TB mycobacteria).[30–34] During our study period, the Air Force (2005), Coast Guard (2005), Army (2008), and Navy/Marine Corps (2009) revised their TB policies to align more with recommendations from the Centers for Disease Control and Prevention for targeted LTBI screening programs.[35–38] Future LTBI prevalence es-

timates limited to after the policy change may be more accurate.

The primary strength of this study was the large population, including all active duty military personnel from all military branches over a 10-year period, which increased the precision of our prevalence estimates. Another strength was the utilization of a centralized military health system, which contained pharmacy and medical information on an active duty service member throughout his or her career, even while deployed. Some commands have internal LTBI tracking procedures used in place of medical record documentation. One unpublished study found that several military treatment facilities used a variety of reporting systems to track compliance and refill management that ranged from paper records, internal electronic spreadsheets, and a number of other military data systems that were not available at all military treatment facilities and clinics, none of which feed into service members medical records directly or easily.[39] A limitation of the pharmacy data utilized for this study was the absence of clinical indication for a specific medication prescription, which can only be extrapolated based on the dosage and strength. Another limitation of our study was the use of particular ICD-9-CM codes for LTBI diagnosis, which may be used inappropriately, although rarely, for other conditions. LTBI coding may be mistakenly used to document a prior history of LTBI or active TB. Finally, inpatient prescriptions were not available until 2012 and could not be included in this study, though LTBI treatment is typically outpatient.

2.6   Conclusions

TB testing and treatment is a crucial part of assessing service members' military readiness and a key component of TB control. This is the first study to investigate the utility of pharmacy data in estimating the burden of LTBI in active duty military personnel. The results of this study suggest that the centralized military medical system, particularly pharmacy data, is useful in identifying and tracking LTBI cases in the absence of a global tracking system. Further evaluation of LTBI coding practices in hospitals and clinics could improve the value of

electronic medical records.

2.7 Acknowledgements

Table 2.1: Definitions for Latent Tuberculosis Infection Classifications

Data source	Criteria
Medical records (ICD-9-CM[1] code)	795.5: Nonspecific reaction to test for tuberculosis without active tuberculosis
	795.51: Nonspecific reaction to tuberculin skin test without active tuberculosis
	795.52: Nonspecific reaction to cell mediated immunity measurement of gamma interferon antigen response without active tuberculosis
Pharmacy records[2] (strength, dosage, and medication)	300mg oral daily of isoniazid for 30 days
	900mg oral twice weekly of isoniazid for 30 days
	600mg oral daily of rifampin for 30 days

[1]International Classification of Diseases, 9th Revision, Clinical Modification.

[2]Service members with isoniazid prescribed and dispensed in combination with rifampin, pyrazinamide, and/or ethambutol were excluded from analyses.

Table 2.2: Concordance Between Latent Tuberculosis Infection (LTBI) Pharmacy and Medical Records in Active Duty Military Personnel (N = 3,089,436)

Results	n	(%)
LTBI pharmacy cases and/or LTBI medical cases	133365	
LTBI pharmacy and medical match cases[1]	51943	(38.9)
LTBI pharmacy cases only	73939	
LTBI pharmacy cases with LTBI diagnoses	51943	(70.3)
LTBI medical cases only	111369	
LTBI medical cases with LTBI prescriptions	51943	(46.6)
Total	3089436	
Agreement	3008014	(97.4)
κ (95% CI[2])[3]	0.55	(0.54, 0.55)

[1]Match between pharmacy and medical records within 180 days of each other.

[2]confidence interval

[3]p<0.001

Table 2.3: Performance Characteristics of Pharmacy Records to Identify Latent Tuberculosis Infection (LTBI) Using Medical Record Diagnoses as a Reference in Active Duty Military Service Members (N=3,089,436)

LTBI cases identified n	51,943	
Sensitivity % (95% CI[1])	46.6	(46.4-46.9)
Specificity % (95% CI[1])	99.3	(99.3-99.3)
Positive predictive value % (95% CI[1])	70.3	(69.9-70.6)
Negative predictive value % (95% CI[1])	98	(98.0-98.0)

[1]confidence interval

Table 2.4: Characteristics of Latent Tuberculosis Infection Match Cases Identified in Pharmacy and Medical Records in Active Duty Military Personnel

Characteristic	n	%	(95% CI[1])[2]
Age, mean (SD[3])	51943	25.7	(6.7)
Gender			
Men	43579	83.9	(83.5-84.3)
Women	8364	16.1	(15.7-16.5)
Race[4]			
White	24123	47.1	(46.5-47.6)
African American	14185	27.7	(27.2-28.2)
Asian	9708	18.9	(18.5-19.4)
Other	3252	6.3	(6.1-6.6)
Ethnicity[5]			
Hispanic	9569	18.7	(18.3-19.1)
Non-Hispanic	41532	81.3	(80.9-81.7)
Education[6]			
High school diploma or equivalent	41194	80.4	(80.0-80.8)
Some college	10035	19.6	(19.2-20.0)
Marital status[7]			
Married	24116	46.6	(46.1-47.2)
Never married	26243	50.8	(50.2-51.3)
Divorced/separated/other	1345	2.6	(2.4-2.8)
Rank[8]			
Junior enlisted	24583	47.6	(47.0-48.1)
Midlevel enlisted	16536	32	(31.5-32.5)
Senior enlisted	6324	12.2	(11.9-12.6)
Warrant/Commissioned Officers	4249	8.2	(7.9-8.5)

Table 2.4: Characteristics of Latent Tuberculosis Infection Match Cases Identified in Pharmacy and Medical Records in Active Duty Military Personnel, continued

Characteristic	n	%	(95% CI[1])[2]
Service			
Army	20033	38.6	(38.0-39.1)
Air Force	10398	20	(19.6-20.5)
Marine Corps	4701	9.1	(8.7-9.4)
Navy	16358	31.5	(31.0-32.0)
Coast Guard	453	0.9	(0.8-1.0)
Occupation[9]			
Infantry	7464	14.5	(14.2-14.9)
Health care specialist	4335	8.5	(8.2-8.7)
Other	39530	77	(76.6-77.5)
Treatment			
Isoniazid	49852	96	(95.8-96.2)
Isoniazid-Rifampin[10]	862	1.7	(1.5-1.8)
Rifampin	1229	2.4	(2.2-2.5)

[1]confidence interval

[2]Data presented as % (95% CI) unless otherwise noted.

[3]standard deviation

[4]missing 675

[5]missing 842

[6]missing 714

[7]missing 239

[8]missing 251

[9]missing 614

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Chapter 3

Latent Tuberculosis Infection in Health Care Workers in the United States Navy

3.1 Abstract

Background: Tuberculosis (TB) has long been recognized as an occupational hazard among health care workers (HCWs). Additionally, HCWs in the Navy may have an increased risk of tuberculosis (TB) infection due to military deployments and assignments to TB endemic areas. Limited studies on latent tuberculosis infection (LTBI) conversion rates in non-outbreak situations among Navy HCWs have been published. The objective of this study was to determine conversion rates among Navy HCWs and identify risk factors associated with LTBI conversion among these service members.

Methods: This retrospective study identified active duty Navy HCWs from October 1, 2001 through February 12, 2009. Overall and annual incidence rates of LTBI were calculated. A Cox proportional hazard model was fitted with covariates that differed significantly between LTBI cases and non-cases.

Results: The overall LTBI incidence among HCWs over the entire study period was 1.7% (95% CI 1.5-1.9) with an incidence density rate of 4.6 per 1,000

person-years (95% CI 4.12-5.13). Being non-white and foreign born were LTBI risk factors for Navy HCWs, while overseas duty stations and Iraq or Afghanistan deployments were inversely associated.

Conclusions: Overall, annual incidence rates of LTBI among HCWs in the Navy were low and comparable to previous studies on Navy personnel. Non-occupational factors, such as race and country/region of birth and service related factors, such as no overseas duty stations and no deployments, appeared to affect LTBI incidence among HCWs.

3.2 Introduction

Tuberculosis (TB) is a recognized public health problem in the United States (US). Almost 10,000 new cases of TB were reported in 2013 and an estimated 11 million people in the US have a latent tuberculosis infection (LTBI).[1,2] The incidence of TB in the US is low; most active TB cases occur among people who were exposed in the past, developed LTBI, then later developed active TB.[3] Because of this, a key component of TB control is the identification and treatment of LTBI cases.[4] Active TB and LTBI among health care workers (HCWs) are known occupational hazards and HCWs are considered a special risk group.[5–8] While TB rates in the US have decreased since the early 1990s, foreign-born persons and racial and ethnic minorities are still disproportionately affected by TB. In particular, foreign-born HCWs are observed to have higher rates of TB.[9–11]

The Navy provides comprehensive medical coverage to Navy and Marine Corps service members and their dependents at all military hospitals, clinics, and dental facilities. Patients requiring services that are unavailable are referred to civilian providers; these referred services are also covered by the Navy. Navy HCWs consist of physicians, dentists, nurses, clinical care providers, medical support personnel that provide clinical care, and administrative, research, and clinical specialists who support laboratories and research facilities in the US and around the world.

Service members may have an increased risk of TB infection through mili-

tary deployments, assignments to high incidence countries, and close contact with refugees, displaced persons and prisoners of war.[12,13] Like TB rates in the US, TB rates in the military are low.[14] But unique congregate settings such as ships, barracks, and other housing and working arrangements, involving close contact with others for extended periods of time can facilitate person-to- person transmission and thus TB outbreaks.[15] Service members are also frequently deployed and have overseas duty stations in TB endemic locales, such as Iraq, Afghanistan, and other parts of Asia. HCWs, in particular, may be in close contact with TB infected persons during these times.

From 1993 to 2009, it was Navy policy to annually screen all HCWs for TB with either the tuberculin skin test (TST) or the Interferon-Gamma Release Assay (IGRA) and treat the service member if medically indicated. In addition, deployed service members were asked about their risk of exposure to TB upon returning from overseas.[16,17] Previous studies found no increase in active TB cases from 2004 to 2006 and no association between active TB and deployments to Iraq or Afghanistan.[18,19]

Limited studies on tuberculin skin test (TST) conversion rates (as defined as a person with a previous negative TST who then has a new positive TST) in non- outbreak situations in the military have been published; these studies found conversion rates ranging from 1.0%-3.1% from 1980 through 2002.[13,20–22] No studies have analyzed risk factors associated with LTBI conversion among Navy HCWs. In addition, identification of occupational and non-occupational risk factors among Navy HCWs would be useful in targeting prevention efforts to those that are at greatest risk.

The objective of this study was to determine conversion rates (incidence rates) among Navy HCWs and identify risk factors associated with LTBI conversion among these service members using personnel, medical, and pharmacy data sources.

3.3 Methods

3.3.1 Data Sources

Medical and pharmacy data were obtained from the Military Health System Data Repository (MDR), which contains information on all outpatient and inpatient visits seen to military hospitals and clinics, and civilian care covered by TRICARE insurance (military insurance) and all outpatient prescriptions dispensed inside and outside the US at military treatment facilities, managed care support contractors, and TRICARE mail order pharmacies. Medical diagnoses were recorded using the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) system. Demographic factors, duty stations, career information, and occupation were obtained from the Career History Archival Medical Personnel System (CHAMPS).[23] Deployment history prior to an LTBI conversion or the end of the period of risk, whichever came first, was obtained from the Defense Manpower Data Center.[24]

3.3.2 Study Design and Study Sample

This retrospective cohort study identified active duty Navy HCWs using data from CHAMPS. Eligible service members were active duty personnel that joined the Navy from October 1, 2001 through February 12, 2009 and were identified as a HCW using occupation codes defined in the Department of Defense Conversion Index.[25] LTBI cases found within 14 days of the start of basic training (accession), incident active TB cases, and service members with a documented personal history of TB or previous service in other branches of the uniformed service were excluded. All new Navy recruits are tested for TB on the first day of arrival at the Recruit Training Center for basic training and evaluations are completed within the first six days. Incident active TB cases were defined as service members that were prescribed a combination of isoniazid (INH), rifampin (RIF), pyrazinamide, and/or ethambutol within 30 days of each prescription and the ICD-9-CM diagnosis code used for personal history of TB was V12.01. From October 1, 2001 through February 12, 2009, there were 732,225 active duty Navy service

members; 78,526 (10.7%) were HCWs of which 18,984 (24.2%) were new recruits. Three service members developed active TB, two had a personal history of TB, and four had LTBI within 14 days of the date of accession. The final sample included 18,975 Navy HCWs with 326 LTBI cases. See Figure 3.1 for the sample selection flow diagram.

3.3.3   Outcome of Interest

Positive LTBI cases were defined as the presence of an LTBI diagnosis and LTBI prescription dispensed within 180 days of each other. LTBI ICD-9-CM diagnosis codes used were: 795.5 (nonspecific reaction to test for tuberculosis), 795.51 (nonspecific reaction to a TST without active tuberculosis), and 795.52 (nonspecific reaction to cell mediated immunity measurement of gamma interferon antigen response without active tuberculosis). LTBI prescriptions were defined as dispensed medications of 300 mg oral daily or 900 mg oral twice weekly of INH, with a minimum prescription of 30 days dispensed; if INH was not dispensed, RIF with an oral daily dose of 600 mg, prescribed for at least 30 days; or, if there was a regimen change, the sequential use of INH and RIF was considered an LTBI case if RIF was dispensed 7 to 180 days after INH was last dispensed. These definitions are based on the guideline recommended regimens for LTBI.[26] The period of risk for LTBI was defined as the number of days between the date a HCW occupation code was first documented and the date of LTBI prescription, date of LTBI diagnosis, date of discharge from active duty status, 365 days from the last date a HCW occupation code was found, or the end of the study period, whichever came first.

3.3.4   Covariates

Demographic factors such as age at accession, gender, rank, race/ethnicity, overseas duty stations, country of birth, years of service, and occupation were evaluated. Age at accession was calculated using the date of accession and date of birth. Military rank was divided into two categories: enlisted and warrant/commissioned

officers. Ethnicity was divided into Hispanic and non- Hispanic and race was categorized as white, African American, Asian/Pacific Islander, and other. Deployments to Iraq, Afghanistan, and Kuwait and any overseas duty stations prior to LTBI conversion or the end of the period of risk, whichever came first, were each dichotomized into yes or no. Country/ region of birth was categorized by US, Europe/Canada, Africa, Asia, Mexico, Central American/Caribbean, and South America. Years of service were calculated using the date of accession and the date of discharge from active duty status or the end of the study period and were categorized into: less than 1 year, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, and 7 years. Specific health care occupations used the Department of Defense Conversion Index25 and consisted of 10 fixed different fields/occupation variables that included physician, nurse, dental, laboratory, general hospitalman/corpsman, surgical technician, medical administration, pharmacy, preventive medical technician, and mental/physical therapy.

3.3.5 Data Analysis

Differences in proportions of LTBI by demographic categorical variables were tested using Pearson's chi-square (or Fisher's exact test where appropriate) and, for continuous variables, the Wilcoxon-Mann-Whitney test. Note that when the Fisher's exact test required a large amount of computational resources, the Monte Carlo estimate of the exact p-value was used instead. The Cochran- Armitage trend test was used to test for trends by the number of years a service member was active duty. The overall incidence rate was calculated for the entire study period using person-years and annual incidence rates for 2003-08 were calculated by dividing the number of incident cases that year by the number of at risk Navy HCWs that year. The annual incidence rates for 2001, 2002, and 2009 were not calculated due to small sample sizes. The Cochran- Armitage trend test was used for trend analysis of annual incidence rates. A Cox proportional hazards model was used to estimate the hazard ratio (HR) of LTBI with 95% confidence intervals (CI) to determine the contribution of each independent variable adjusted by all the other variables. Variables analyzed via chi-square, Fisher's exact, Wilcoxon-Mann-

Whitney, Monte Carlo estimate, or Cochran-Armitage trend test with a p-value <0.1 were included in the final model. Multicollinearity was tested using variance inflation factor with a cutoff of less than five. The proportional hazards assumption was assessed using Kaplan-Meier curves and Schoenfeld residuals (threshold p<0.05) were used to evaluate specific variables. Two-sided hypotheses testing with an alpha level of 0.05 was used, unless otherwise specified. Analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC). This study was reviewed and approved by the Naval Health Research Center Institutional Review Board, San Diego, California.

3.4   Results

The overall crude incidence of LTBI among the sample of HCWs during the entire study period, October 1, 2001 through February 12, 2009, was 1.71% (326/18,975). The incident density rate over the study period, October 1, 2001 through February 12, 2009, was 4.60 (95% CI: 4.12-5.13) cases per 1,000 person -years. For years that annual incidence rate was calculated, 2003-2008, no statistically significant trend was observed (p-value=0.865, Figure 3.2).

The sample consisted largely of US-born (91.5%), non-Hispanic (80.3%), white (60.5%) men (73.1%). The average age at accession was 20.4 (SD=3.7) years with an average of 3.8 (SD=1.9) years of service by the end of the study. The majority of the sample was enlisted (89.2%) hospitalman/corpsman (88.9%) without an overseas duty station (80.7%), and without deployments to Iraq, Kuwait, or Afghanistan (71.4%). See Table 3.1 for additional details.

LTBI cases were slightly older at the age of accession (mean 21.1 (SD=4.3) vs. 20.4 (SD=3.7) years) than non-cases. LTBI cases also tended to be non-white (67.7% vs. 39.0%), foreign born (29.9% vs. 8.2%), were in the Navy longer (Cochran-Armitage trend p<0.001), had only been stationed within the US (85.3% vs. 80.6%), had no deployments to Iraq (95.4% vs. 80.8%), and were non- nurses (98.5% vs. 96.4%) than non-cases, (p<0.05 for each comparison). The median follow-up time in the study for LTBI cases was 291 days (mean 439 (SD=430))

and for non-cases was 742 days (mean 887 (SD=631)).

Based on analyses (p<0.1), age at accession, race, country/region of birth, rank, years in the Navy, overseas duty station, nurse occupation, and deployments to Iraq or Afghanistan were included in the final model. Compared to non-cases, cases diagnosed with and treated for LTBI were more likely to be foreign born, non-white, in the military longer, had no overseas duty stations, and had no deployments to Iraq or Afghanistan in the multivariable model (Table 3.2). Specifically, service members born in Africa (HR=6.68, 95% CI 4.2-10.6), Asia/Pacific Islands (HR=2.06, 95% CI 1.3-3.3), Mexico, (HR=4.64, 95% CI 2.6-8.2), Central America (HR=3.25, 95% CI 1.9-5.5), and South America (HR=3.30, 95% CI 1.8-5.9) had a higher risk of being an LTBI case. Reporting Asian, African American, or another non-white race had increased risk of LTBI (HR=4.48, 95% CI 3.3-6.0; HR=2.11, 95% CI 1.6-2.9; HR=1.60, 95% CI 1.0-2.5, respectively). Having been assigned to overseas duty stations and combat deployments to Iraq and Afghanistan were associated with lower risk of LTBI (HR=0.46, 95% CI 0.3-0.6 for overseas duty station; HR=0.13, 95% CI 0.07- 0.22 for Iraq deployment; HR=0.21 for Afghanistan deployment, 95% CI 0.07- 0.66). Age at accession, rank, time in service, and nursing occupation were not associated with a risk of LTBI. Tests for multicollinearity were not significant and the proportional hazards assumption was met for all variables included in the final model. All estimations remained stable after expanding the exclusion criteria for recruits with LTBI from within 14 days of the date of accession to within 63 days (data not shown).

3.5   Discussion

The objective of this study was to determine the conversion rates among Navy HCWs and identify risk factors associated with LTBI conversion among these service members. This study evaluated LTBI incidence rates and the risk of LTBI for 18,975 new accession Navy HCWs from October 1, 2001 through February 12, 2009. The LTBI incidence was relatively low among US Navy HCWs, with an overall calculated LTBI incidence rate of 1.7%, and an incidence density rate of

4.60 per 1,000 person-years.

From 2003-2008, the conversion rate ranged from 4.2 to 7.2 cases per 1,000 person years. No statistically significant trend was observed in the annual incidence rates and, in general, annual LTBI incidence rates in HCWs in this study were low. Two studies have looked at conversion rate trends in the Navy and Marine Corps. One study looking at conversion rates in all Navy and Marine Corps personnel shore-based and shipboard reported a significant decreasing trend from 1.43% in 1980 to 0.92% in 1986 (p<0.001).[20] Another study on Navy and Marine Corp personnel from 1999-2002 reported an increasing trend; 1.35% in 1999 and 1.61% in 2002 (p<0.001).[13] That study was not in line with reported TB trends for the overall US population and military, which both reflected a decrease since the 1990s.[10,14] The annual rates calculated in our study were 0.58% in 2003 and 0.46% in 2008 among HCWs with no significant statistical trend. The two previously published studies estimated prevalence by year while our study calculated the incidence rate. Because of this, we would expect previous studies would have higher rates than our study. Additionally, the two previous studies included all Navy and Marine service members, while our study included only HCWs that joined the service after October 2001, with positive LTBI recruits removed from the population for survival analysis. Since all HCWs were not included in the study, the LTBI rate and risk may be underestimated. Some studies reported prevalence rates among Navy and Marine recruits ranging from 1.5%-5.1%.[20,27-30] Limited studies on TST conversion among non-recruits in non-outbreak situations among military personnel have reported a range of 1.0%-2.0%.[13,20,22] Our study's 1.7% conversion rate over the entire study period (October 1, 2001-February 12, 2009) among Navy HCWs falls within previously published conversion rates in the military. A recent study on HCWs found 1.2% conversion and a review of 15 studies calculated a median of 1.1% (range <0.1-12%).[6,31] One study in HCWs at a military medical center calculated a 2.8% conversion rate among all HCWs (including civilians and service members) and a 3.1% rate among active duty military HCWs.[21] The lower rate found in our study could be due to differences in overseas assignments at the time of that study; in 1995-1996, when the study took place, frequent overseas

deployments were to Somalia, Haiti, and Korea, while during our study, 2001-2009, deployments were to Iraq, Kuwait, and Afghanistan. Country of birth and non-white race were strong predictors for LTBI. Our results support previous research that found similar results.[6,27,28] Navy HCWs born in Africa had over six times the hazards of LTBI compared to US born HCWs. Latin American countries of birth had increased hazards as well; Mexico had more than four times the hazards of LTBI while Central and South America had over three times the hazards. It is possible that past history of the bacille Calmette-Guerin (BCG) vaccine may affect the high rate of LTBI in foreign-born service members. The BCG vaccine is not generally recommended for use in the US because of the low risk of TB infection, but many foreign-born persons from countries with a high prevalence of TB may have been vaccinated. The BCG vaccine may cause false positives in LTBI tests, but it does not influence clinical care.[26] However, these cases would have been detected and treated upon accession. While Asian/Pacific Islander race itself had the highest hazards in the race category, Asia/ Pacific Islands as a country/region of birth had a lower risk of hazards than Africa and Latin America. Non-white race was significantly associated with LTBI even when controlling for country of birth. It may be that these racial groups and foreign-born service members were exposed to TB through other avenues, such as personal travel to foreign countries with high TB prevalence or other personal contacts, such as living with a foreign-born family member.[29,32]

Combat deployments to Iraq and Afghanistan and overseas duty stations did not emerge as risk factors for LTBI; in fact they appeared to be protective. This was unexpected because Iraq and Afghanistan have higher prevalence rates of TB compared to the US.[33] It is possible that service members with overseas duty stations and deployments to Iraq and Afghanistan may not experience prolonged, frequent, or close contact (as defined by Centers for Disease Control and Prevention (CDC)) with foreign nationals or with persons with infectious TB.[34] Comparatively, US military service members are relatively younger and healthier than adults in the general US population due to the medical and physical requirements to join the military.[35,36] Our results on deployments are similar to one study in

the Navy and Marines that found US shore-based facilities reported consistently higher LTBI rates compared to ships (1.00% vs. 0.78%, p<0.001), though this study did not evaluate specific occupations.[20] A previous study showed no association between active TB and deployments to Iraq or Afghanistan, nor an increase in active TB incidence, which is similar to what was reported during World War II, the Korean War, and the Vietnam War.[18] A possible explanation for this phenomenon is the "healthy warrior effect," which describes the systematic differences in the health of military personnel of those deployed versus those not deployed.[37] The "healthy warrior effect" can be attributed to the fact that deployed service members are medically evaluated prior to deployment to assure that they have no health issues likely to pose problems while deployed.[38–40] It's possible that such health issues may also affect their susceptibility to TB infection. Specific health care occupations in this study were not risk factors for LTBI. In one review of nine studies, nurses were reported to be at increased risk of TB, but two more recent studies did not find nurses to be at higher risk.[7,11,41] In one study on HCWs in a military medical facility from 1995-1996, nurses had a 0.73% conversion rate, while active duty military HCWs had a 3.1% conversion rate.[21] That study was not able to evaluate specific occupations within military HCWs. In our study, analyses showed that nurses had lower rates of LTBI, but after adjusting for other covariates, the protective effect disappeared. The low rate of infection and null findings among nurses in the survival model could be due to the role that nurses have in the military. Nurses are officers in the Navy and may have a more managerial role compared to hospitalmen and corpsmen and therefore have relatively less risk exposure.

One of the strengths of this study is its large sample size and long study period, inclusive of new active duty Navy HCWs over 7 years. Another strength is the utilization of a centralized military health system through MDR and administrative information through CHAMPS. MDR contains pharmacy and medical information on all active duty service members, even while deployed. CHAMPS contains information on any changes to specific occupations, duty stations, and rank over the service member's entire military career. Additionally, during this

study period, it was Navy policy for all HCWs to be annually screened for TB and service members found to have LTBI were prescribed the appropriate treatment.[16]

One of the limitations to this study is the potential misclassification of occupation categories. The occupation categories may not reflect actual day-to-day job duties and risks or may be non-specific. Service members could have multiple occupations, changing throughout the study period, which could have diluted the study results. Also, while it was policy for HCWs to be screened for TB annually, medical and dental treatment facility workers who are not members of the medical team were not included in this study since this study identified HCWs using an administrative database and not the service member's actual work location. Another limitation is that LTBI cases were defined as cases that had the ICD-9-CM code for LTBI and LTBI appropriate treatment. There is no "gold standard" to diagnose LTBI; LTBI is diagnosed by having a positive reaction to the TST (determined by measurement of on duration), negative bacteriologic studies, and no clinical, bacteriological, or radiographic evidence of active tuberculosis.[42] The LTBI ICD-9-CM code was based on results from the TB tests, TST and IGRA, both of which have limitations in sensitivity and specificity.[43,44] Given data were not available prior to October 2001 and survival analysis was the purpose, HCWs that joined the military before the start of the study and were active duty during the study were not included. A large proportion of at risk HCWs was not included and may represent different risk factors of LTBI. Lastly, this study was not able to determine service members' BCG vaccination history and could not control for it in the final model. On February 12, 2009, the Navy changed their TB screening and testing policy to be more aligned with CDC's policy of targeted testing, which discourages TB testing among persons at lower risk and emphasizes targeted testing among persons at higher risk for recent LTBI or with clinical conditions that increase the risk for TB.[26,45,46]

3.6   Conclusions

Limited research on targeted testing in the military is available and focuses on recruits, though currently no research is available regarding LTBI rates and risk factors in HCWs in the Navy.[47] Overall, annual incidence rates of LTBI among HCWs in the Navy were low and comparable to previous studies on Navy and Marine personnel. This is the most recent and largest study to calculate incidence rates in Navy HCWs and identify potential risk factors for LTBI. Non-occupational factors, such as race and country/region of birth, appeared to be risk factors for LTBI, while service related factors such as overseas duty stations and Iraq or Afghanistan deployments were protective. The identification and treatment of LTBI cases is an important component of TB control in the US military. Our results, with this finding, emphasize the importance of TB surveillance that includes monitoring LTBI, to detect and characterize continued transmission, evaluate ongoing prevention efforts, and to better focus and target policies and practices.

3.7   Acknowledgements

Chapter 3, in full, is currently being prepared for submission for publication of the material. Tang JJ, Macera CA, MacGregor AJ, Woolpert T, Jain S, Woodruff SI, and Galarneau MR. Latent Tuberculosis Infection in Health Care Workers in the United States Navy. The dissertation author was the primary investigator and author of this paper.
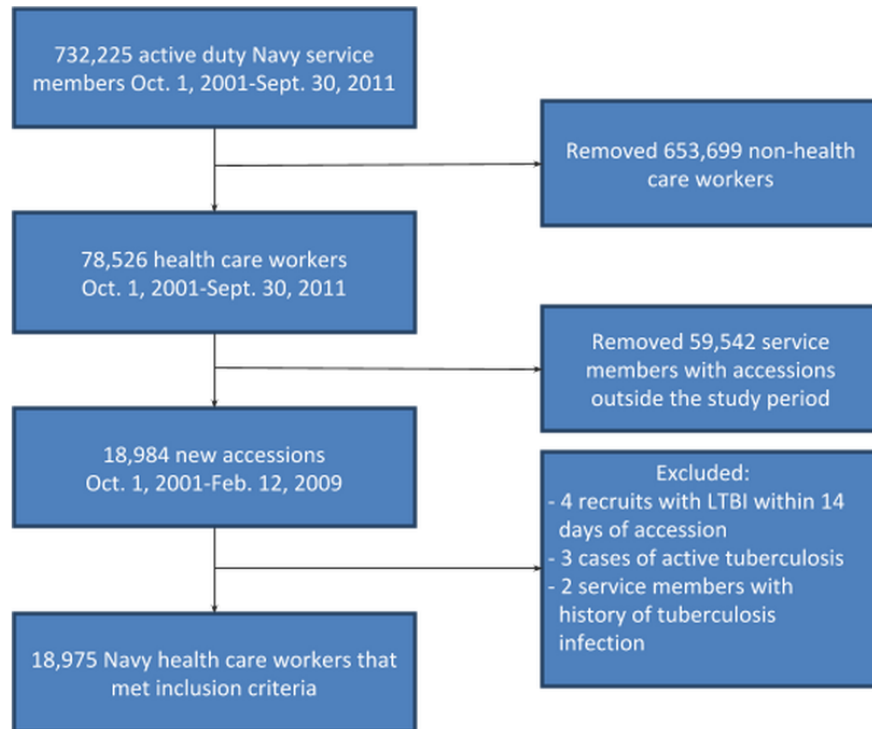
Figure 3.1: Study Sample Flowchart

Table 3.1: Select Characteristics of Active Duty Navy Health Care Workers (October 1, 2001-February 12, 2009)

Characteristic	Total (n=18,975)		Non-LTBI converters (n=18,649)		LTBI converters (n=326)		p-value
	n	(%)	n	(%)	n	(%)	
Demographics							
Age at accession (years; mean [SD][1])	20.4	[3.7]	20.4	[3.7]	21.1	[4.3]	0.017[2]
Gender							0.219
Men	13867	(73.1)	13619	(98.2)	248	(1.8)	
Women	5108	(26.9)	5030	(98.5)	78	(1.5)	
Race[3]							<0.001
White	11463	(60.5)	11358	(99.1)	105	(0.9)	
African American	3605	(19)	3508	(97.3)	97	(2.7)	
Asian/Pacific Islander	2022	(10.7)	1923	(95.1)	99	(4.9)	
Other	1858	(9.8)	1834	(98.7)	24	(1.3)	
Ethnicity[4]							0.138
Non-Hispanic	14738	(80.3)	14489	(98.3)	249	(1.7)	
Hispanic	3607	(19.7)	3533	(97.9)	74	(2.1)	
Country of birth (overall)[5]							<0.001
United States	16513	(91.5)	16290	(98.6)	223	(1.4)	
Foreign	1543	(8.5)	1448	(93.8)	95	(6.2)	
Country/region of birth (global)[5]							<0.001[6]
United States	16513	(91.5)	16290	(98.6)	223	(1.4)	
Europe/Canada	280	(1.6)	275	(98.2)	5	(1.8)	
Africa	206	(1.1)	180	(87.4)	26	(12.6)	
Asia/Pacific Islands	337	(1.9)	315	(93.5)	22	(6.5)	
Mexico	207	(1.1)	193	(93.2)	14	(6.8)	
Central America/Caribbean	291	(1.6)	275	(94.5)	16	(5.5)	
South America	222	(1.2)	210	(94.6)	12	(5.4)	
Service history							
Rank							0.098
Enlisted	16926	(89.2)	16626	(98.2)	300	(1.8)	
Warrant/commissioned officer	2049	(10.8)	2023	(98.7)	26	(1.3)	
Time in service							<0.001[7]

Table 3.1: Select Characteristics of Active Duty Navy Health Care Workers (October 1, 2001-February 12, 2009), continued

Characteristic	Total (n=18,975)		Non-LTBI converters (n=18,649)		LTBI converters (n=326)		p-value
	n	(%)	n	(%)	n	(%)	
Less than 1 year	1770	(9.3)	1761	(99.5)	9	(0.5)	
1 year	2391	(12.6)	2364	(98.9)	27	(1.1)	
2 years	3293	(17.4)	3260	(99)	33	(1)	
3 years 0	2214	(11.7)	2172	(98.1)	42	(1.9)	
4 years	2608	(13.7)	2552	(97.9)	56	(2.1)	
5 years	4060	(21.4)	3967	(97.7)	93	(2.3)	
6 years	2182	(11.5)	2136	(97.9)	46	(2.1)	
7 years	457	(2.4)	437	(95.6)	20	(4.4)	
Overseas duty station							0.034
Yes	3665	(19.3)	3617	(98.7)	48	(1.3)	
No	15310	(80.7)	15032	(98.2)	278	(1.8)	
Combat deployment history							
Iraq, Kuwait or Afghanistan	5418	(28.6)	5380	(99.3)	38	(0.7)	<0.001
Iraq	3598	(19)	3583	(99.6)	15	(0.4)	<0.001
Afghanistan	473	(2.5)	470	(99.4)	3	(0.6)	0.066
Kuwait	1347	(7.1)	1327	(98.5)	20	(1.5)	0.494

Table 3.1: Select Characteristics of Active Duty Navy Health Care Workers (October 1, 2001-February 12, 2009), continued

Characteristic	Total (n=18,975)		Non-LTBI converters (n=18,649)		LTBI converters (n=326)		p-value
	n	(%)	n	(%)	n	(%)	
Health care occupation							
Physician	620	(3.3)	610	(98.4)	10	(1.6)	0.838
Nurse	674	(3.6)	669	(99.3)	5	(0.7)	0.047
Dental	1740	(9.2)	1707	(98.1)	33	(1.9)	0.548
Laboratory	547	(2.9)	539	(98.5)	8	(1.5)	0.641
General hospitalman/corpsman	16861	(88.9)	16567	(98.3)	294	(1.7)	0.443
Surgical technician	449	(2.4)	443	(98.7)	6	(1.3)	0.529
Medical administration	496	(2.6)	491	(99)	5	(1)	0.218
Pharmacy	265	(1.4)	262	(98.9)	3	(1.1)	0.634[8]
Preventive medical technician	149	(0.8)	149	(100)	0	(0)	0.189[8]
Mental/physical Therapy	164	(0.9)	161	(98.2)	3	(1.8)	0.761[8]

[1]standard deviation

[2]Wilcoxon-Mann-Whitney test

[3]missing 27

[4]missing 630

[5]missing 919

[6]Monte Carlo estimate of Fisher's exact test

[7]Cochran-Armitage trend test

[8]Fisher's exact test
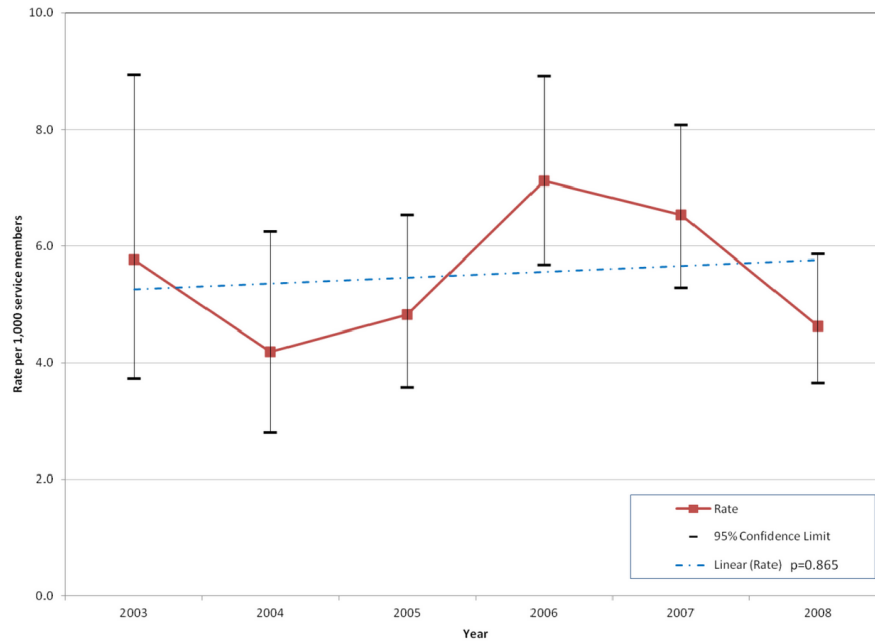
Figure 3.2: Latent Tuberculosis Infection Incidence Rates in Navy Health Care Workers (2003-2008)

Table 3.2: Risk Factors of Latent Tuberculosis Infection in Navy Health Care Workers. Adjusted Cox Proportional Hazard Model. Hazard Ratio, 95% Confidence Interval (October 1, 2001-February 12, 2009)

Characteristic	Hazard Ratio	(95% Confidence Intervals)
Demographics		
Age at accession (years)	1.02	(0.99-1.05)
Race		
White	reference	-
African American	2.11	(1.56-2.85)
Asian/Pacific Islander	4.48	(3.33-6.02)
Other	1.6	(1.02-2.49)
Country/region of birth		
United States	reference	-
Europe/Canada	1.46	(0.60-3.55)
Africa	6.68	(4.22-10.58)
Asia/Pacific Islands	2.06	(1.29-3.30)
Mexico	4.64	(2.63-8.16)
Central America/Caribbean	3.25	(1.94-5.45)
South America	3.3	(1.83-5.93)
Service history		
Rank		
Enlisted	1.17	(0.66-2.07)
Warrant/Commissioned Officer	reference	-
Time in service (years)	1.04	(0.97-1.11)
Overseas duty station	0.47	(0.34-0.64)
Combat deployment history		
Iraq	0.13	(0.07-0.22)
Afghanistan	0.21	(0.07-0.66)
Health care occupation		
Nurses	0.62	(0.20-1.89)

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Chapter 4

Adverse Events Related to Latent Tuberculosis Infection Treatment in the United States Military

4.1 Abstract

Background: Treatment of latent tuberculosis infection (LTBI) is a key component of tuberculosis control in the United States (US). Because tuberculosis is a concern in the military, service members with LTBI are routinely treated, even though treatment may lead to adverse events. However, there are no studies of active duty US military personnel investigating LTBI treatment-associated adverse events. The objectives of this study were to quantify the rate of adverse events and identify associated risk factors among those treated for LTBI.

Methods: This retrospective study used demographic, medical, and pharmacy data from all active US duty military service members treated for LTBI from October 1, 2001 through September 30, 2011. The outcomes of interest included hepatic, gastrointestinal, hematologic, allergy, poisoning, and peripheral neuropathy adverse events occurring from the starting date until 14 days after the end of the prescription interval. The main exposures of interest were the type of LTBI treatment and potential confounders such as sociodemographic characteris-

tics, vitamin B6 co-prescriptions, and certain pre-existing conditions. A logistic regression model for any adverse event was developed to generate odds ratios (OR) and 95% confidence intervals (CI).

Results: During this study period, 74,537 people were prescribed LTBI treatment, of which 96% (71,427) were dispensed isoniazid and 4% (3,110) rifampin. About 7.0% of service members experienced an adverse event and while the number of service members starting treatment decreased over time (p<0 .001), the percent with adverse events did not change during the study period (p=0.914). Isoniazid was a risk factor for any adverse event compared to rifampin (OR: 1.4, 95% CI 1.2-1.7) while having vitamin B6 co-prescribed was associated with lower odds of any adverse event (OR: 0.7, 95% CI 0.7-0.8). Compared to service members younger than 25 years, the odds of having any adverse event increased as age group increased (35-44 years, OR: 1.3, 95% CI 1.2-1.5; 45-54 years, OR: 1.6, 95% CI 1.3-2.0; 55+ years, OR: 4.2, 95% CI 1.8-9.8).

Conclusions: The decision to treat LTBI in military populations requires careful consideration of the risk of reactivation, the benefits of treatment, and the risk of treatment-related adverse events.

4.2   Introduction

An estimated 11 million persons have latent tuberculosis infection (LTBI) in the United States (US).[1] While the current incidence of active tuberculosis (TB) in the US is low (3.0 cases per 100,000) most active TB cases occur among people who were exposed in the past, developed a latent infection, and then later developed active TB.[1,2] Approximately 5-10% of people with LTBI will develop active TB.[3,4] For this reason, identification and treatment of LTBI is a key component of TB control.[5] Military personnel have an increased risk of TB infection due to military deployments, assignments to high incidence regions, and close contact with refugees and displaced persons.[6,7] Additionally, environments such as ships, barracks, and other housing and working arrangements involve close contact with others for extended periods of time, which can facilitate person-to-person trans-

mission. Because TB is a heightened concern in the US military, service members are routinely screened for TB and those who test positive for active TB or LTBI are prescribed treatment.[8–11]

While treating LTBI is important for TB control, the probability of developing active disease after LTBI and the risk of adverse events related to treatment must be carefully evaluated. Isoniazid (INH), the preferred medication for LTBI treatment, has been shown to be very effective, but is associated with notable adverse events.[5] In particular, hepatotoxicity has been reported in a number of studies.[12–16] Lower rates of adverse events have been reported with an alternative LTBI treatment, rifampin (RIF).[17] In response to concerns about adverse events related to LTBI treatment, in 2004 the Centers for Disease Control and Prevention (CDC) began a national project to monitor severe LTBI treatment-associated adverse events and quantify and characterize these events, particularly hepatic ones.[12] Recent studies have reported rates for any adverse events from LTBI treatment ranging from 4.4%-9.4% within the general population.[14,18–21] No research on LTBI treatment-associated adverse events among active duty military has been reported. The objectives of this study were to quantify adverse events of interest and assess their association with LTBI treatment, controlling for other potential risk factors among active duty US military service members.

4.3 Methods

4.3.1 Study Design and Study Population

For this retrospective population-based study active duty service members were identified through the Pharmacy Data Transaction Service system, stored within the Military Health System Data Repository (MDR). Eligible service members were active duty military personnel with pharmacy and outpatient or inpatient records between October 1, 2001 and September 30, 2011 who were dispensed medication for LTBI treatment. LTBI prescriptions were defined as the dispensing of 300 mg daily or 900 mg twice weekly by mouth of INH, with a minimum prescription interval of 30 days dispensed; if INH was not dispensed, RIF with

an oral dose of 600 mg, prescribed for at least 30 days; or, if there was a regimen change, the sequential use of INH and RIF was considered an LTBI case if RIF was dispensed 7 to 180 days after INH was last dispensed. These definitions are based on the treatment guidelines recommended for LTBI.[5] Those dispensed RIF and pyrazinamide (PZA) simultaneously were included because this regimen was a viable treatment option during the study period.[5] Service members who were dispensed INH in combination with PZA and/or ethambutol (EMB) within 30 days, or if RIF was dispensed in combination with EMB within 30 days, were excluded, since these combinations are prescribed as treatment for active TB and other mycobacterial diseases.[22–24]

4.3.2   Data Sources

Medical and pharmacy data were obtained from MDR, which contains information on all outpatient and inpatient visits occurring in military hospitals and clinics, civilian care covered by TRICARE insurance (military insurance) and all outpatient prescriptions dispensed inside and outside the US at military treatment facilities, managed care support contractors, and TRICARE mail order pharmacies. Medical diagnoses were recorded using the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) system. Demographic and career information were obtained from the Career History Archival Medical Personnel System (CHAMPS), a database maintained at the Naval Health Research Center.[25]

4.3.3   Outcome of Interest

The outcomes of interest were the occurrence of particular adverse events in six categories: hepatic (e.g. noninfectious or toxic hepatitis), gastrointestinal (e.g. dyspepsia, vomiting), hematologic (e.g. thrombocytopenia), allergy (e.g. dermatitis), poisoning, or peripheral neuropathy. The individual adverse events of interest in each category were identified from outpatient and inpatient visits using ICD-9-CM codes that were used, in part, in a previous study (see Table 4.1).[15]

Service members were considered at risk for any adverse event from the date their prescription began until 14 days after the end of the prescription interval.

4.3.4 Covariates

The main exposure of interest was the type of treatment for LTBI, which was dichotomized into two treatments: INH or RIF. Service members that changed LTBI treatment from INH to RIF remained in the INH group for analyses. A concomitant course of vitamin B6 was also assessed because it was common practice within the Department of Defense TB control program during the study period to prescribe it with LTBI treatment to prevent peripheral neuropathy and central nervous system effects, though current guidelines only recommend it for select groups.[5] Age at the start of LTBI treatment was calculated using the date of the first LTBI prescription and date of birth and divided into five categories: 17-24 years, 25-34 years, 35-44 years, 45-54 years, and 55 years and older. Additional variables such as gender, race, ethnicity, marital status, educational level, branch of service, rank, and occupation were also evaluated. Race was categorized as white, African American, Asian/Pacific Islander, and other, while ethnicity was categorized as Hispanic and non- Hispanic. Marital status was categorized as married, never married, and divorced/separated/other. Educational level was dichotomized into high school diploma or equivalent and some college or more. Branch of service was separated into Army, Air Force, Marine Corps, Navy, and Coast Guard. Military rank was divided into three categories: junior enlisted, midlevel/senior enlisted, and warrant/commissioned officers. Occupation was based on the Department of Defense Conversion Index and categorized into infantry, health care, and other.[26] Five pre-existing medical conditions were assessed: diabetes mellitus; HIV/AIDS; carcinoma in situ; malignant neoplasms and neuroendocrine tumors; and viral hepatitis, chronic liver disease, cirrhosis or other liver disorders. Pre-existing medical conditions were identified from ICD-9-CM codes from all outpatient and inpatient visits that occurred prior to the start of LTBI treatment (see Table 4.2).

4.3.5 Data Analysis

The Cochran-Armitage trend test was used to test for trends in the number of service members starting treatment and the proportion of adverse events observed by year. Differences in proportions of the presence to absence of any adverse event for demographic categorical variables were tested using Pearson's chi-square or Cochran-Armitage trend test for age. Variables that were below 0.1 p-value threshold were included in the final multivariable model. A logistic regression model was used to evaluate the associations of each risk factor with any of the LTBI adverse events of interest. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Multicollinearity was tested using variance inflation factor with a cutoff of less than five. The final model fit was assessed using the Hosmer and Lemeshow Goodness-of-Fit Test. Additional analyses on LTBI treatment and select covariates (vitamin B6, pre-existing medical conditions, age at the start of treatment, gender, and service) using Pearson's chi-square for categorical variables or Cochran- Armitage trend test for age were performed to evaluate differences that assisted in understanding the treatment patterns and the population. Two-sided hypotheses testing with an alpha level of 0.05 was used, unless otherwise specified. Analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC). This study was reviewed and approved by the San Diego State University, University of California San Diego, and Naval Health Research Center Institutional Review Boards, San Diego, California.

4.4 Results

During the study period, 74,537 people were prescribed LTBI treatment. Of those, 71,427 were prescribed INH (including 981 who were initially prescribed INH and later transferred to RIF), and 3,110 prescribed RIF. In the first full calendar year of data, 2002,10,392 service members started LTBI treatment; the count decreased continuously to 3,566 service members in 2010, the last full year of the study period (p<0.001). While the number of service members that started LTBI treatment decreased from 2002-2010, the percentage of adverse events observed

did not. See Figure 4.1.

The study population consisted largely of White (48.8%) non-Hispanic (81.1%) men (85.0%). The average age at the start of treatment was 25.5 years old (median 24.0 years, standard deviation=6.7) and most were enlisted (92.1%). Of the 74,537 service members on LTBI treatment, 7.0% had an adverse event. Service members who experienced any adverse event were older at the start of LTBI treatment (p<0.001). Approximately 77% of service members treated were dispensed a concomitant course of vitamin B6. Higher percentages of adverse events were found among service members who were in the Air Force, women, married, had some college, were non-Hispanic, were non-White, served as a health care specialist, had select pre-existing medical conditions, were dispensed INH, and not dispensed a concomitant course of vitamin B6 (Table 4.1).

The percentage of any adverse event by LTBI treatment differed by medication: 7 .0% associated with INH treatment and 6.1% for RIF (p<0.038, See Table 4.4). Adverse events most commonly documented were allergy (4.0%) and hepatic (2.1%). No statistically significant differences were observed for hepatic events by LTBI treatment (p=0.188).

Age at the start of treatment, gender, race, ethnicity, marital status, education, service, occupation, treatment medication, vitamin B6, and four pre- existing medical conditions (diabetes mellitus; HIV/AIDS; malignant neoplasms and neuroendocrine tumors; and viral hepatitis, chronic liver disease, cirrhosis or other liver disorders) were found to be associated with adverse events of interest via chi-square test (p<0.1 as seen in Table 4.3) and therefore included in the final model (Table 4.5). Controlling for demographic characteristics, service members treated with INH had increased odds of any adverse event compared to RIF (OR=1.43, 95% CI 1.22-1.69) while a concomitant course of vitamin B6 was found to be protective (OR=0.71, 95% CI 0.66-0.77). The likelihood a service member experienced any adverse event was higher with older age at treatment onset, after 35 years, and increased for each 10 year increment. From 35-44, the OR was 1.30 (95% CI 1.17-1.45), for 45-54 the OR was 1.62 (95% CI 1.29-2.03), and for 55 and older, the OR was 4.20 (95% CI 1.80-9.78) compared to 17-24 years old, controlling for

all other variables. Women (OR=1.42, 95% CI 1.32-1.53) compared to men also had higher odds. Service members with pre-existing medical conditions such as diabetes mellitus (OR=1.53, 95% CI 1.15-2.04), HIV/AIDS (OR=2.06, 95% CI 1.14-3.71), malignant neoplasms and neuroendocrine tumors (OR=1.47, 95% CI 1.07-2.03), and viral hepatitis, chronic liver disease, cirrhosis or other liver disorders (OR=2.77, 95% CI 2.19-3.49) had increased odds of experiencing any adverse event. Race, ethnicity, and education were not significant in the model. Tests for multicollinearity and the Hosmer and Lemeshow Goodness-of-Fit Test were not significant (p=0.240) suggesting the model did not have issues with multicollinearity and the data fit the model well.

Additional analyses found that vitamin B6 was concomitantly prescribed with INH 80.3% (57,322 people) of the time (data not shown). Adverse events occurred in 6.7% of those treated with INH and B6 compared to 8.5% of those that were on INH alone (p<0.001). No statistically significant differences were observed in peripheral neuropathy rates among those prescribed INH and B6 compared to INH alone (p=0.750). INH was dispensed more often to women (97.1% vs. 95.6% men p<0.001), younger service members (Cochran-Armitage trend test p <0.001), and service members in the Air Force and Navy (97.9% for both vs. 96.5% Coast guard, 94.5% Marine Corps, and 93.1% Army, p<0.001). Additionally, service members with certain pre-existing medical conditions, such as diabetes, malignant neoplasms and neuroendocrine tumors, and viral hepatitis, chronic liver disease, cirrhosis or other liver disorders, were more likely to have been prescribed RIF (p<0.05). No statistically significant differences in risk of any adverse or hepatic event were observed among the 54 people who were dispensed the RIF plus PZA treatment regimen (p=0.24, p=1.000, respectively) compared to those dispensed other regimens.

4.5   Discussion

This is the first study to attempt to quantify the relationship between LTBI treatment regimen, adverse events, and additional risk factors among active duty

military service members. The overall percentages of adverse and hepatic events and related risk factors found in this study were comparable to previously published studies in civilians.

The number of service members who started LTBI treatment dramatically decreased over the time period of the study, with over 10,000 service members starting LTBI treatment in 2002 and under 4,000 starting treatment in 2010, while the percent of those that experienced an adverse event did not change. This decrease in service members being treated is likely due to the change in TB testing policies in the military. During the study period the Air Force (2005), Coast Guard (2005), Army (2008), and the Navy/Marine Corps (2009) revised their TB policies to align more with CDC's recommendations for targeted testing programs (testing only people that are at increased risk for TB infection).[27-30] This change may have resulted in fewer personnel being tested for TB, which may have led to fewer cases identified, in turn leading to fewer service members starting treatment.

The 7.0% rate of any adverse events found in the study fell within the range of similar recently published studies that evaluated INH and RIF use in the general population (4.4%-9.4%).[14,18-21] Service members treated with INH had significantly higher overall adverse events than those prescribed RIF, which is supported by existing literature. Recent studies found adverse event rates ranging from 5.7%-17.7% in those treated with INH and 3.1%-8.3% in those treated with RIF.[14,16,18-21,31,32] With an estimated LTBI reactivation rate is 5-10% and the risk of treatment-associated adverse events, LTBI treatment is still important and estimated to prevent 44-55 active TB cases per 1,000 people treated.[33] Lack of significant association via chi-square test of hepatic events with INH in this study was interesting, given that a recent meta -analysis found INH caused significantly more events of hepatotoxicity than RIF.[17] In five recent studies, the reported rates of hepatotoxicity in those treated with either INH or RIF ranged from 1.4%-6.1% for INH and 0.0%-2.0% for RIF, though two studies found no statistically significant difference between INH and RIF.[14,18-21] A possible explanation for the lack of association between hepatotoxicity and treatment found in this study could be due to the outcome definition. When service members attend monthly clinical evaluation

appointments, detection of adverse events generally relies on clinical evaluations rather than biochemistry testing, which may detect true cases of hepatotoxicity that may not be clinically significant. While RIF is associated with fewer adverse events than INH, unfortunately, limited efficacy and clinical data combined with numerous drug interactions prevent RIF from being the preferred treatment over INH.

While 88% of the study population was less than 35 years old when treatment was started, the odds of any adverse event increased as age increased: 30% at 35-44, 62% at 45-54, and 420% at 55 and older, compared to 17-24 years controlling for all other variables in the model. This is likely due to person's diminished capacity to heal bodily damage as you get older. This supports existing literature reports of increasing risk with older age among those that were treated for LTBI.[15,32]

Service members with diabetes, HIV/AIDS, malignant neoplasms and neuroendocrine tumors, or viral hepatitis, chronic liver disease, cirrhosis or other liver disorders had increased odds of adverse events, which are in alignment with the results of a recent study.[15]

Women have been previously shown to have a higher risk of adverse events during INH LTBI treatment.[16,31,32] Possible explanations for the gender differences could be related to LTBI treatment dose, body weight, and adherence. The recommended dose for daily LTBI treatment is 5 mg/kg for INH (maximum dose 300 mg daily) and 10 mg/kg for RIF (maximum dose 900 mg daily). Tablet formulations and single pill preferences may cause some people that weigh less than 60 kg to receive the max dose. This may occur more frequently in women since they tend to weigh less than men. Additionally, women have been reported to have higher treatment completion rates, which could also explain the gender differences found in our study.[16,32]

In our study population, vitamin B6 was concomitantly prescribed with INH more than 80% of the time, and 4% with RIF. Vitamin B6 is only recommended for pregnant women, people with seizure disorders, and people with health conditions in which neuropathy is common (e.g., diabetes, uremia, alcoholism, mal-

nutrition, and HIV/AIDS) yet was widely dispensed in our population.[5] In the full model, vitamin B6 was found to reduce the odds of any adverse event by 29%. Adverse events occurred at a lower rate among those treated with INH and B6 compared to those that were prescribed INH alone. Peripheral neuropathy associated with INH is occasionally seen in patients taking INH, but is unusual in healthy individuals and usually prevented by concomitant prescription of vitamin B6.[5,22] Our study found no significant statistical differences specifically with peripheral neuropathy with B6 and INH versus INH alone.

LTBI treatment differed by gender and age; a higher percentage of women were on INH than men and service members prescribed RIF were older. Additionally, service members with select pre-existing medical conditions, such as diabetes, malignant neoplasms and neuroendocrine tumors, and viral hepatitis, chronic liver disease, cirrhosis or other liver disorders, were more likely prescribed RIF. Differences in treatment are likely related to treatment recommendations and concerns for adverse events.[5] About 1.3% of service members were initially prescribed INH and then later switched to RIF. The percent of adverse events and hepatic events among those that switched from INH to RIF were significantly higher when compared to those that did not switch. Reasons why these service members changed LTBI medication were unknown for this study, but are likely related to the occurrence of an adverse event or issues with adherence (RIF regimens are shorter than INH).[5] During the beginning of this study period, the RIF and PZA regimen was a viable short treatment option, but became no longer recommended after August 2003.[34] Thus only 54 people were dispensed this combination, with no statistical significance with any adverse or hepatic event. Despite controlling for variables such as a higher proportion of women, increased likelihood of being dispensed INH, and older age when starting treatment, individuals in the Air Force, Navy, and Army exhibited an elevated risk (data not shown). This may be related to unknown factors in environmental exposures, access to care, and willingness to report adverse events.

The primary strength of this study is its large population size, including all active duty military personnel from all military branches over a 10 year period,

which allows for the evaluation of the main LTBI treatment modalities, risk factors, possible confounding of other variables, and detection of small effects. A number of published studies use data from TB clinics or public health clinics in the general population, where LTBI treatment is only recommended; this study draws from a population where it was military policy that all active duty service members with LTBI be treated.[27–30,35–38] Additionally, the results represent outcomes in a young, healthy population, which was not previously evaluated. Another strength is the utilization of comprehensive, centralized military health and administrative information systems, which captures all pharmacy and medical information on all active duty service members, even while stationed overseas.

Our study's main limitations stem from using health administration databases for research. The pharmacy data utilized for this study lacked information on the specific purpose of medications being dispensed and can only be extrapolated based on the medication, dosage, and strength. However, the treatment for LTBI is limited to the use of INH and RIF. While INH or RIF may be prescribed for active TB and other mycobacterial diseases, those regimens include simultaneous co-prescription of at least two other mycobacterial agents (e.g. RIF, PZA, or EMB) or have different dosages and lengths of time prescribed, both of which would have excluded the subject from the study. Since ICD-9-CM codes were used in case definitions, in some cases there is the potential for misdiagnoses. However, all diagnoses reported in this study originated from government-reimbursed private clinics and credentialed providers at military treatment facilities, both of which are required to perform monthly audits and medical coding accuracy reports by the US Department of Defense. Due to these quality controls, there is no reason to suspect widespread misclassifications occurred. Lastly, concomitant medications used during the course of the LTBI treatment were not evaluated. While some information is available, there was too much variability to accurately categorize other medications into groups for adjustment.

4.6   Conclusions

Adverse events can negatively impact the adherence to and efficacy of LTBI treatment. Identifying the rates of such events and associated risk factors in a military population may assist researchers and providers in being more cognizant of those that may be susceptible to an adverse event. For example, adverse events from INH and the combination of RIF and PZA were observed after their clinical use became more widespread.[12,34] The overall adverse event rates were low and risk associations reported in our study were similar to those found in previously published literature. The data sources used in this study are a promising potential source for monitoring adverse events on a larger scale (i.e., populations like the military). Adverse events caused by LTBI treatment limit the effectiveness of the TB control program. The risk of reactivation and the benefit of treating LTBI must be carefully weighed against the risk of adverse events associated with LTBI treatment.

4.7   Acknowledgements

Chapter 4, in full, is currently being prepared for submission for publication of the material. Tang JJ, Macera CA, Woolpert T, MacGregor AJ, Woodruff SI, Jain S, and Galarneau MR. Adverse Events Related to Latent Tuberculosis Infection Treatment in the United States Military. The dissertation author was the primary investigator and author of this paper.

Table 4.1: ICD-9-CM Codes for Adverse Events

Adverse events	ICD-9-CM codes
Hepatic	277.4, 570, 571.4, 572.8, 573, 573.1, 573.3, 573.8, 576.8, 780.7, 782.4, 789.1, 789.2, 789.5, 790.4, 790.5, 790.6, 794.8
Allergy	693.0, 287.0, 693, 695.1, 695.9, 698.9, 780.6, 782.1, 995.2, 995.3
Gastrointestinal	536.8, 555, 564, 562.0, 562.1, 564.1, 783.0, 783.2, 783.3, 787.0, 789.0
Hematologic	284.8, 287.2, 287.4, 287.5, 288
Poisoning	960, 960.6, 961, 961.8, E930, E931.8, E930.6
Peripheral neuropathy	356.8, 356.9, 357.6, 357.89, 357.9

Table 4.2: ICD-9-CM Codes for Pre-existing Medical Conditions

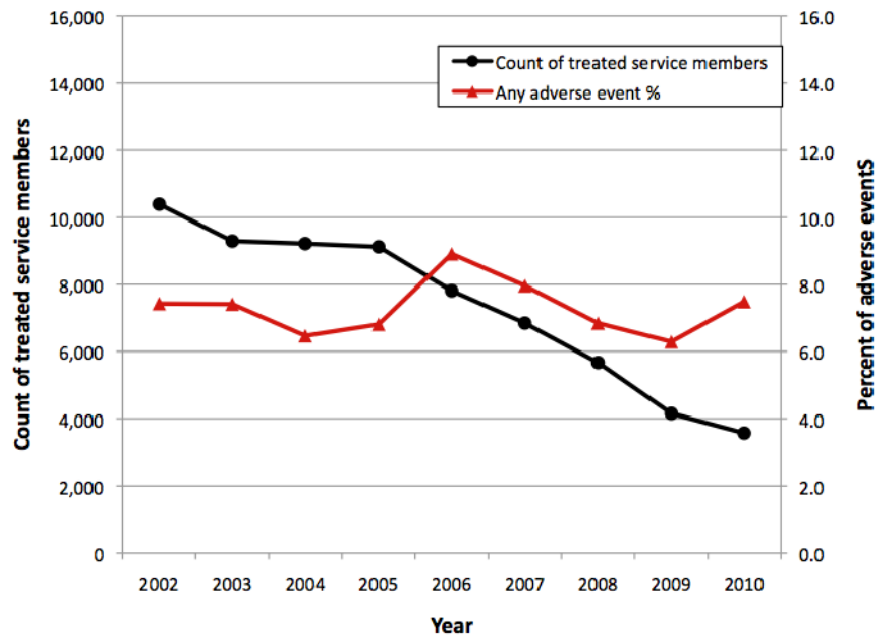| Medical conditions	ICD-9-CM codes
Diabetes mellitus	250
HIV/AIDS	42
Viral hepatitis	70
Chronic liver disease and cirrhosis	571
Other disorders of liver	573
Carcinoma in situ	230-234
Malignant neoplasms and neuroendocrine tumors	140-209

Figure 4.1: Count of Service Members that Started Latent Tuberculosis Infection Treatment and Percentage of those that Experienced Any Adverse Event (2002-2010).

Table 4.3: Select Characteristics of Active Duty Military Service Members Treated for Latent Tuberculosis Infection (2001-2011).

Characteristic	Total (n=74,537)		No adverse events (n=69,314)		Any adverse events (n=5,223)		p-value[4]
	n	(%[1])	n	(%[2])	n	(%[2])	
Latent tuberculosis infection treatment							
Treatment[3]							0.038
Isoniazid	71427	(95.8)	66393	(93)	5034	(7)	
Rifampin	3110	(4.2)	2921	(93.9)	189	(6.1)	
Vitamin B6 (concomitant course)	57447	(77.1)	53607	(93.3)	3840	(6.7)	<0.001
Demographics							
Age at start of treatment (years)					<0.001[5]		
17-24	41695	(55.9)	38959	(93.4)	2736	(6.6)	
25-34	24073	(32.3)	22386	(93)	1687	(7)	
35-44	7817	(10.5)	7127	(91.2)	690	(8.8)	
45-54	918	(1.2)	816	(88.9)	102	(11.1)	
55	34	(0.0)[6]	26	(76.5)	8	(23.5)	
Gender							<0.001
Men	63327	(85)	59145	(93.4)	4182	(6.6)	
Women	11210	(15)	10169	(90.7)	1041	(9.3)	
Race[7]							0.044
White	35811	(48.8)	33383	(93.2)	2428	(6.8)	
African American	19879	(27.1)	18428	(92.7)	1451	(7.3)	
Asian/Pacific Islander	13260	(18.1)	12283	(92.6)	977	(7.4)	
Other	4408	(6)	4090	(92.8)	318	(7.2)	
Ethnicity[8]							0.001
Non-Hispanic	59442	(81.1)	55179	(92.8)	4263	(7.2)	
Hispanic	13825	(18.9)	12948	(93.7)	877	(6.3)	
Marital status[9]							<0.001
Never married	39438	(53)	36901	(93.6)	2537	(6.4)	
Married	33299	(44.7)	30744	(92.3)	2555	(7.7)	
Divorced/separated/other	1738	(2.3)	1608	(92.5)	130	(7.5)	

Table 4.3: Select Characteristics of Active Duty Military Service Members Treated for Latent Tuberculosis Infection (2001-2011), continued.

Characteristic	Total (n=74,537)		No adverse events (n=69,314)		Any adverse events (n=5,223)		p-value[4]
	n	(%[1])	n	(%[2])	n	(%[2])	
Education[10]							<0.001
High school diploma or equivalent	60020	(81.2)	55916	(93.2)	4104	(6.8)	
Some college or more	13851	(18.8)	12768	(92.2)	1083	(7.8)	
Service history							
Service							<0.001
Marine Corps	10541	(14.1)	10118	(96)	423	(4)	
Army	24496	(32.9)	22956	(93.7)	1540	(6.3)	
Air Force	13226	(17.7)	11967	(90.5)	1259	(9.5)	
Navy	25529	(34.3)	23571	(92.3)	1958	(7.7)	
Coast Guard	745	(1)	702	(94.2)	43	(5.8)	
Rank[11]							0.126
Junior enlisted	36961	(49.6)	34383	(93)	2578	(7)	
Midlevel/senior enlisted	31610	(42.5)	29420	(93.1)	2190	(6.9)	
Warrant/commissioned officers	5892	(7.9)	5441	(92.4)	451	(7.7)	
Occupation[12]							<0.001
Other	49307	(66.9)	45957	(93.2)	3350	(6.8)	
Infantry	18910	(25.7)	17545	(92.8)	1365	(7.2)	
Health care specialist	5506	(7.5)	5043	(91.6)	463	(8.4)	

Table 4.3: Select Characteristics of Active Duty Military Service Members Treated for Latent Tuberculosis Infection (2001-2011), continued.

Characteristic	Total (n=74,537)		No adverse events (n=69,314)		Any adverse events (n=5,223)		p(value[4]
	n	(%[1])	n	(%[2])	n	(%[2])	
Pre-existing medical conditions							
Diabetes mellitus	443	(0.6)	386	(87.1)	57	(12.9)	<0.001
HIV/AIDS[13]	87	(0.1)	73	(83.9)	14	(16.1)	0.001
Carcinoma in situ	85	(0.1)	81	(95.3)	4	(4.7)	0.406
Malignant neoplasms and neuroendocrine tumors	380	(0.5)	335	(88.2)	45	(11.8)	<0.001
Viral hepatitis, chronic liver disease, cirrhosis, or other liver disorders	503	(0.7)	409	(81.3)	94	(18.7)	<0.001

[1] Column percent

[2] Row percent

[3]If a change in regimen occurred during the course of therapy, service members were classified according to the initial regimen dispensed.

[4]Pearson's chi-square

[5]Cochran-Armitage trend test

[6]less than 0.05%

[7]missing 1,179

[8]missing 1,270

[9]missing 62

[10]missing 666

[11]missing 74

[12]missing 814

[13]human immunodeficiency virus/acquired immune deficiency syndrome

Table 4.4: Adverse Events by Latent Tuberculosis Infection Treatment (2001-2011).

Outcomes	Isoniazid[1] (n=71,427)		Rifampin (n=3,110)		Total (n=74,537)	
	n	%	n	%	n	%
Any adverse event	5034	7	189	6.1	5223	7
Hepatic	1510	2.1	55	1.8	1565	2.1
Allergy	2881	4	128	4.1	3009	4
Gastrointestinal	375	0.5	12	0.4	387	0.5
Hematologic	51	0.1	6	0.2	57	0.1
Poison	418	0.6	9	0.3	427	0.6
Peripheral neuropathy	139	0.2	2	0.1	141	0.2

[1]If a change in regimen occurred during the course of therapy, service members were classified according to the initial regimen dispensed.

Table 4.5: Characteristics Associated with any Adverse Event Among Military Service Members that Received Treatment for Latent Tuberculosis Infection 2001-2011 (n=74,537). Adjusted Logistic Regression Model.

Characteristic	Odds Ratio	(95% Confidence Interval)
Latent tuberculosis infection treatment		
Treatment[1]		
Isoniazid	1.43	(1.22-1.69)
Rifampin	reference	
Vitamin B6 (concomitant course)	0.71	(0.66-0.77)
Demographics		
Age at start of treatment (years)		
17-24	reference	
25-34	1.04	(0.97-1.12)
35-44	1.3	(1.17-1.45)
45-54	1.62	(1.29-2.03)
55	4.2	(1.80-9.78)
Gender		
Men	reference	
Women	1.42	(1.32-1.53)
Race		
White	reference	
African American	1.03	(0.96-1.11)
Asian/Pacific Islander	1.05	(0.97-1.13)
Other	1.06	(0.93-1.20)
Ethnicity		
Non-Hispanic	reference	
Hispanic	0.98	(0.90-1.06)

Table 4.5: Characteristics Associated with any Adverse Event Among Military Service Members that Received Treatment for Latent Tuberculosis Infection 2001-2011 (n=74,537). Adjusted Logistic Regression Model, continued.

Characteristic	Odds Ratio	(95% Confidence Interval)
Marital status		
Never married	reference	
Married	1.14	(1.07-1.22)
Divorced/separated/other	0.99	(0.81-1.20)
Education		
High school diploma or equivalent	reference	
Some college or more	0.99	(0.91-1.07)
Service history		
Service		
Marine Corps	reference	
Army	1.29	(1.14-1.45)
Air Force	2.28	(2.03-2.57)
Navy	1.67	(1.49-1.88)
Coast Guard	1.38	(0.99-1.94)
Occupation		
Other	reference	
Infantry	1.09	(1.01-1.17)
Health care specialist	1.08	(0.98-1.20)

Table 4.5: Characteristics Associated with any Adverse Event Among Military Service Members that Received Treatment for Latent Tuberculosis Infection 2001-2011 (n=74,537). Adjusted Logistic Regression Model, continued.

Characteristic	Odds Ratio	(95% Confidence Interval)
Pre-existing medical conditions		
Diabetes mellitus	1.53	(1.15-2.04)
HIV/AIDS[2]	2.06	(1.14-3.71)
Malignant neoplasms and neuroendocrine tumors	1.47	(1.07-2.03)
Viral hepatitis, chronic liver disease, cirrhosis, or other liver disorders	2.77	(2.19-3.49)

[1]If a change in regimen occurred during the course of therapy, service members were classified according to the initial regimen dispensed.

[2]human immunodeficiency virus/acquired immune deficiency syndrome

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Chapter 5

Overall Conclusions and Discussion

5.1 Research Contributions

Tuberculosis (TB) has long been a concern in the military, as it can have an effect on operational readiness and has the potential to spread among members. The identification and treatment of latent tuberculosis infection (LTBI) is a key component of TB control.[1] With limited information on LTBI among military service members available and no global LTBI reporting system, exploring new ways to monitor LTBI is important to the overall goal of infection control. The goals of this research were to: 1) investigate a novel approach to monitor LTBI, 2) calculate conversion rates and identify risk factors among Navy health care workers (HCWs), and 3) quantify treatment-associated adverse event rates and analyze the association with LTBI medication. This research was conducted using electronic medical and pharmacy data obtained from the Military Health System Data Repository (MDR), which contains information on all outpatient and inpatient visits seen in military hospitals and clinics, civilian care covered by TRICARE military insurance, and all outpatient prescriptions dispensed inside and outside the US at military treatment facilities, managed care support contractors, and TRICARE mail order pharmacies. Medical diagnoses were recorded using the *International*

Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) system. Demographic factors, duty stations, career information, and occupation were obtained from the Career History Archival Medical Personnel System (CHAMPS).[2] Deployment information was obtained from the Defense Manpower Data Center.[3] The results of this research are important to providers and policymakers that are invested in TB control in the military, as it demonstrates the ability to monitor LTBI and identify risk factors for conversion and treatment-associated adverse events.

5.2 Summary of Findings

5.2.1 Concordance of Pharmacy and Medical Records for Surveillance of Latent Tuberculosis Infection in the United States

This study sought to determine the concordance of pharmacy and medical records for LTBI among US active duty military service members. During the study period, October 1, 2001 through September 30, 2011, 3,089,436 active duty military personnel had both pharmacy and medical records. There were 321,592 medical records from 114,542 service members with LTBI diagnosis documented, and 357,819 pharmacy records from 74,537 service members with LTBI prescriptions. Of those with LTBI prescriptions, 94.5% (70,446) were prescribed isoniazid (INH), 4.2% (3,110) were prescribed rifampin (RIF), and 1.3% (981) were initially prescribed INH then later prescribed RIF.

Overall, LTBI prevalence rates ranged from 1.7% to 4.3% in service members depending if there was match between pharmacy and medical records, only pharmacy record present, only a medical record present or the presence of either record was used. Approximately 39% of service members that had records indicating LTBI in either pharmacy or medical records had records matching within 180 days of each other. Calculated prevalence rates fell within the range of other published studies on the US military during this study period (0.5%-4.3%), and

included a number of TB exposure events.[4-9] This study found LTBI diagnoses occurred frequently without any corresponding LTBI prescriptions and to a lesser degree, LTBI prescriptions lacked corresponding LTBI diagnoses.

The agreement between pharmacy and medical records was high at 97.4% with the majority of service members having no record of an LTBI diagnosis or prescription. Moderate concordance was observed between the LTBI medical and pharmacy data sources ($\kappa = 0.55$; 95% CI 0.54-0.55). Sensitivity of LTBI prescriptions using LTBI medical diagnoses as a reference was relatively low at 46.6% and the specificity was high at 99.3%. The positive and negative predictive values were relatedly high at 70.3% and 98.0%, respectively.

Combined with the military's policy to treat those who are diagnosed with LTBI, the results of this study suggest that a centralized military medical system, particularly utilizing pharmacy data, would be useful in identifying and tracking LTBI cases in the absence of a global tracking system.[10-13]

5.2.2 Latent Tuberculosis Infection in Health Care Workers in the United States Navy

This study identified 18,975 HCWs from October 1, 2001 through February 12, 2009. The overall crude incidence of LTBI was 1.71% (326 cases) with an incidence density rate of 4.60 (95% CI 4.12-5.13) cases per 1,000 person- years. From 2003-2008, during years that annual incidence rate was calculated, no statistically significant trend was observed. The sample consisted largely of US-born, non-Hispanic, white men. The average age at accession was 20.4 years with an average of 3.8 years of service by the end of the study. The majority of the sample was enlisted hospitalmen/corpsmen without an overseas duty and without deployments to Iraq, Kuwait, or Afghanistan. LTBI cases were slightly older at the age of accession, non-white, foreign born, in the Navy longer, historically stationed within the US, not deployed to Iraq, and non- nurses compared to non-cases.

In the final Cox regression model, cases diagnosed with and treated for LTBI were more likely to be foreign born, non-white, in the military longer, with no overseas duty stations, and no deployments to Iraq or Afghanistan compared

to non-cases. Navy HCWs born in Africa had over six times the hazards of LTBI compared to US born HCWs. A Latin American country of birth had increased hazards as well; Mexico had more than four times the hazards of LTBI while Central and South America had over three times the hazards. Asian/Pacific Islander race had the highest hazards in the race category, while Asia/Pacific Islands as a country/region of birth had lower hazards than Africa and Latin America. Nonwhite race was significantly associated with LTBI even when controlling for country of birth. It may be that these racial groups and foreign-born service members were exposed to TB through other avenues, such as personal travel to foreign countries with high TB prevalence or other personal contacts, such as living with a foreignborn family member.[4,14] Combat deployments to Iraq and Afghanistan and overseas duty stations had a protective effect even though Iraq and Afghanistan have higher prevalence rates of TB compared to the US.[15] It is possible that service members with overseas duty stations and deployments to Iraq and Afghanistan may not experience prolonged, frequent, or close contact with foreign nationals or with persons with infectious TB.

Overall, annual incidence rates of LTBI among HCWs in the Navy were low and comparable to previous studies on Navy and Marine personnel. Most importantly, non-occupational factors, such as race and country/region of birth, appeared to be risk factors for LTBI, while service related factors such as overseas duty stations and Iraq or Afghanistan deployments were protective. These results demonstrate the importance of monitoring these service members in these nonoccupational groups.

5.2.3 Adverse Events related to Latent Tuberculosis Infection Treatment in the United States Military

From October 1, 2001 through September 30, 2011, 74,537 people were prescribed LTBI treatment. Of those, 71,427 were prescribed INH (including 981 who were initially prescribed INH and later transferred to RIF) and 3,110 prescribed RIF. The number of service members who started LTBI treatment dramatically decreased over the time period of the study, with over 10,000 service members start-

ing LTBI treatment in 2002 and under 4,000 starting treatment in 2010. Despite this statistically significant decrease, the percentage of adverse events observed remained constant.

The study population consisted largely of white, non-Hispanic men. The average age at the start of treatment was 25.5 years old and most service members were enlisted. The 7.0% rate of any adverse events found in the study fell within the range of similar recently published studies that evaluated INH and RIF use in the general population (4.4%-9.4%).[16–20] Service members who experienced any adverse event were older at the start of LTBI treatment and approximately 77% of those treated were dispensed a concomitant course of vitamin B6. A higher percentage of adverse events was found among service members who were in the Air Force, women, married, had some college, were non- Hispanic, were non-white, served as a health care specialist, had select pre- existing medical conditions, were dispensed INH, or not dispensed a concomitant course of vitamin B6.

In the final multivariable logistic regression model, service members treated with INH had increased odds of any adverse event compared to RIF (OR=1.43, 95% CI 1.22-1.69), while a concomitant course of vitamin B6 was found to be protective (OR=0.71, 95% CI 0.66-0.77), after controlling for demographic characteristics. While 88% of the study population was less than 35 years old when treatment started, the odds of any adverse event increased as age increased: 30% at 35-44, 62% at 45-54, and 420% at 55 and older, compared to 17-24 years, controlling for all other variables in the model. Women and service members with pre-existing medical conditions such as diabetes mellitus, HIV/AIDS, malignant neoplasms and neuroendocrine tumors, and viral hepatitis, chronic liver disease, cirrhosis or other liver disorders had increased odds of experiencing any adverse event.

Overall adverse event rates were low and risk associations reported in our study were similar to those found in previously published literature.[16–20] The complete health data available on a captured population like the military makes this type of pharmacoepidemiology research possible and our study results suggest that MDR is a potential source for monitoring adverse events related to medication on

a larger scale.

5.3 Limitations and Strengths

The limitations of this study stem from using health administration databases for research. The first limitation is that the pharmacy data utilized for this study lacked clinical indication on the specific purpose of medications being dispensed and the purpose could only be extrapolated based on the medication, dosage, and strength. However, the treatment for LTBI is limited to the use of INH and RIF, and while INH or RIF may be prescribed for active TB and other mycobacterial diseases, those regimens include simultaneous co-prescription of at least two other mycobacterial agents (e.g. RIF, PZA, or EMB) or have different dosages and lengths of time prescribed, both of which would have excluded the service member from this research. Additionally, inpatient prescriptions were not available until 2012 and could not be included in this research, though LTBI treatment is typically outpatient. Another limitation is the medical data. Since ICD-9-CM codes were used in case definitions, in some cases there is the potential for misdiagnoses of LTBI. However, all diagnoses reported in this study originated from government-reimbursed private clinics and credentialed providers at military treatment facilities, both of which are required to perform monthly audits and medical coding accuracy reports by the US Department of Defense. Due to these quality controls, there is no reason to suspect widespread misclassifications occurred. Finally, LTBI cases were defined as cases if an ICD-9-CM code for LTBI and LTBI appropriate treatment were present in medical and pharmacy records within 180 days from each other. This case definition would miss cases if an LTBI diagnosis was not documented or if LTBI treatment was not prescribed or was delayed more than 180 days after a diagnosis. However, it is military policy to treat LTBI cases if medically indicated and overseas duty stations and deployments do not affect or delay LTBI treatment. If LTBI treatment was not prescribed due to medical contraindications, those service members' risk factors will be missed and may drive those risk estimates towards the null.

The primary strength of this study is its large population size, including all active duty military personnel from all branches over seven to ten years. This allows for the evaluation of the main LTBI treatment modalities, risk factors, possible confounding of other variables, and detection of small effects. Another strength is the utilization of MDR and CHAMPS, which are comprehensive, centralized military health and administrative information systems, that capture all pharmacy and medical information on all active duty service members, even while stationed overseas and deployed and contains information on any changes to specific occupations, duty stations, and rank over the service member's entire military career. Lastly, it is military policy that all active duty service members diagnosed with LTBI be treated, leading to a more comprehensive set of data about the population; previously published studies used data from TB clinics or public health clinics in the general population, where LTBI treatment is only recommended.[10,21–27]

5.4   Future Directions

Due to the concern with TB in the military, the identification and treatment of LTBI is a cornerstone of TB control. This research presented a viable option for a global LTBI reporting system that allows for the monitoring of LTBI and treatment-associated adverse events. More research is needed on the viability and timeliness of maintaining the methodology presented here as an LTBI surveillance system. The changing demographics in the military and the shifting focus from the Middle East to Asia and the Pacific requires a surveillance system that can monitor the changing epidemiology over time. Future research should investigate the LTBI medication adherence and the interacting factors related to non-adherence. Treatment adherence and completion are imperative to effective LTBI control. This research was unable to investigate medication adherence due to changes in the preferred LTBI treatment during the study period. No published literature is available on LTBI treatment adherence in the military. Specific research should be performed on how the policy change to targeted testing programs has affected the different military branches. Only one study on targeted testing in

the military was available; it focused on recruits and had no trend data available.[28] Finally, going beyond LTBI, the methodology in the presented research suggests the use of the pharmacy and medical data to identify and monitor other diseases has potential. This type of pharmacoepidemiological research is a new area and the data involved has low collection and reporting biases making it a promising direction for the future.

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