ABSTRACT

Title of Document: ANALYSIS OF FACTORS ASSOCIATED WITH TUBERCULOSIS OUTCOMES IN DISTRICT KULLU, INDIA

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India is the country with the largest number of tuberculosis (TB) cases, contributing 20% of the global burden of infection (1) and 2 million cases annually (2). However, few if any studies have examined the epidemiology of TB in the Northern state of Himachal Pradesh.

This study is a retrospective review of medical records of all tuberculosis patients (N=1086) seen at the two hospitals in Manali, District Kullu, Himachal Pradesh, India between 2008 and 2011.

The analysis determined that being younger, female, living in a town, and/or a patient at Mission Hospital, were factors significantly associated with having extrapulmonary versus pulmonary tuberculosis (EPTB). Being older was associated with an increased likelihood of previous/complex treatment compared to new patients. Being female, from a town, and/or older was associated with receiving a non-standard regimen. Finally, patients who were previously treated/complex were significantly more likely to receive a non-standard regimen than new patients.

ANALYSIS OF FACTORS ASSOCIATED WITH TUBERCULOSIS OUTCOMES IN DISTRICT KULLU, INDIA

By

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Dedication

This work is dedicated to the people of Manali and District Kullu, India who continue to suffer unnecessarily from the burden of tuberculosis.

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Chapter 1: Introduction

I. Background

Tuberculosis, HIV/AIDS, and Malaria are considered the world's three most devastating infectious diseases (Hotez, et al., 2006). The disease is estimated to have resulted in 1.7 million deaths in 2009 (WHO, 2010) and 34.2 million disability adjusted life years (DALY's) in 2004 (WHO, 2004). The infection which is caused by *Mycobacterium tuberculosis* bacilli disproportionately affects countries in the developing world – particularly in South-East Asia and Africa (WHO, 2010). The global prevalence of tuberculosis in 2010 was 164 cases per 100,000 population, with an annual incidence rate of 140 cases per 100,000 population (WHO, 2010).

Due to its population of 1.2 billion people and the relatively high prevalence of the disease in the region, India is the country with the largest number of tuberculosis cases of any country in the world. It contributes 20% of the global burden of tuberculosis infection (SEARO/WHO, 2009) and nearly 2 million cases annually (RNTCP, 2011).

Given the high prevalence of tuberculosis in the Indian sub-continent, the distribution of the disease has been studied in detail in certain major urban centers and at the national level (SEARO/WHO, 2009). However, few if any studies have examined the distribution and risk factors for tuberculosis in the Northern state of Himachal Pradesh. Differences in socio-economic status, access to care, and topography of the region may impact the epidemiology of the disease in this region.

II. Research Question/Specific Aims

1. Overall Goal:

This research project seeks to contribute to an improved knowledge of tuberculosis infection among patients seen by two of the major healthcare providers in District Kullu, Himachal Pradesh – Lady Willingdon (Mission) Hospital and the government's Civil Hospital, by analyzing variations in the demographic composition of disease by hospital, site of infection, category of treatment, and type of treatment regimen received. The independent variables to be studied include age, gender, and residence (town vs. village), as well as the hospital where treatment was received and the treatment category the patient was prescribed. Efforts will also be made to identify further research questions and areas where additional study is needed. The research questions broadly fall into two categories: distribution of TB infection by demographic characteristics and characteristics by treatment regimen.

This research will contribute to the body of knowledge on the characteristic presentation of tuberculosis within the population of District Kullu. In order for effective public health systems to be in place and targeted control efforts to be utilized, baseline data on the distribution and risk factors for tuberculosis needs to be understood within the specific context of the population in this region.

2. Research Questions and Hypotheses to be tested:

Q1. Are the people seen at the government hospital different than those seen at the private hospital with regard to the demographic characteristics of: age, gender, or residence in village/town? (Descriptive)

Null Hypothesis: There will be no difference between the people seen at the government and private hospital with regard to the demographic characteristics of age, gender, and/or residence.

Alternative Hypothesis: There will be one or more differences between the people seen at the government and private hospital with regard to the demographic characteristics of age, gender, and/or residence.

Variables to Include:

- Age, Gender, Residence, Hospital

Q2. Is there an association between the demographic characteristics (age, gender, village/town), and site of TB infection (pulmonary, extrapulmonary-EPTB)? (Analytic)

Null Hypothesis: There will be no association between the demographic characteristics (age, gender, residence, and/or hospital) and the site of tuberculosis infection, adjusting for potential demographic characteristic confounders.

Alternative Hypothesis: There will be one or more associations between the demographic characteristics (age, gender, residence, and/or hospital) and the site of tuberculosis infection, adjusting for each of the other demographic characteristics, adjusting for potential demographic characteristic confounders.

Variables to Include:

- Independent Variables: Age, Gender, Residence, Hospital
- Dependent Variable: Site of Tuberculosis Infection (P/EP)

Q3. Is there an association between demographic characteristics and presenting with disease after treatment (DAT) – shown as classification in Category II/IV as opposed to a first instance of TB shown by classification in Category I/III? (Analytic) (see pg. 12 for more detail)

Null Hypothesis: There will be no association between the demographic characteristics (age, gender, residence, and/or hospital) and presenting with disease after treatment (DAT – Cat. I/III vs. Cat. II/IV), adjusting for potential demographic characteristic confounders.

Alternative Hypothesis: There will be one or more associations between the Demographic characteristics (age, gender, residence, and/or hospital) and presenting with disease after treatment (DAT – Cat. I/III (New) Cat. II/IV (Previously Treated/Complex - PTC)), adjusting for potential demographic characteristic confounders.

Variables to Include:

- Independent Variables: Age, Gender, Residence, Hospital
- Dependent Variable: Category of Treatment (N, PTC)

Q4. Is there an association between demographic variables and type of treatment regimen received?

Null Hypothesis: There will be no association between the demographic characteristics (age, gender, residence, and/or hospital) and type of treatment regimen received (standard vs. non-standard), adjusting for potential demographic characteristic confounders.

Alternative Hypothesis: There will be one or more associations between the demographic characteristics (age, gender, residence, and/or hospital) and type of treatment regimen received (standard vs. non-standard), adjusting for potential demographic characteristic confounders.

Variables to Include:

- Independent Variables: Age, Gender, Residence, Hospital
- Dependent Variable: Treatment Regimen (S, NS)

Q5. Is there an association between category of treatment and type of treatment regimen received (standard vs. non-standard), adjusting for all other covariates (demographic variables)?

Null Hypothesis: There will be no association between category of treatment (N, PTC) and type of treatment regimen received (standard vs. non-standard), adjusting for potential demographic characteristic confounders?

Alternative Hypothesis: There will be an association between category of treatment (N, PTC) and type of treatment regimen received (standard vs. non-

standard), adjusting for potential potential demographic characteristic confounders.

Variables to Include:

- Independent Variables: Category of Treatment (N, PTC)
- Dependent Variable: Treatment Regimen (S, NS)

The majority of the initial chi-squared tests have demonstrated statistically significant differences between the observed and hypothesized proportions of the independent variables (age, gender, residence, hospital), and dependent variables (treatment category, TB type, and regimen), and this led to further analysis. Univariate and multivariate-adjusted logistic regression will be performed to determine the associations between the independent and dependent variables explained above.

III. Background and Literature Review

1. Tuberculosis Treatment System in India:

Tuberculosis is treated in India by a complex system of public and private providers. All citizens of India are supposed to be able to access tuberculosis case detection and treatment services through the Government of India's Revised National Tuberculosis Control Program (RNTCP). The RNTCP principally implements a version of the World Health Organization's STOP TB recommended directly observed treatment short-course program (DOTS) (RNTCP, 2011). This program is intended to standardize case detection, treatment regimens, and improve program implementation. Treatment is provided in pre-formed patient-wise boxes based on patient weight through a system of more than 300,000 DOTS centres/providers (SEARO/WHO, 2009). However, many Indians prefer to seek treatment from private providers. While the RNTCP maintains strong records and thus is able to provide a relatively high quality of information, there is generally a dearth of data and information from the providers in the private sector. Furthermore, lack of infrastructure makes data collection difficult as patient records are recorded in hand-written TB registers, even in the government hospitals.

2. District Kullu, State of Himachal Pradesh:

Located in the far north of the country, much of the state of Himachal Pradesh lies in the Himalayan mountain range, with 90% of the population living in rural areas (*Census of India 2011: Administrative Atlas of India*, 2011). The mountainous terrain can make access to health facilities difficult, particularly for diseases requiring ongoing

treatment for many months or years, as is the case with tuberculosis. A survey by the National Rural Health Mission found that only 8.4% of the villages had Primary Health Centres (PHCs) and 17.4% had private clinics. It was found that there was a severe shortage of doctors, with only 15.5% of the villages having a doctor (Sciences, 2010).

Himachal Pradesh's status as a relatively advanced state means that little attention has been focused upon it with regard to diseases linked to poverty, including tuberculosis. Also, the state has an extremely low rate of HIV infection. HIV infection is an important risk factor for tuberculosis and has resulted in much higher incidence rates of TB in regions endemic with both HIV and TB. Because of its very low levels of HIV infection, this area serves as an important reference for understanding risk factors and distribution of tuberculosis in the absence of high rates of HIV. Analysis of risk factors for tuberculosis in the absence of high rates of HIV is critical because these factors are significantly altered by co-infection. Further, there remains a significant burden of tuberculosis that clearly impacts the functioning of society. Tuberculosis is identified by local medical practitioners as the greatest health problem affecting the region (personal communication P. Alexander, 2010).

Kullu is one of 12 districts in the state of Himachal Pradesh. The town of Manali is the home of two hospitals – one government (Civil) hospital, and the other a mission hospital (LWH). Due to the lack of quality health care available within much of the district and the state as a whole, many residents choose to seek care from one of the two hospitals in Manali. The population of the district was recorded in the 2011 Census as

437,474 – of which 91% live in rural areas (India, 2011). The district sex ratio is 950 females per 1000 males (India, 2011). As the major hub of care for the region, the two hospitals in Manali can provide much needed information on the distribution of tuberculosis in the community served, as well as features of the site of infection and the treatment received.

3. Mortality, Incidence and Prevalence of TB in India:

The South-East Asian Regional Office of the World Health Organization (SEARO/WHO) estimates that 331, 268 deaths in India in 2006 were due to tuberculosis (SEARO/WHO, 2009). In 2008, the incidence rate of tuberculosis in India was estimated to be 168 cases per 100,000 population and the prevalence rate 283 cases per 100,000 population for all forms of tuberculosis (SEARO/WHO, 2009). The rate of new infection does not appear to have decreased over the past two decades, despite the implementation of programs such as RNTCP (John, Dandona, Sharma, & Kakkar, 2011).

While efforts are being made to improve the quality of information and the estimates available regarding the prevalence and incidence of infection in India, even the current estimates contain uncertainty and few if any estimates are available at the district or state level. There are currently not routine notification data systems in place for measuring disease incidence and there is a considerable need to continue to improve the use of population-based surveys and to work towards the use of routine case notifications for more accurate estimates (SEARO/WHO, 2009).

4. Literature Review:

4.1 - Age:

In India, the majority of cases are found in the 15-54 year old age group (SEARO/WHO, 2009). However, in a study conducted in Iran, the majority of cases were among patients aged 55 and above (Khazaei, 2005). Another investigation in Taipei found a predominance of cases among patients aged 25-34 and above 65 years of age (Wang 2002). In contrast, a study conducted in Mexico found a linear trend associated with age (OR= 1.02 per year) (Bustamante-Montes et al., 2000). In a study of risk factors among household contacts of tuberculosis patients in The Gambia, age was associated with risk of infection. Risk of infection was highest among ages 25-34 and 35-49 year olds, (OR = 8.55, 95% CI: 6.31-11.58 and OR=8.35, 95% CI: 6.05-11.53, respectively) when compared to the age group 0-14 years (Lienhardt et al., 2003).

While there is some variation in the literature, much of the data supports the claim that tuberculosis most heavily effects the most productive groups in society, largely those aged 25-34 years. In some circumstances, older adults are also heavily impacted.

4.1.1 - Age and Site of TB Infection

Age is considered a risk factor for extrapulmonary tuberculosis (EPTB) in some scenarios. For example, a study conducted in France found that risk factors for EPTB, including age, varied according to area of birth. For patients born in Sub-Saharan Africa, age was associated with EPTB, however, this was not the case for individuals born in other regions, and this may be due in part to the high burden of co-infection with HIV in

Sub-Saharan Africa. The risk of EPTB in sub-saharan Africa was highest among individuals aged 40-59 years (OR=1.63, 99% CI=1.14-2.32) when compared to the reference group of 0-24 years (Cailhole et al., 2005). This study suggests that it may be important to consider interaction effects that may modify the association of age with tuberculosis outcomes. In contrast, a study from Taiwan found that the incidence of EPTB vs. pulmonary TB decreased significantly as age increased by decades, again compared to the referent age group 0-24 years (OR = 0.85, 95% CI = 0.75-0.95) (Lin et al., 2009). This evidence suggests that there are inconsistent findings on associations between age and type of tuberculosis, and that this association shows geographic variation.

4.1.2 - Age and Disease after Treatment

Little data exists on any associations between age and category of treatment. Those patients with a very young age are less likely to be Category II, because they are unlikely to have been previously treated. Similarly, one would expect the likelihood of being Category II versus I or III to increase with age, as the opportunity for previous disease and treatment grows over time. A study among children in Northern India found that among a total of 459 patients started on therapy, 323 patients were in Category I, 120 in Category III, 12 in Category II and 4 in Category IV. This means that 443 of the 459 pediatric patients (96.5%) were new patients and only 16 (3.5%) were patients who had previously been treated or were complex (Kabra, Lodha, & Seth, 2004). Therefore, disease after treatment is very unusual in young patients, and becomes more common as age increases.

Disease after treatment is a method of classification that is being used as a proxy for previous treatment resulting in treatment failure, default, or relapse, or for multi-drug resistant (MDR) TB cases. Literature on previously treated and MDR cases were reviewed for associations with age. A study of 11 countries by the WHO found that patients in all age groups above age 15 were significantly more likely to have resistant strains of tuberculosis than those aged 0-14 years; particularly age groups 35-44 years and 55-64 years (OR= 3.0, 95% CI: 1.7-5.3; OR=2.7, 95% CI: 1.5-3.8, respectively). Likelihood of resistance however was lowest in the age group over 65 years, after the youngest group, which was used as the reference (OR= 1.9, 95%CI: 1.0-3.4) (Espinal 2001). In a study of treatment non-adherence, which is a risk factor for treatment failure, relapse, and MDR (Category II and Category IV patients), older and younger age groups were identified as high-risk for non-adherence (Munro et al. 2007). Again, there is conflicting evidence in the literature about which age groups are most likely to experience disease after treatment. Children are least at risk, and the risk also appears to be low for older adults. Those in middle-age are at the highest risk of MDR (Category IV), however younger and older groups are more likely to be non-adherent, making them more likely to become (Category II).

4.1.3 - Age and Receipt of Treatment Regimen

To the best of my knowledge, little research has explicitly examined associations between age and receipt of a standard versus non-standard regimen. What has been studied is receipt of DOTS versus non-DOTS, which could serve as a proxy measure (DOTS- standard regimen; non-DOTS – non-standard regimen). Researchers in India

found that there was no significant difference in age among patients who received DOTS versus non-DOTS treatment (Balasubramanian et al., 2000). Studies have found that previous treatment is one of the most significant risk factors for MDR-TB. Estimates from the WHO indicate that patients who have previously been treated are 2.5 times more likely to develop MDR-TB then those who are new patients (OR= 2.5, 95%CI: 2.1-3.0) (Espinal 2001). Given the increasing complexity of the regimen for patients who have been previously treated or are suspected to be MDR, one would anticipate that these patients would be more likely to receive a non-standard regimen. This would suggest that patients in the age ranges of 35-44 and 55-64 years (Espinal 2001) would be the most likely to receive a non-standard regimen, as they are the most likely to have been previously treated and/or be MDR. It is believed that non-standard regimens lead to drug resistance and that this is more common in previously-treated patients and those that have received longer courses of therapy. Espinal et al. (2001) found that drug resistance was significantly associated with an overall prior treatment period of greater than or equal to 6 months(OR=7.6, 95%CI: 2.6-22.4), and that the risk increased with longer treatments. Evidence from their study supports the hypothesis that inappropriate and/or interrupted treatment resulted in higher rates of drug resistance among patients receiving longer courses of therapy previously (Espinal 2001). This suggests that there may also be an association between age and the receipt of a non-standard regimen, in the patients who are more likely to be treated in Category II or IV.

4.2 - Gender:

Indian men are disproportionately affected by TB at the country-level with a male-female ratio of newly detected cases of 2:1 (SEARO/WHO, 2009). In most countries, according to case notification figures, more men than women are diagnosed with tuberculosis, although this could be the result of sociological differences in access to care or biological differences, or a combination of both (Thorson and Garcia-Moreno, 2009). Epidemiologic data shows that there are differences between men and women in terms of "prevalence of infection, rate of progression from infection to disease, incidence of clinical disease, and mortality due to tuberculosis" (Diwan & Thorson, 1999). "The higher proportion of male cases consistently reported by TB programmes may accurately reflect a greater prevalence among men, or it may be an artifact of persisting geographic, socioeconomic, cultural, and health service-related barriers that disproportionately affect timely diagnosis and treatment in women" (Weiss et al. 2006).

A 2005 study from Iran, however, found that women resulted in 58.1% of the cases, although the proportion changed with older age (Khazaei 2005). According to reports on the global epidemiology of tuberculosis, the disease primarily affects men, particularly after adolescence (Dye, 2009; Holmes, Hausler, and Nunn, 1998). Recent analyses however, suggest that women of reproductive age have a higher propensity for developing TB disease after infection than men of the same age (Holmes, Hausler, and Nunn, 1998). Studies from the 1960's in Bangalore and Chingleput, India found the prevalence of tuberculosis was similar in males and females until the age of 14, after which the prevalence among men was 20-71% higher than the prevalence among females

(Gothi et al., 1974 and Baily et al., 1980 in Homes, Hausler, and Nunn, 1998). One study trying to determine whether gender differences in tuberculosis prevalence were due to biological differences or sociological factors found that the female/male "sex ratio of prevalent cases was similar or lower than that in notified cases, suggesting that F/M differences in notified cases may be largely due to epidemiological differences in biological risk by sex rather than to differential access to health care by gender." However, the authors suggest that these rates of notification may be distorted in parts of Asia (e.g. India) because so many patients are seen by private practitioners who rarely report case notifications accurately. Thus it is difficult to determine if gender differences in tuberculosis infection and treatment are the result of biological differences or socio-cultural factors (Borgdorff, Nagelkerke, Dye, and Nunn, 2000). In a study of risk factors among household contacts of tuberculosis patients in Africa, sex was determined to be a risk factor for infection. Women were less likely to be infected than men with tuberculosis (OR = 0.84, 95% CI: 0.73-0.97) (Lienhardt et al., 2003). Finally, a study comparing prevalence of tuberculosis among men and women in the National Family Health Survey of India rounds 2 and 3, found that the gender gap increased (more men were infected than women in both years, but the difference increased in the 3rd round), and that this difference was three times larger in rural areas then in urban areas (Sharma, Kumar, and Singh, 2010). A study of gender and TB in Bangladesh found that the Female/Male (F/M) ratio of individuals started on TB treatment was 0.35. They also found that this association declined steeply with age. The ratio for under age 15 was 2.20 and decreased to 0.08 among patients over age 65 (Begum et al. 2001). Given similar socio-cultural environments in India and Bangladesh, this research suggests that

the relationship between gender and tuberculosis may be modified by age. This may be in part due to the fact that younger women with children are likely to have more frequent contact with outpatient services because of their children (Begum et al. 2001).

Together, the literature indicates that men in India are more likely to be diagnosed with tuberculosis then women, and that this is the result of both biological and sociological differences.

4.2.1 - Gender and Type of Tuberculosis (P/EP)

Type of tuberculosis and site of infection are thought to be differentially affected by gender. A study of risk factors for extrapulmonary tuberculosis (EPTB) found that women were nearly twice as likely to develop EPTB as men (OR = 1.98, 95% CI: 1.25-3.13) (Yang et al. 2004). A study in the U.S. from 1993-2006 found that compared to pulmonary tuberculosis, cases of extrapulmonary TB were 1.7 times more likely to be female than male (OR = 1.7, 95% CI: 1.7-1.8) (Peto et al., 2009). A study from Taiwan also found that being female was an independent risk factor for EPTB when examined by multivariate regression (OR=1.69, 95%CI: 1.02–2.80) (Lin et al., 2009). The literature on site of infection and gender seems to consistently find that women are more likely to have EPTB then men.

4.2.2 - Gender and Treatment Category

Little information has been found on associations between gender and treatment category.. This may be due in part to the fact that treatment categories is an unusual outcome and is not typically studied. The proportion of new pulmonary smear-positive

and smear negative patients (Category I or III) that were women were each 31-32% according to a study conducted by the RNTCP (RNTCP 2004). Research on risk factors for MDR-TB found that women were slightly less likely than men to have a drug resistant strain (Category IV), however the association did not reach the level of significance (OR=0.93, 95%CI: 0.83-1.0) (Espinal 2001). Treatment category is directly related to patient adherence to tuberculosis treatment. Patients who fail to adhere to their treatment are much more likely to become Category II or Category IV cases (previously treated, MDR, complex) (Munro et al, 2007). Thus, differences in treatment adherence by gender may help to explain possible differences in treatment category by gender. Females were perceived as being more motivated to adhere to their treatment, but they are also more likely to have their access to treatment be mitigated by the requirement that they have permission from their father or husband and/or be accompanied to attain treatment (Munro et al. 2007). Two studies in this meta-analysis also found that female patients who were, or wanted to become, pregnant were less likely to adhere to their treatment because they perceived the medication to be harmful (Munro et al. 2007). Research from sites on multiple continents, including India, found that women are more likely to drop out during the course of diagnosis, while men are less likely to successfully complete treatment one started (Weiss et al. 2006). Either of these factors could lead to higher proportions of Category II/IV patients. Therefore, the evidence remains inconclusive as to whether there is an association between gender and category of treatment.

4.2.3 - Gender and Treatment Regimen

Researchers in India found that there was no significant difference in gender among patients who received DOTS versus non-DOTS treatment (Balasubramanian et al., 2000). Using DOTS vs. non-DOTS as a proxy for treatment regimen (DOTS = standard regimen), the study in India did find that women were less likely to receive DOTS, although this association was only marginally significant (p=.06). This suggests that women may be slightly more likely to receive a non-standard regimen than men. Women commonly cited social stigma as the reason for not receiving DOTS (Balasubramanian et al., 2000). A study of gender and tuberculosis in Bangladesh found that women had less access to public out-patient clinics than men (OR=0.86, 95%CI: 0.85-0.88) and that this lack of access to public services correlates with the higher use of private service providers among women in some situations (Begum et al. 2001). Given that accessing care from a private provider is causally linked to an increased risk of receipt of a non-standard regimen, this suggests that women may be more likely to receive a non-standard regimen because of their greater use of private providers.

4.3 - Residence:

Rural residence is associated with delays in accessing diagnosis and ongoing treatment for tuberculosis (Storla, Yimer, Bjune 2008). Research from a remote district in Southeastern Iran found that 67.1% of the tuberculosis cases were from rural villages, compared to 28.7% from urban areas (Khazaei 2005). Tuberculosis is often associated with urban areas due to crowded living which increases transmission of the infection. However, it is also associated with poverty and low socio-economic status which is a

feature of both rural and some urban areas of India. Rural villages in this part of India generally have higher levels of poverty. In Himachal Pradesh, 7.94% of the rural population lives below the poverty line, compared to 4.63% of the population in the urban areas (Planning Commission of Himachal Pradesh, 2002?). A study from the 1960's in Mysore District, India found that the prevalence of infection was 43.9% in semi-urban areas compared to 37.9% in rural villages (Narain et al., 1963). While not conclusive, the literature suggests that rural villages may have higher rates of TB than towns.

4.3.1 - Residence and Type of Infection

Residence has been associated with EPTB infection, with higher rates of EPTB found in semi-urban areas, however, this relationship is often confounded by HIV rates. A study in Malawi found that there was a significantly higher incidence of TB, particularly new smear-negative and extrapulmonary cases in semi-urban townships, compared to rural areas (Banerjee, Harries, Salaniponi, 1999). Higher rates of extrapulmonary TB are often due to high rates of co-infection with HIV.

4.3.2 – Residence and Category of Treatment

Little literature has been found on associations between residence and category of treatment. Category of treatment is directly related to accessing treatment over an extended period of time. Individuals living in rural areas (villages) are less likely to be able to access ongoing treatment and to adhere to their regimen, indicating that they may be more likely to fall into the previously treated/complex (PTC) category of treatment. A

study in Nepal found that treatment adherence (a predictor of category of treatment – non-adherence more likely to result in Cat. II/IV treatment) was associated with cost of travel to the TB treatment facility (versus no cost), which is likely to be greater for patients living in villages which are typically more remote (OR=3.0, 95%CI: 1.2-7.3) (Mishra et al., 2005). Patients who default from treatment are more likely to be Category II/IV. Research on default found that distance from home to treatment center was found to be positively associated with risk of default (HR=2.59, $p<0.001$) when walking distance of more than two hours to the nearest treatment center was compared to walking distance of less than two hours (Shargie & Lindtjorn 2007) .

4.3.3 - Residence and Treatment Regimen

Using DOTS vs. non-DOTS as a proxy for treatment regimen (DOTS = standard regimen), the literature suggests that patients who are not on DOTS are more likely to live far from the health center (Naing et al. 2001). This suggests that patients living in villages may be more likely to receive non-DOTS, and thus more likely to receive a non-standard regimen.

It is important to recognize that the distinction between village and town in the context of this study may be blurred and difficult to interpret. A number of areas designated as villages are on the perimeter of towns, and thus are actually very close to treatment centers, while others are inaccessible via road and require trekking for days to reach the facilities.

4.4 - Hospital type in India

Little data exists on the potential differences in risk of tuberculosis among patients seeking treatment at public vs. private providers in India, particularly when distinguishing mission/private hospitals from independent private practitioners. The public system of care is supposed to be free of cost, reducing the socio-economic determinants of diagnosis and care. However, in practice, government providers may demand payment, or the quality of care may be considered lower than at private providers. Less of a concern for risk of infection, but certainly a concern for treatment outcomes; some studies have found that private providers make more frequent errors in prescribing anti-tuberculosis treatment and are less likely to follow the standardized regimen developed by the government (Rao et al., 2000). A greater use of the private health sector has been reported among women aged 15-24 in India (George et al. 1997 in RNTCP 2004). While some policy analysts and medical providers view the private system as less effective in some cases for treating tuberculosis with standardized regimens, many patients in India remain dissatisfied with the quality of treatment they receive at government facilities, with the stigma they may face from government workers, and with the accessibility of the government healthcare providers. Many believe the quality of care received at the private practitioners is better, not based on empirical evidence, but simply on feeling and reputation (Narayanan, Santha, & Paul Kumaran).

4.4.1 – Hospital and Type of TB

At this time, no literature has been found on differences between public and mission/private hospitals and site of TB infection. It should be noted that extrapulmonary TB is more difficult to diagnose and often requires invasive procedures (including surgery) to obtain specimens for histopathological examination (Jawahar 2004). The government hospital has very limited, if any, surgical facilities, and thus may be less likely to identify extrapulmonary cases than the mission hospital which has excellent surgical facilities.

4.4.2 – Hospital and Category of Treatment

Category of treatment is based on the inclusion of second-line drugs. Categories II and IV include one or more secondary drugs, whereas Categories I and III are made up of first-line drugs only. Researchers in Gujarat, India found that public and private physicians differed significantly in their views of the effectiveness of second-line drugs. Private physicians were five times more likely to believe that second-line drugs were more effective than first line (Category I/III) drugs (37% compared to 7.1%) (Vyas, Small, & DeRiemer 2003). This suggests that patients at the private hospital may be more likely to receive Category II or IV treatments because of their inclusion of second-line drugs.

4.4.3 – Hospital and Treatment Regimen

Hospital type is most likely to be associated with treatment regimen received, because government hospitals are required to provide standardized DOTS regimens in India

through the RNTCP. Literature has been found on private providers being less likely to provide standardized regimens (Uplekar & Shepard 2004), however, this is not necessarily representative of the Mission hospital which used to participate as a DOTS center and is aware of the recommended standard regimen, whether they follow it or not. Also, the previous information presented on Indian private practitioners' belief in the increased effectiveness of second-line drugs could also indicate that private practitioners are more likely to prescribe a non-standardized regimen because they augment the regular regimen with additional second-line drugs.

4.5 - Category of Treatment and Type of Treatment Regimen Received

Little information was found on the possible association between category of treatment and receipt of a standard or non-standard regimen. One review of the tuberculosis control program in Tajikistan did find that MDR (Category IV) patients often did not receive one of the standardized regimens recommended by the international guidelines under WHO (WHO Europe 2009). This research also found that the patients who were most likely to not receive DOTS (standard) treatment were chronic or drug-resistant patients who would most likely be classified as Category II. Therefore, one would expect that placement in the previously treated/complex (PTC – Cat. II/IV) would be associated with receipt of a non-standard regimen.

While tuberculosis is generally a curable disease, it continues to exact an enormous toll on the country of India through lives lost and minimized productivity and the stress caused by the inability to work during the prime years of life (RNTCP, 2011). An

improved understanding of the groups of people most affected by TB in this region can help to target treatment programs, improve surveillance systems, and better understand the prescription of treatment regimens which in turn significantly affect treatment outcomes.

IV. Research Design and Methods

1. Study Design:

The study is a retrospective review of medical records of all tuberculosis patients seen at the two hospitals in the town of Manali, District Kullu, Himachal Pradesh, India. The majority of the data was obtained at the initial diagnosis of disease, making it cross-sectional in design.

2. Description of the Participants and Criteria for Selection:

Participants are all patients who visited the government or mission hospital and received a diagnosis of active tuberculosis disease between Jan 1, 2008 and Dec. 31, 2011. Patients under the age of 5 were excluded because of their different risk of infection and the variation in treatment. Patients who tested positive for their purified protein derivative (PPD+) only (latent infection) were also excluded, as they do not have active disease. Individuals missing data on any of the six variables analyzed were removed (N (original) = 1144, N (removed) = 58, N (total remaining) = 1086).

Table 1: Demographic Frequencies by Outcome of Site of TB Infection (N= 1086)		
	Site of TB Infection	
	Extrapulmonary, N(%)	**Pulmonary, N(%)**
Age (Mean, (SD))	32.17 (16.16)	35.11 (16.42)
Age (Categorical)	N (%)	N (%)
<=25	135 (12.43%)	293 (26.98%)
26-50	130 (11.97%)	341 (31.40%)
>50	38 (3.50%)	149 (13.72%)
Sex		
F	152 (14.00%)	299 (27.53%)
M	151 (13.90%)	484 (44.57%)
Residence		
Town	66 (6.08%)	121 (11.14%)
Village	237 (21.82%)	662 (60.96%
TOTAL	303 (27.90%)	783 (72.10%)

Table 2: Demographic Frequencies by Outcome of Treatment Category (N=1086)		
	Treatment Category	
	New, N(%)	**Previously Treated/ Complex (PTC), N(%)**
Age (Mean, (SD))	33.52 (16.72)	36.37 (15.32)
Age (Categorical)		
<=25	337 (31.03%)	91 (8.38%)
26-50	321 (29.56%)	150 (13.81%)
>50	135 (12.43%)	52 (4.79%)
Sex		
F	340 (31.31%)	111 (10.22%)
M	453 (41.71%)	182 (16.76%)
Residence		
Town	138 (12.71%)	49 (4.51%)
Village	655 (60.31%)	244 (22.47%)
TOTAL	793 (73.02%)	293 (26.98%)

Table 3: Demographic Frequencies by Outcome of Treatment Regimen (N=1086)

	Treatment Regimen	
	Standard (S), N(%)	**Non-Standard (NS), N(%)**
Age (Mean, (SD))	34.65 (16.26)	32.17 (17.35)
Age (Categorical)		
<=25	353 (32.50%)	75 (6.91%)
26-50	411 (37.85%)	60 (5.52%)
>50	164 (15.10%)	23 (2.12%)
Sex		
F	372 (34.25%)	79 (7.27%)
M	556 (51.20%)	79 (7.27%)
Residence		
Town	152 (14.00%)	35 (3.22%)
Village	776 (71.45%)	123 (11.33%)
TOTAL	928 (85.45%)	158(14.55%)

Table 4: Variable Frequencies by Hospital (N=1086)

	Hospital	
	LWH (Mission)	**CIVIL (Government)**
Age (Mean, (SD))	33.45 (16.40)	34.68 (16.39)
Age (Categorical)		
<=25	142 (13.08%)	286 (26.34%)
26-50	151 (13.90%)	320 (29.47%)
>50	53 (4.88%)	134 (12.34%)
Sex		
F	168 (15.47%)	283 (26.06%)
M	178 (16.39%)	457 (42.08%)
Residence		
Town	81 (7.46%)	106 (9.76%)
Village	265 (24.40%)	634 (58.38%)
TB Site		
EP	137 (12.62%)	166 (15.29%)
P	209 (19.24%)	574 (52.85%)
Treatment Category		
N	244 (22.47%)	549 (50.55%)
PTC	102 (9.39%)	191 (17.59%)
Regimen		
S	190 (17.50%)	738 (67.96%)
NS	156 (14.36%)	2 (0.18%)
TOTAL	740 (68.14%)	346 (31.86%)

3. Data Collection:

Data were collected from the Tuberculosis Registers (hand-written and excel files) maintained by each of the two hospitals in Manali for the years 2008-2011. Tuberculosis patients are recorded into these registers at the time of diagnosis. All information from the tuberculosis registers (medical records) were transcribed into an electronic format using Microsoft Excel. Then the variables of age, gender, residence, treatment category, site of infection, and treatment regimen prescribed were abstracted and standardized for use in data analysis.

4. Independent Variable Definition:

Information was collected from medical records on the following independent variables: age, gender, residence, hospital, and category of treatment.

4.1 - Age:

Age was collected as a continuous variable. In some cases, for the purpose of analysis, the variable was categorized into three groups (Var = Age_Cat3). The three age categories are: (A) </= 25 years; (B) 26-50 years; and (C) >50 years.

4.2 - Gender:

Gender was collected as a binary variable of either male or female

4.3 - Residence:

Residence information was collected initially based on village name recorded for patient's residence. These names were then classified as either a village or town based upon the 2011 Census records for Himachal Pradesh. If the name was listed as one of the 59 Census Towns in the State, it was assigned as a "Town", otherwise, if not classified as a town, the name was classified as a "Village".

A Census Town is defined by the 2011 Census of India as "a village with minimum population of 5000; population density of at least 400 persons/sq km; and where >75% of male main workers are engaged in non-agricultural activities (Census of India, 2011)).

4.4 - Hospital:

Information on hospital was collected based on the hospital where the patient was registered and received tuberculosis treatment. The two hospitals that were studied were the mission hospital: Lady Willingdon Hospital, and the government's hospital: Civil Hospital. Patients were classified as having been treated at one of these two hospitals.

4.5 - Category of Treatment:

Category of treatment was also used as an independent variable in one research question. Category of treatment was recorded in the medical records as one of fours categories – I, II, III or IV. The definitions of these categories are (Satyanarayana et al. 2010; WHO 2003):

Table 5: Treatment Categories WHO	
Category	**Type of Patients**
Category 1	New sputum smear-positive PTB New sputum smear-negative PTB, seriously ill New EPTB, seriously ill
Category II	Sputum smear-positive relapse Sputum smear-positive treatment failure Sputum smear-positive treatment after default
Category III	New sputum smear-negative, not seriously ill New EPTB, not seriously ill
Category IV	Suspect and Lab-Confirmed MDR (multi-drug resistant TB)

Table 6: Treatment Categories Revised	
Category	**Type of Patients**
New (N) – (WHO Cat. I/III)	New sputum smear-positive PTB New sputum smear-negative PTB, seriously ill New EPTB, seriously ill New sputum smear-negative, not seriously ill New EPTB, not seriously ill
Previously Treated/Complex (PTC) – (WHO Cat. II/IV)	Sputum smear-positive relapse Sputum smear-positive treatment failure Sputum smear-positive treatment after default Suspect and Lab-Confirmed MDR (multi-drug resistant TB)

Given changes to the categorization system, which now couples Categories I and III into a single Category I – and lack of accuracy in assigning patients into either Category II or IV because of uncertainty as to their resistance patterns, these four categories were then combined into two groups – N = newly treated patients (Cat. I and III), and PTC = Previously Treated or Complex patients (Cat. II and IV) (see Table: Categories Revised). Code 14 - Code 13 is a dosing for pediatric weight bands found occasionally in the data from Civil Hospital. These cases were classified as Category I if not otherwise specified, as the likelihood of a previously treated pediatric case is low.

5. Dependent Variable Definition:

Information was collected from medical records on the following dependent variables: category of treatment, site of infection, and treatment regimen.

5.1 - TB Type:

Site of Infection is listed in the medical records as either pulmonary or extrapulmonary. Definitions of site of infection are based on the 2003 WHO Tuberculosis Guideline definitions, as well as the clinical judgment of the physician.

"Pulmonary tuberculosis (PTB) refers to disease involving the lung parenchyma. Therefore tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.1

Extrapulmonary tuberculosis (EPTB) refers to tuberculosis of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Diagnosis should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of tuberculosis chemotherapy. The case definition of an extrapulmonary TB case with several sites affected depends on the site representing the most severe form of disease." (WHO 2003)

In the event that a patient was diagnosed with both pulmonary and extrapulmonary forms of tuberculosis, they were classified as pulmonary.

5.2 - Category of Treatment:

Category of treatment was recorded in the medical records as one of fours categories – I, II, III or IV. The definitions of these categories are as shown in the table and explanation above under the independent variable definition

5.3 - Treatment Regimen:

Treatment regimens were shown in different ways based upon the hospital where the patient was treated. For the Civil Hospital, standard pre-formed treatment boxes are provided to the patients based upon their weight and category of treatment. Thus, unless the patient from Civil Hospital was classified as NDI or NDII – standing for Non-DOTS Treatment, they were classified as having been given a standardized treatment regimen. The two patients who received ND II were classified as having received a non-standardized regimen. For the mission hospital, the drug names and dosages prescribed were recorded from the tuberculosis registers. These were then classified into standard or non-standard regimens, based upon the WHO tuberculosis treatment guidelines from 2003 and 2010. The definition of non-standard treatment was operationalized as follows:

Non-Standard if any of the following:

a. Dose not contain HRZE for Cat. I/III (Isoniazid-INH, Rifampicin, Pyrazinamide, Ethambutol)
b. Does not contain HRZES for Cat. II (Isoniazid-INH, Rifampicin, Pyrazinamide, Ethambutol, Streptomycin)
c. Augmented with second-line drugs (ex. Amikacin, Ethinoamide, etc.)
d. Dosage is less than minimum of range recommended by WHO 2003 (see tables 1 and 2 in appendix for reference) within 5kg weight bands
e. For Suspect MDR (multi-drug resistant TB) – must <u>not</u> contain R or H. If they received Ethionamide and Pyrazinamide + second line drugs, or a group of second-line drugs, then it was classified as Standard
f. If no weight was recorded for the patient, the reasonability of the dosages were assessed based upon how the drugs are generally prescribed. If the doses were within reason, the regimen was classified as Standard.

*Note: Patients could be classified as MDR (or Suspect-MDR) and still receive a "standard" regimen, if they were identified as MDR and their regimen followed the prinicples of any standardized MDR regimen (see e.).

6. Data Collection and Efforts to Reduce Bias

Significant efforts were made to reduce the possibility of bias in the collection of data. Data were obtained from handwritten TB registers of both the Civil and Mission Hospitals. In some circumstances, partial information was missing from the register. In these instances, the patients were contacted by telephone to verify details and to record any missing information. This enabled details of all variables to be available for all but ~50 records, out of more than 1000 patients. Patient records from the registers were also reviewed with the outpatient/tuberculosis staff at the hospitals, to ensure inclusion in proper categories and to minimize any misclassification.

7. Data Analysis:

Q1. Are the people seen at the government hospital different than those seen at the private hospital with regard to the demographic characteristics of: age, gender, or residence in village/town?

Descriptive analysis will be conducted by testing the differences between the observed and hypothesized proportions of each of the independent (age, gender, residence, hospital, category of treatment) and dependent variables (category of treatment, type of TB, and treatment regimen) using chi-squared analysis. Initial chi-squared tests revealed a number of significant differences between the observed and hypothesized proportions (see Table 9 in Appendix).

Q2. Is there an association between the demographic characteristics (age, gender, residence, hospital), and site of TB infection (pulmonary, extrapulmonary-EPTB)?

Analysis will begin with univariate analysis of the relationship between:

- The independent variable (age) and the dependent variable (site of TB infection);
- the independent variable (gender) and the dependent variable (site of TB infection);
- the independent variable (residence) and the dependent variable (site of TB infection);
- the independent variable (hospital) and the dependent variable (site of TB infection).

$$\text{Log (Odds) } y = \text{Intercept} + B_1X_1$$

$$\text{Log (Odds) Site of Infection} = B_0 + B_1 \text{ (age)}$$

$$\text{Log (Odds) Site of Infection} = B_0 + B_1 \text{ (gender)}$$

$$\text{Log (Odds) Site of Infection} = B0 + B1 \text{ (residence)}$$

$$\text{Log (Odds) Site of Infection} = B0 + B1 \text{ (hospital)}$$

Then, additional analysis of multivariate regression could be conducted to test for potential confounding.

$$\text{Log (Odds) } y = \text{Intercept} + B_1X_1 + B_2X_2 + B_3X_3 + B_4X_4$$

Confounders:

Among the variables for which data is available, age and gender are expected to be potential confounders. Previous research examining the outcome of site of infection considered gender and age to be confounders (Yang 2004).

Effect Modifiers:

Age and gender are hypothesized to be effect modifiers. The association between age and the outcome of site of TB infection is expected to be different for men and women (gender). This association is anticipated to differ when stratified by the third variable of gender. Similarly, it is anticipated that the association between gender and site of infection may be different between different age groups. Thus, interaction tests will be used to assess whether an interaction effect is present in this case. Then stratified analysis can be conducted to compare the stratum specific odds ratios. Research on site of infection of TB in Nepal found that the association between age and site of infection was different for men and women (Sreeramareddy 2008).

$$\text{Log (Odds) } y = \text{Intercept} + B_1(\text{age}) + B_2(\text{gender}) + (B_1(\text{age})*B_2(\text{gender}))$$

Q3. Is there an association between demographic characteristics and presenting with disease after treatment (DAT) – shown as classification in Category II/IV (PTC) as opposed to a first instance of TB shown by classification in Category I/III (N)?

Analysis will begin with univariate analysis of the relationship between:

- The independent variable (age) and the dependent variable (Category of Treatment);
- the independent variable (gender) and the dependent variable (Category of Treatment);
- the independent variable (residence) and the dependent variable (Category of Treatment);
- the independent variable (hospital) and the dependent variable (Category of Treatment).

$$\text{Log (Odds) } y = \text{Intercept} + B_1X_1$$

$$\text{Log (Odds) Category of Treatment} = B_0 + B_1 \text{ (age) Log}$$

$$\text{(Odds) Category of Treatment} = B_0 + B_1 \text{ (gender) Log}$$

$$\text{(Odds) Category of Treatment} = B_0 + B_1 \text{ (residence) Log}$$

$$\text{(Odds) Category of Treatment} = B_0 + B_1 \text{ (hospital)}$$

Then, additional analysis of multivariate regression could be conducted to test for potential confounding.

$$\text{Log (Odds) } y = \text{Intercept} + B_1X_1 + B_2X_2 + B_3X_3 + B_4X_4$$

$$\text{Example: Log (Odds) Category of Treatment} = B_0 + B_1 \text{ (gender)} + B_2 \text{ (age)}$$

Confounding:

Age is a potential confounder for associations looking at outcomes of category of treatment. Research examining gender differences in TB diagnosis and treatment adjusted for age in their presentation of odds ratios (Begum et al. 2001). Therefore, one may need to consider age as a potential confounder of the relationship between TB diagnosis and treatment.

Effect Modification:

It is hypothesized that there will be an interaction effect between age and gender. Interaction tests will be used to assess whether an interaction effect is present in this case. Then stratified analysis can be conducted to compare the stratum specific odds ratios.

For example, the association between age and the outcome of category of treatment may be different for men and women (gender). Thus interaction tests and crude odds ratios, stratified by gender will be examined to determine if effect modification is occurring. Similarly it is anticipated that the association between gender and category of treatment is different between different age groups. Research from Bangladesh has shown differences in the male/female ratio observed for diagnosis, corresponding to category of treatment when stratified by age (Begum et al. 2001).

Q4. Is there an association between demographic variables and type of treatment regimen received?

Analysis will begin with univariate analysis of the relationship between:

- The independent variable (age) and the dependent variable (Regimen);
- the independent variable (gender) and the dependent variable (Regimen);
- the independent variable (residence) and the dependent variable (Regimen);
- the independent variable (hospital) and the dependent variable (Regimen).

$$\text{Log (Odds) } y = \text{Intercept}(B_0) + B_1X_1$$

$$\text{Log (Odds) Regimen} = B_0 + B_1 \text{ (age) Log}$$

$$\text{(Odds) Regimen} = B_0 + B_1 \text{ (gender) Log}$$

$$\text{(Odds) Regimen} = B_0 + B_1 \text{ (residence) Log}$$

$$\text{(Odds) Regimen} = B_0 + B_1 \text{ (hospital)}$$

Then, additional analysis of multivariate regression will be conducted to test for potential confounding, particularly by hospital type. Hospital type is a potential confounder because it is causally associated with the outcome of interest of treatment regimen, due to the fact that the hospital type largely determines which treatment regimen is prescribed. It is also hypothesized to be associated with the exposures of age, gender and residence. No literature has been found to substantiate this hypothesis due to the unusual nature of the potential confounder and its specificity to this study, however, given the estimated strength of the association with the outcome of regimen and the suggested variability of the proportions of age, gender and residence between the two hospitals based on initial chi-squared analysis, it is reasonable to test for potential confounding.

$$\text{Log (Odds) } y = \text{Intercept} + B_1X_1 + B_2X_2 + B_3X_3 + B_4X_4$$

$$\text{Log (Odds) Regimen} = B_0 + B_1 \text{ (age)} + B_4 \text{ (hospital) Log}$$

$$\text{(Odds) Regimen} = B_0 + B_2 \text{ (gender)} + B_4 \text{ (hospital) Log}$$

$$\text{(Odds) Regimen} = B_0 + B_3 \text{ (residence)} + B_4 \text{ (hospital)}$$

I believe that there may also be several interaction effects and so therefore will consider effect modification in my final model between age and gender, age and hospital and gender and hospital.

$$\text{Log (Odds) Regimen} = B_0 + B_1\,(\text{age}) + B_2\,(\text{gender}) + (B_1(\text{age})*B_2(\text{gender}))$$

$$\text{Log (Odds) Regimen} = B_0 + B_1\,(\text{age}) + B_4\,(\text{hospital}) + (B_1(\text{age})*B_4(\text{hospital}))$$

$$\text{Log (Odds) Regimen} = B_0 + B_2\,(\text{gender}) + B_4\,(\text{hospital}) + (B_2(\text{gender})*B_4(\text{hospital}))$$

I hypothesize that the association between age and treatment regimen is different for men and women due to cultural attitudes related to both age and gender and sickness. I also hypothesize that there will be an interaction effect between age and hospital where the association between age and treatment regimen is different for the two different hospitals, and similarly the association between gender and treatment regimen is different for the two different hospitals because of differences in treatment practices and prescribing patterns.

Q5. Is there an association between category of treatment and type of treatment regimen received (standard vs. non-standard), adjusting for other covariates (demographic variables)?

Analysis will begin with univariate analysis of the relationship between:

The independent variable (Category of Treatment) and the dependent variable (Regimen);

$$\text{Log (Odds) } y = \text{Intercept} + B_1X_1$$
$$\text{Log (Odds) Regimen} = B_0 + B_1 \text{ (Category of Treatment)}$$

Then, additional analysis of multivariate regression will be conducted to test for potential confounding.

$$\text{Log (Odds) } y = \text{Intercept} + B_1X_1$$
$$\text{Log (Odds) Regimen} = B_0 + B_1 \text{ (Category of Treatment)} + B_2 \text{ (hospital)}$$

I believe that there may also be an interaction effect and so therefore will consider effect modification in my final model between category of treatment and age, and between category of treatment and hospital type.

$$\text{Log (Odds) Regimen} = B_0 + B_1 \text{ (Category of Treatment)} + B_2 \text{ (hospital)} + (B_1 \text{ (Category of Treatment)} * B_2 \text{ (hospital)})$$

It is unclear at this time whether hospital type is more likely to act as a confounder or an effect modifier, and since this exposure has not been studied in the literature, it is not possible to classify it based upon previous research. Thus, I propose to assess the interaction tests and crude odds ratios of the association between category of treatment and treatment regimen, stratified by hospital type, to determine whether hospital type is acting as either an effect modifier or a confounder in this instance.

V. Results:

Research Q1. Are the people seen at the government hospital different than those seen at the private hospital with regard to the demographic characteristics of: age, gender, or residence in village/town?

Q1 Results:

Signficant differences were found between patients at the government and mission hospitals according to chi-squared tests in the areas of:

- Age and Category of Treatment
- Age and Type of TB Infection (P/EP)
- Gender and Type of TB Infection
- Gender and Treatment Regimen
- Residence and Type of TB Infection
- Hospital and Type of TB Infection
- Hosptial and Treatment Regimen
- Hospital and Gender
- Hospital and Residence

In these analyses, the expected proportions differed significantly from the observed proportions.

Therefore we must reject the null hypothesis which stated that no significant differences would be observed between the patients from the two hospitals.

Research Q2. Is there an association between the demographic characteristics (age, gender, residence, hospital), and site of TB infection (pulmonary, extrapulmonary-EPTB)?

Null Hypothesis: There will be no association between the demographic characteristics (age, gender, residence, and/or hospital) and the site of tuberculosis infection, adjusting for potential demographic characteristic confounders.

Q2 Results:

Statistically significant associations were found between each of the independent variables (age, gender, residence, and hospital) and the dependent variable of site of infection (P).

Univariate Results (See Table 10):

- Age:

Older patients (Age Cat. C: 50+years) are 45% less likely to develop EPTB as opposed Pulmonary TB, when compared to the reference age group (Cat. A: 0-25years) (OR = 0.55, 95% CI: 0.37-0.83).

Patients in the middle age category were also slightly less likely than the youngest patients to have EPTB, however, this association did not reach the level of significance (OR = 0.83, 95% CI: 0.62-1.10).

- Gender:

  Females are 1.63 times as likely to develop EPTB rather than pulmonary TB compared to males (OR = 1.63, 95% CI: 1.25-2.13).

- Residence:

  Patients who live in villages are 34% less likely to develop EPTB versus pulmonary TB compared with patients who resided in towns (OR = 0.66, 95%CI: 0.47-0.92).

- Hospital:

  Patients attending LWH were 2.27 times as likely to have EPTB versus pulmonary TB compared to patients at Civil Hospital (OR = 2.27, 95% CI: 1.72-2.99).

Thus, being younger, being female, living in a town, and being a patient at LWH were all factors significantly associated with an increased likelihood of having EPTB.

Multivariate Adjusted Analysis (See Table 10):

Age and Sex were tested as potential confounders, however, neither appear to be confounding any of the above relationships. Age and Sex were also evaluated as effect modifiers, but were not found to be a significant interaction.

Therefore, we must reject the null hypothesis which states that there are no significant associations between the demographic variables and site of TB infection. After adjusting,

little significant change was found, so it appears that there is not any significant confounding.

Table 10: Question 2 Odds Ratios

	Outcome: TB Type (Extrapulmonary vs. Pulmonary)			
	Unadjusted		**Adjusted***	
Model	**Odds Ratio**	**95%CI**	**Odds Ratio**	**95%CI**
Age (B - 25-50 y.o. vs. A – 0-25 y.o.)	0.83	0.62 - 1.10	0.86	0.64 -1.16
Age (C – 50+ y.o. vs. A – 0-25 y.o.)	0.55	0.37 - 0.83	0.62	0.41 - 0.94
Sex (Female vs. Male)	1.63	1.25 - 2.13	1.47	1.12 - 1.94
Residence (Village vs. Town)	0.66	0.47 - 0.92	0.74	0.53 - 1.05
Hospital (LWH vs. Civil)	2.27	1.72 - 2.99	2.12	1.60 - 2.81

* Adjusted for all variables in the table.

Research Q3. Is there an association between demographic characteristics and presenting with disease after treatment (DAT) – shown as classification in Category II/IV (PTC) as opposed to a first instance of TB shown by classification in Category I/III (N)?

> Null Hypothesis: There will be no association between the demographic characteristics (age, gender, residence, and/or hospital) and presenting with disease after treatment (DAT – Cat. I/III vs. Cat. II/IV), adjusting for potential demographic characteristic confounders.

Q3 Results:

A statistically significant association was found between Age and Category of Treatment (Disease after Treatment – PTC).

Univariate Results (See Table 11):

- Age:

Patients in the middle age category (Age Cat. B: 26-50 years) were 1.73 times as likely to be a PTC patient, rather than new, compared to the youngest group (Cat. A: 0-25 years) (OR = 1.73. 95% CI: 1.28-2.34).

Patients in the oldest age category (C: 50+ years) were 1.43 times as likely to be a PTC patient, rather than new, when compared to the youngest group age 0-25 years, and this result is marginally significant (OR = 1.43, 95% CI: 0.96-2.12, p=0.08).

Thus, being older was associated with an increased odds of having been previously treated/complex, rather than a new patient.

Multivariate Adjusted Results (See Table 11):

Age was assessed as a potential confounder in testing each of the associations between the demographic variables and the outcome of category of treatment, but was determined not to be confounding any of the relationships.

Therefore, we must reject the null hypothesis which stated that there were no significant associations between the demographic variables and the outcome of disease after treatment/category of treatment.

In the final model, with the inclusion of all independent variables, age was the only demographic variable which was significantly associated with the outcome of disease after treatment/category of treatment (OR = 1.71, 95% CI: 1.26-2.31).

Table 11: Question 3 Odds Ratios

	Outcome: Category of Treatment (PTC vs. New)			
	Unadjusted		**Adjusted***	
Model	**Odds Ratio**	**95%CI**	**Odds Ratio**	**95%CI**
Age (B - 25-50 y.o. vs. A – 0-25 y.o.)	1.73	1.28 – 2.34	1.71	1.26 – 2.31
Age (C – 50+ y.o. vs. A – 0-25 y.o.)	1.43	0.96 – 2.12	1.39	0.93 – 2.07
Sex (Female vs. Male)	0.81	0.62 – 1.07	0.83	0.63 – 1.10
Residence (Village vs. True)	1.05	0.73 – 1.50	1.06	0.74 – 1.53
Hospital (LWH vs. Civil)	1.20	0.91 – 1.60	1.24	0.93 – 1.66

* Adjusted for all variables in the table.

Research Q4. Is there an association between demographic variables and type of treatment regimen received?

> Null Hypothesis: There will be no association between the demographic characteristics (age, gender, residence, and/or hospital) and type of treatment regimen received (standard vs. non-standard), adjusting for potential demographic characteristic confounders.

Q4 Results:

Age and sex were significantly associated with treatment regimen received. The association between residence and treatment regimen was marginally significant. Hospital type could not be included in the analysis because of the small number of Civil Hospital patients who received a non-standard regimen (N=2).

Univariate Results (See Table 12):

- Age:

  Patients in the middle age category (B: 26-50 years) are 31% less likely to receive a non-standard regimen, rather than the standard regimen compared to age category A (0-25 years) (OR = 0.69, 95% CI: 0.48-0.99).

Patients in the oldest age category (C: 50+ years) are 34% less likely to receive a non-standard regimen, rather than the standard regimen, compared to age category A (0-25 years), and this result is marginally significant (OR = 0.66, 95% CI: 0.40-1.09).

- Sex:

Females are 1.5 times as likely to receive a non-standard regimen, rather than the standard regimen, compared with males (OR = 1.50, 95% CI: 1.07-2.10).

- Residence:

Patients from villages are 31% less likely to receive a non-standard regimen, rather than the standard regimen, when compared to patients from towns, and this association is marginally significant (OR = 0.69, 95% CI: 0.46-1.04).

Multivariate Adjusted Results (See Table 12):

In the multivariate adjusted model including the variables of age, sex and residence, sex is the only variable which remains statistically significant. Age and Residence become marginally significant.

According to the final adjusted model, females are 1.4 times as likely to receive a non-standard regimen as men (OR=1.44, 95% CI: 1.02-2.02).

While it was not possible to calculate a stable odds ratio for the association between hospital type and regimen received, it is clear just from examining the frequencies of the treatment regimen type for each hospital that patients at LWH were substantially more likely to receive a non-standard regimen compared to their Civil Hospital counterparts. At LWH, 156 patients received a non-standard regimen, while 190 received the standard treatment. In contrast, at Civil Hospital only 2 patients received a non-standard regimen, while 738 patients received the standard WHO/DOTS treatment protocol.

Therefore, we must reject the null hypothesis which stated that there was no significant association between any of the demographic variables and the treatment regimen received.

Table 12: Question 4 Odds Ratios

	Outcome: Treatment Regimen (Non-Standard vs. Standard)			
	Unadjusted		**Adjusted***	
Model	**Odds Ratio**	**95%CI**	**Odds Ratio**	**95%CI**
Age (B - 25-50 y.o. vs. A – 0-25 y.o.)	0.69	0.48 – 0.99	0.71	0.49 – 1.03
Age (C – 50+ y.o. vs. A – 0-25 y.o.)	0.66	0.40 – 1.09	0.72	0.43 – 1.20
Sex (Female vs. Male)	1.50	1.07 – 2.10	1.44	1.02 – 2.02
Residence (Village vs. Town)	0.69	0.46 – 1.04	0.70	0.46 – 1.06

* Adjusted for all variables in the table.

Research Q5. Is there an association between category of treatment and type of treatment regimen received (standard vs. non-standard), adjusting for other covariates (demographic variables)?

Null Hypothesis: There will be no association between category of treatment (N, PTC) and type of treatment regimen received (standard vs. non-standard), adjusting for potential demographic characteristic confounders?

Q5 Results:

Previously treated/complex category patients were more likely to receive a non-standard treatment regimen.

Univariate Results (See Table 13):

An advanced treatment category (Disease after treatment/PTC) showed a marginally significant association with the outcome of treatment regimen as non-standard (OR = 1.40, 95% CI; 0.97-2.01) in the univariate model.

Multivariate Adjusted Results (See Table 13):

Age, sex and residence were all tested as potential confounders and were determined to not be confounding the relationship between treatment category and regimen. Age was also assessed as a potential effect modifier with treatment category and did not show a significant interaction. Hospital type could not be

included in this model because of the extremely small number of Civil Hospital patients who received a non-standard regimen (N=2).

A final model was tested with the inclusion of all variables (age, sex, residence, and treatment category). In the final model, all variables were significant (with the exception of residence which reached a level of marginal significance).

- Treatment Category:

Patients in the PTC treatment category were 1.5 times as likely to receive a non-standard regimen, compared to new patients (OR=1.5, 95% CI: 1.04-2.17).

- Age:

Patients in the middle age category (Age Cat. B: 25-50 y.o.) were 32% less likely to receive a non-standard regimen, compared to patients in the young age category (Age Cat. A: 0-25 y.o.).

- Sex:

Females were 1.46 times as likely to receive a non-standard regimen, compared to men, in the multivariate model (OR=1.46, 95%CI: 1.03-2.06).

- Residence:

Residents of villages were 30% less likely to receive a non-standard regimen, compared to residents from towns, and this result was marginally significant (OR=0.70, 95%CI: 0.46-1.06).

Treatment category of PTC, middle age (25-50y.o.), and being female were significantly associated with an increased likelihood of receiving a non-standard regimen.

Therefore, we must fail to reject the null hypothesis which stated that there would be no significant associations between treatment category and the type of regimen received.

Table 13: Question 5 Odds Ratios

	Outcome: Treatment Regimen (Non-Standard vs. Standard)			
	Unadjusted		**Adjusted***	
Model	**Odds Ratio**	**95%CI**	**Odds Ratio**	**95%CI**
Treatment Category (PTC vs. New)	1.40	0.97 – 2.01	1.50	1.04 – 2.17
Age (B - 25-50 y.o. vs. A – 0-25 y.o.)	0.69	0.48 – 0.99	0.68	0.47 – 0.99
Age (C – 50+ y.o. vs. A – 0-25 y.o.)	0.66	0.40 – 1.09	0.70	0.42 – 1.17
Sex (Female vs. Male)	1.50	1.07 – 2.10	1.46	1.03 – 2.06
Residence (Village vs. Town)	0.69	0.46 – 1.04	0.70	0.46 – 1.06

* Adjusted for all variables in the table.

VI. Discussion:

This study begins to fill an important gap in the literature on tuberculosis in India. Analysis of data showed significant differences in the relative distbribution of pulmonary and extrapulmonary tuberculosis between various demographic sub-groups. Older patients were found to be more like to have been previously treated/complex. Patients attending the private hospital were more likely to receive a non-standard treatment regimen, while treatment at the government hospital adhered to a strict regimen with little possible alteration. Finally, women, patients under age 25 and residents of towns were found to be more likely to receive a non-standard regimen. These findings provide important insight into the distribution of disease in the population of District Kullu, as well as patterns of treatment. The results can be used by the hospitals to target care and case-finding to the most at-risk populations, and to ensure the provision of the highest quality treatment to all individuals. By highlighting areas where differences in associations have been found, this research has highlighted the areas which require critical analysis to determine if the differences are the result of nature or whether disparities exist which need to be addressed.

Significant differences were found between patients at the Civil and Mission Hospitals when analyzing the observed and expected proportions through chi-squared tests of a number of variables. These findings indicate the need for additional analysis to determine the direction of the differences. However, based on previous literature, differences were anticipated between the two hospitals, and between different demographic groups. For instance, the risk of extrapulmonary TB is generally higher in

women, while more men are infected with TB overall (SEARO/WHO 2009). Also, treatment regimens are expected to vary between public and private providers in India (Vyas 2003). These findings are consistent with the published literature on demographic distribution of site of infection, differences in treatment categories and regimens prescribed, and differences between public and private hospital's treatment of TB (SEARO/WHO 2009; Sharma, Kumar, and Singh 2010; Naing et al. 2001; Rao et al. 2000).

Patients in the oldest age group (50+ y.o.) were the least likely to develop EPTB, while the patients in the youngest age category (0-25 y.o.) were the most likely. This is in line with the findings of other research on the distribution of EPTB by age (Yang et al. 2004). A study from Nepal which also found that age less than 25 years was significantly associated with EPTB, whereas older age was associated with a decreased probability of EPTB compared to PTB, found that a large number of cases of TB in the older age group appeared to be re-activation cases in the lungs (which would result in PTB) (Sreeramareddy et al. 2008). They argue that "this may be due to decreased local immunity in the lungs in the elderly as a result of associated life-style factors (smoking) or co-morbid conditions which may predispose to re-activation in the lungs." They also cite a study from the UK which reported that co-mordid conditions, such as emphysema and bronchitis, which are typical among older patients, were independent risk factors for PTB (Jick et al., 2006). However, it is also possible that the association between age and site of infection is confounded by smoking status, which was not examined in this study.

In this study, females were 1.63 times more likely to develop EPTB than males. The gender difference in site of infection is consistent with other studies which have repeatedly found the risk of EPTB to be higher in women (Sreeramareddy et al. 2008).

The gender difference may be attributed to biological differences (e.g. genital tuberculosis in women), social differences in exposure (e.g. smoking), and/or differences in access to healthcare, particularly in rural areas of developing countries such as India.

Smoking is a major risk factor for pulmonary tuberculosis, and while highly prevalent among men (nearly 40% of adult men smoke in India), is not nearly as common amongst women (5% of adult women smoke) resulting in a higher likelihood of women developing EPTB then PTB (Jha et al. 2008).

A study from Peshawar, Pakistan found that women were 2 times as likely to develop EPTB as their male counterparts. They too have found an explanation for this difference to be elusive, however do identify that the burden of EPTB was particularly high in women of reproductive age (15-45 y.o.) which points to the possible role of the endocrine system and hormones in effecting rates of EPTB vs. PTB infection (Ullah et al., 2008).

Another consideration is the variation in exposure to other risk factors for pulmonary TB which vary significantly between men and women. Men are more likely to drink alcohol excessively, smoke, or be in small poorly ventilated spaces which might

increase the transmission of pulmonary TB from person to person. Reactivation of a previously latent infection also impacts the site of tuberculosis. A study by Musellim et al. (2005) found that reactivation of TB in the form of a pulmonary site occurred within the first five years in ~75% of the cases. However, the infection reoccurred in the form of an extrapulmonary site within the first five years after contact in only 23.6% of the cases. Men may be exposed to more factors and co-morbid conditions which would result in them being more likely to have reactivation in a shorter period of time, in which case it is significantly more likely to be in the form of pulmonary TB.

Patients who live in villages rather than towns were 34% less likely to develop EPTB (more likely to present with PTB), meaning patients who lived in towns were more likely to present with EPTB.

Little if any previous research has divided residence into towns and villages. Research that has compared residence of TB patients, typically looks at urban vs. rural. However, the state of Himachal Pradesh is extremely rural. The only town that could by any reasonable standard be classified as urban in District Kullu is the district capital (Kullu). Even classifying this as an urban center would be a stretch- it is best described as a relatively large town.

A classification system of towns versus villages was chosen, because there are no urban areas, and because there are important differences between the towns and villages in the region. In particular, the type of housing found in villages can be quite different

from that found in the towns. Some villagers, particularly in the more remote villages, live in thatched houses. Typically the homes are two stories with the cows and hay on the first level, and the people on the second. These homes are particularly sensitive to the harsh weather conditions of the region. Also, many family members may live in close quarters. Houses in the more rural villages are also more likely to use cooking stoves which produce significant amounts of smoke from the use of biomass cooking fuels, whereas individuals living in towns are more likely to have electric or kerosene stoves. The higher rates of PTB in the villages may be related to the use of indoor cooking fuels (wood/dung) which produce a lot of smoke. Higher incidence of TB has been found among houses that use biomass cooking fuels in India (Mishra, 1999). Logically, exposure to excess smoke from biomass cooking fuels should have a greater impact on pulmonary tuberculosis than EPTB, because of the co-effect on the lungs.

LWH is a higher level care facility and thus is more likely to receive patients who are sicker or for whom it is less clear what illness they have (e.g. EPTB). Also, EPTB is frequently determined by surgical biopsy and histopathological exam. LWH has surgical facilities, whereas Civil Hospital does not, making it more likely for EPTB patients to be correctly diagnosed and treated by LWH.

Patients in the middle age group were 1.73 times more likely to be PTC compared to the youngest age group.

Patients in the oldest age group were 1.43 times more likely to be PTC compared to the youngest age group. It is logical that patient's who are previously treated/complex are likely to be older. To fall into the previously treated category, the patient must have had active tuberculosis disease in the past for which they received treatment. The likelihood of multiple instances of active disease will increase with age, as more time has past during which this might occur.

Patients in the oldest category also had an elevated risk; however, this was somewhat less than the middle age group. This may be the result of differences in the likelihood of reactivation of prior existing disease versus a new, unrelated infection.

Patients in the middle age category (25-50 y.o.) were 31% less likely to receive a non-standard regimen then patients in the youngest age group. The oldest patients were also less likely to receive a non-standard regimen then the youngest age group, but this result was marginally significant.

Younger patients may have been most likely to receive a non-standard regimen because of the emotional toll on the prescribing physician of a very sick, young, patient, otherwise in the prime of their life. A doctor who is confronted with a patient who is not only very sick, but also very young, may be more likely to treat the disease more aggressively.

In addition, it may be thought that a younger patient can better handle/cope with the side of effects of the second-line drugs, which tend to be more difficult to take. Further, younger patients may be more willing to take injectables, which are the form that many of the second-line drugs take. Younger patients are also less likely to have co-morbidities, or be taking drugs for other conditions which might interact with the less frequently used drugs which are prescribed when the regimen is altered.

Females were 1.4 times more likely to receive a non-standard regimen compared to males. This finding is consistent with previous research which found that women were slightly more likely to receive a non-DOTS (non-standard regimen). This was thought to be primarily due to the increased use of private practitioners by women (Balasubramanian et al., 2000).

Another factor which may contribute to the higher use of non-standard treatment regimens in women may be the way in which they present with illness. Many of the regimens were classified as non-standard because they were augmented with additional second-line drugs, often after the patient appeared to not be responding to initial treatment with a standard regimen. Prescribing physicians may have viewed the female patients as more frail, and thus more sick, making them more aggressive in their treatment strategy. Also, the fact that many of the female patients are mothers, who serve a critical role in providing and raising their children, may have encouraged the physicians to augment the regimens in hopes of treating the disease more quickly and insistently.

This could also be the result of a tendency towards a nurturing behavior towards women, especially those who are younger.

It is also possible that women were less likely to respond to their initial treatment (thus, leading the physician to augment the regimen) because they were less compliant with taking their drugs suffered from malnutrition, or had a co-morbidity, such as diabetes. Women may have been more likely to put their family's needs before their own, including by sacrificing the maintenance of an appropriate treatment regimen. Many Indian women in this community also suffer from serious malnutrition. Patients who are malnourished may be less responsive to treatment, thus increasing the likelihood of their regimen being augmented (Paul, 2012). Diabetes mellitus is both a significant risk factor for tuberculosis and is known for making tuberculosis very difficult to treat. Patients with TB and diabetes often do not respond to the standard treatment regimen (Dooley and Chaisson 2009). While diabetes is typically thought to occur more commonly in Indian men, it may be seriously under-diagnosed, particularly in women (Ramachandran 1993). It is possible that more women are diabetic, and may not realize this, and thus fail to respond to the standard tuberculosis treatment, increasing the likelihood that their regimen will be augmented.

Patients from villages were 31% less likely to receive a non-standard regimen compared to patients who resided in a town.Patients from villages may have more trouble accessing the second-line, less frequently used drugs, which are often added to a regimen, making it non-standard. This may have made doctors less likely to prescribe a non-

standard regimen, because they were concerned about the patient's ability to access the drugs on an ongoing basis. Patients have to come to the hospital or village health worker for injectables (which is the form many of the second-line drugs take) and this is harder for patients who live in villages. Doctors may therefore be more hesitant to prescribe these drugs.

Previously Treated/Complex patients were more likely to receive a non-standard regimen that new patients. New patients receive a simple, drug cocktail that is generally not altered, unless the patient fails to respond or has unexpected side effects. Thus, one would expect new patients to generally receive the standard regimen. PTC patients require a more elaborate regimen that is subject to greater interpretation and in some cases, alteration by the physician. Therefore, it makes sense that at least a marginal association would be seen between PTC category of treatment and receipt of a non-standard regimen.

The results of this study provide significant insight into the distribution and factors associated with tuberculosis in District Kullu, India. The data indicates that certain sub-populations (females, young ages, and residents of towns) are significantly more at risk of presenting with extrapulmonary infections, and thus this site of infection should be suspected when clinical symptoms are present. This is particularly true among patients seen at the Mission Hospital. However, it is also likely that extrapulmonary cases are being missed at the Civil Hospital due to the lack of surgical facilities. Thus, the inclusion of basic surgical and histopathological facilities and/or the transfer of suspected

extrapulmonary cases from Civil to Mission Hospital may help to identify additional cases of EPTB.

The results of this analysis also demonstrate that older patients (especially in the middle age group of 26-50 years) are significantly more likely to be patients who are previously treated/complex. This finding is in line with anticipated outcomes, as older individuals would have had more opportunity to be treated in the past, however, it does indicate that physicians should recognize the increased likelihood of previous treatment and ensure the appropriate regimen is prescribed.

The data from this retrospective review of medical records also reveals that particular sub-categories of patients are significantly more likely to be prescribed a non-standard regimen. The issue of the superiority of standard versus non-standard regimens is not entirely straightforward. Generally, the World Health Organization and other international bodies recommend that physicians prescribe a standard drug regimen for the treatment of TB patients; however, there are circumstances where an altered regimen may be more appropriate (e.g. managing side effects, not responding appropriately). However, it is best to limit the number of patients receiving non-standard treatments, as this is more likely to result in increased drug resistance. Thus, it is important to determine which populations are receiving more non-standard treatments, and then to identify the reasons behind these treatment decisions. Knowledge that females, residents of towns, and young patients (under age 25) receive more non-standard regimens at Mission Hospital (very few non-standard regimens are prescribed at Civil Hospital) can

inform the physicians prescribing practices. This may help to ensure that certain groups are not unnecessarily receiving these treatments for reasons other than clinical need.

VII. Study Strengths and Limitations:

Strengths:

This study contained a number of important strengths. First, the data was collected onsite in India by the researchers, with the full cooperation and collaboration of the participating hospitals. The study was conducted at the request of the Medical Superintendent of the Mission Hospital, so it was both considered a priority, and the hospital staff were open to learning from the results of the analysis and making changes accordingly. Because this consisted of primary data collection, it resulted in information that is not otherwise readily available or collected. Also, being able to compare the government and mission hospital systems allowed for an additional depth to the analysis and provides useful insights which may be applied to other similar scenarios. Importantly, the results of this study can be applied directly to the implementation of treatment by both hospitals. Understanding the factors associated with different types of TB and treatments received can improve the quality of care provided, improve collection of surveillance date, target certain groups for outreach activities, and help to ensure that all sub-groups are receiving equal treatment. Highlighting the issues of non-standard regimens can also provide the hospitals with an opportunity to re-evaluate their treatment practices and ensure they are in line with international guidelines, while tailoring to the specific needs of their patients. An additional strength is the completeness of the variables which have been included for analysis. The data from the two hospitals on the six variables described above is 95% complete and represents a significant sample size, as three years of data have been included. Particularly, for research in India where data

systems are poorly maintained, this is a very small amount of missing data for these specific variables. Through its collection of primary data, this study contributes to the body of literature on one of the major causes of morbidity and mortality in India, and addresses the epidemiology of the disease in a region where it has not been previously examined in depth.

Limitations:

The study was not, however, without it's limitations. The quality of the data was at times problematic. Hand-written records were often difficult to read and frequently were missing important pieces of information. This may at times have affected the quality of the data (about 30% of the time). However, efforts were made to enhance the data quality by review and confirmation with staff members who originally recorded the information. For example, names of villages were checked with the staff to determine if they had been recorded correctly and were adjusted when errors were found. Records often contained partial information as sections were not recorded in the register, largely due to the high volume of patients seen by the outpatient department of the hospital, thus the majority of analysis is limited to information that was collected at the first patient visit. Treatment outcomes can not be studied because of missing data, and thus the ability to examine the data as a cohort over time is lost and it is reduced to a cross-sectional format. This data would also have allowed for the study of possible associations between both demographic characteristics, treatment categories, regimens and sites of infection and patient outcomes. An additional limitation is that the data only

includes records from the government and mission hospitals. It does not include tuberculosis patients who were seen by other providers in the region including private practitioners and the District Hospital in Kullu. The lack of information from these sources limits the generalizability of any findings.

Also, the extremely low number of patients who received a non-standard regimen from the Civil Hospital meant that the hospital variable could not be included in some of the analysis. It is possible that this variable is confounding the relationship between the demographic variables and treatment regimen. It is also possible that other unknown confounders have been missed because of the lack of additional data and the fact that the patients were not randomized. While every effort was made to reduce bias, it is possible that some may have occurred.

VIII. Public Health Significance -

Tuberculosis is one of the leading causes of morbidity and mortality in India. It typically exerts its greatest toll on the young adult, most economically productive sector of society. Better understanding of the distribution of the disease and factors associated with infection can improve surveillance, treatment, and education efforts.

Given the paucity of information available on tuberculosis in this region, this study helps fill the void of data which exists. This information is needed to understand the epidemiologic situation and provide analysis of demographic variables, types of tuberculosis, and treatment factors. This is particularly important because characteristics of tuberculosis infection within a population are known to vary considerably based on a wide variety of factors including geography and topography, access to care, and socioeconomic and cultural variables. Thus, it is critical to examine tuberculosis within the context of a specific region. Better understanding of the unique features of the distribution of tuberculosis among patients in this region, and the treatment mechanisms which are employed by the health systems will allow for improved diagnosis and treatment of this condition which results in significant morbidity and mortality amongst the population.

Knowledge of the populations most at risk for tuberculosis and the way treatment differs based on these factors can also be used to affect the care patients receive. For example, it is important to know if one gender is more likely to receive treatment at the private hospital than another, and similarly, if women or young adults, for instance are

more likely to receive a non-standard regimen. This information can inform treatment practices and outreach services for detection of new cases. Finally, this data and analysis is being used to improve the provision of treatment for tuberculosis by the hospitals in the region.

IX. Conclusions:

Tuberculosis remains one of the most prevalent and devastating infectious diseases in the world, exacting significant morbidity and mortality on it's victims. Identifying the populations most at risk for certain clinical presentations of TB, as well as the receipt of treatment can inform public health systems and improve the care provided to patients. This research determined that females, patients in the youngest age category (0-25 years), residents of towns, and patients seen at the Mission Hospital are significantly more likely to present with extrapulmonary TB. This is critical knowledge, as EPTB can be difficult to diagnose. Further, it was determined that older patients (especially those aged 26-50 years) were significantly more likely to be in a more advanced category of treatment/disease after treatment. In addition, females, residents of towns, and the youngest age group (0-25 years) were most likely to receive a non-standard treatment regimen. Also, patients who were in the previously treated/complex category were significantly more likely to receive a non-standard regimen. These findings raise important questions about the use of non-standard regimens and the practice of augmenting regimens with additional second-line drugs. Together these results can help to target case finding efforts and to improve the quality of care and disease management provided to patients at two of the major health care facilities in District Kullu, India.

This study provides the basis for many recommendations of areas for future study. More in-depth study is needed to better understand the differences in treatment regimen prescribing patterns, and to understand the effect this may have on patient outcomes.

Greater insight into the gender differences in accessing care, as well as the difference in rates of extrapulmonary TB is also needed. Better understanding of the roles of biologic versus social aspects of the disease and its treatment would enable the provision of more tailored care. Also, improved study design (cohort study rather than cross-sectional) with information on treatment outcomes and temporality would provide more robust findings.

X. MPH Competencies Addressed –

1. Demonstrate the importance of epidemiology for informing scientific, ethical, economic, and political discussion of health issues.
    a. Measures of association found through epidemiologic techniques will be used to inform the scientific conduct of the medical professionals treating tuberculosis patients in this region. Information on the different application of treatment regimens may also inform important political, economic, and ethical discussions of equality of treatment access.
2. Assess a public health problem in terms of magnitude, person, time and place.
    a. This research seeks to assess the burden of tuberculosis on the communities in District Kullu from 2008-2011.
3. Distinguish among the basic terminology and definitions of epidemiology.
    a. The research conducted distinguishes between statistically significant association, marginally significant association, bias, causality, p-values, and 95% confidence intervals.
4. Discriminate key sources of data for epidemiological purposes.
    a. Key sources of data for this particular study include data from the World Health Organization, peer-reviewed scientific literature, and primary data collected in India.
5. Calculate basic epidemiology measures.
    a. Measures of association, 95% Confidence intervals and p-values are being calculated.
6. Evaluate the strengths and limitations of epidemiologic reports.
    a. Epidemiologic reports have been reviewed as part of the literature review and have been shown to include important information related to the variables associated with tuberculosis, as well as demonstrating the lack of information available with regard to this particular region.
7. Draw appropriate inferences from epidemiologic data.

a. Measures of association are being used to draw appropriate inferences of association (not causation) between independent and dependent variables related to tuberculosis.

8. Explain criteria for causality.
   a. This study will demonstrate the inability to determine causality because of its cross-sectional design.
9. Calculate advanced epidemiology measures.
   a. Multiple logistic regression is being used to determine measures of association and significance.
10. Communicate epidemiologic information to lay and professional audiences.
    a. This data and report are being communicated to professional audiences through the thesis review. In addition, the results of the study will be shared with the physicians and community in India that are affected.
11. Compare basic ethical and legal principles pertaining to the collection, maintenance, use, and dissemination of epidemiologic data and findings.
    a. Discussion may include the differing ethical and legal expectations regarding privacy and the collection, maintenance and dissemination of epidemiologic data, according to different regional contexts.
    b. The issue of data collection and use during investigation in a developing country was also addressed when approval was sought from the IRB.
12. Design, analyze, and evaluate an epidemiologic study.
    a. This research is an example of the design of a cross-sectional study through the review of medical records. Possible associations will then be analyzed, and the research will be evaluated based on its merit and contribution to the scientific literature on the subject.
13. Demonstrate program administration and organizational leadership.
    a. The research demonstrates program administration and organizational leadership through the design of the study, collection of data from the international site, and analysis of the data collected.

Appendix

Table 7: Dosages

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Table 4.1 **Essential antituberculosis drugs**

Essential drug (abbreviation)	Recommended dosage (dose range) in mg/kg	
	Daily	3 times weekly[a]
isoniazid (H)	5 (4–6)	10 (8–12)
rifampicin (R)	10 (8–12)	10 (8–12)
pyrazinamide (Z)	25 (20–30)	35 (30–40)
streptomycin (S)	15 (12–18)	15 (12–18)
ethambutol (E)	15 (15–20)	30 (20–35)

Table 8: Minimum Adequate Dosages by Weight Band

Minimum Adequate Dose										
	30kg	35kg	40kg	45kg	50kg	55kg	60kg	65kg	70kg	Daily Max
Pyrazinamide (20mg/kg)	600mg	700mg	800mg	900mg	1000mg	1100mg	1200mg	1300mg	1400mg	
Rifampicin (8mg/kg)	240mg	280mg	320mg	360mg	400mg	440mg	480mg	520mg	560mg	600mg
INH (4mg/kg)	120mg	140mg	160mg	180mg	200mg	220mg	240mg	260mg	280mg	300mg
Ethambutol (15mg/kg)	450mg	525mg	600mg	675mg	750mg	825mg	900mg	975mg	1050mg	
Streptomycin (12mg/kg)	360mg	420mg	480mg	540mg	600mg	660mg	720mg	800mg	860mg	-
EOD Therapy (3x weekly)	30kg	35kg	40kg	45kg	50kg	55kg	60kg	65kg	70kg	Daily Max
Pyrazinamide (30mg/kg)	900mg	1050mg	1200mg	1350mg	1500mg	1650mg	1800mg	1950mg	2000mg	2000mg
Rifampicin (8mg/kg)	240mg	280mg	320mg	360mg	400mg	440mg	480mg	520mg	560mg	900mg
INH (8mg/kg)	240mg	280mg	320mg	360mg	400mg	440mg	480mg	520mg	560mg	600mg
Ethambutol (20mg/kg)	600mg	700mg	800mg	900mg	1000mg	1100mg	1200mg	1300mg	1400mg	2500mg
Streptomycin (12mg/kg)	-	-	-	-	-	-	-	-	-	

Table 9: Chi-Squared Summary Table (N=1086)

Variable 1	Variable 2	Chi-Squared Value	P-Value
Hospital	Age	1.1468	0.4924
Hospital	Gender	10.3239	0.0013
Hospital	Residence	13.6549	0.0002
Hospital	Treatment Category	1.611	0.2044
Hospital	TB Type	34.5237	<0.0001
Hospital	Treatment Regimen	380.8967	<0.0001
Age	Treatment Category	12.8325	0.0016
Age	TB Type	8.1831	0.0167
Age	Treatment Regimen	5.0482	0.0801
Gender	Treatment Category	2.195	0.1385
Gender	TB Type	12.909	0.0003
Gender	Treatment Regimen	5.4647	0.0194
Residence	Treatment Category	0.0691	0.7926
Residence	TB Type	6.1387	0.0132
Residence	Treatment Regimen	3.1563	0.0756

Key:

Variable Name	Categories Included
Hospital	LWH (Mission) Hospital **/** Civil Hospital
Age	A:0-25 **/** B:26-50 **/** C:>50 years
Gender	Male **/** Female
Residence	Town/Village
Treatment Category	New (N) **/** Previously Treated-Complex (PTC)
TB Type/Site of infection	Pulmonary (P) **/** Extrapulmonary (EP)
Treatment Regimen	Standard (S) **/** Non-Standard (NS

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