CHAPTER 1

Introduction

Tuberculosis (TB) remains one of the most important infectious diseases worldwide, with approximately one-third of the world's population infected with the Mycobacterium tuberculosis bacillus and more than 9 million new cases and 1.7 million deaths annually (WHO 2009). The current global epidemic of TB is enormous and growing and becoming more dangerous. The spread of human immuno-deficiency virus (HIV/AIDS) and the emergence of multidrug-resistant TB (MDR-TB) are contributing to the worsening impact of this disease (Lopez et al 2001). TB is a leading cause of death among people who are HIV-positive. It is also a disease of poverty; it has the greatest impact on youth and adults and has become common cause of death among adults (WHO 2009).

This thesis focuses on investigating spatial and temporal variations of TB incidence and the treatment outcome of MDR–TB in Nepal and forecasting TB mortality in Thailand using appropriate statistical methods. Data for Nepal were obtained from National Tuberculosis Control (NTC), specific information system managed by the NTC coordination team, working for prevention and control of TB and HIV/AIDS in the Region. Data for Thailand were obtained from the national vital registration database, Bureau of Policy and Strategy, Ministry of Public Health. This chapter presents an overview of TB in Nepal and Thailand, rationales of the studies and literature reviews.

1.1 Tuberculosis

TB is the leading cause of death from single infectious disease in the developing countries. It is the greatest single infectious killer of all time over the 20th century; having taken more than one billion human lives (WHO 2001). The tremendous impact of TB is particularly evident in Asia (South-East Asia and Western Pacific Regions) and Africa. Approximately 86 percent of all TB cases reported worldwide occur in these regions, where 60 percent of the world's population lives (WHO 2009).

The South East Asia region alone carries one third of global burden of TB as shown in Figure 1.

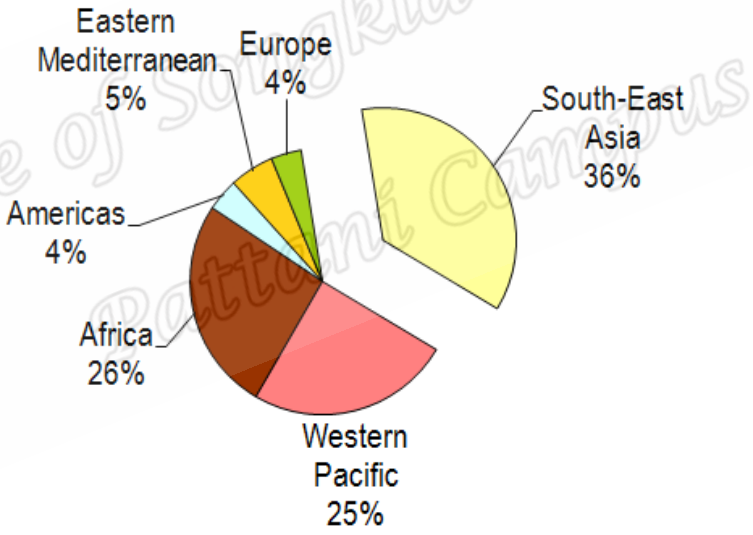


Figure 1.1: Global situation of TB worldwide

Source: TB in the South-East Asia Region, WHO/SEARO, March 2008

Multidrug-resistance TB (MDR-TB) is an emerging public health problem and is considered a threat to TB control in several settings. Multidrug resistance, resistance to at least H (Isoniazid) and R (Rifampicin), requires prolonged treatment with more

toxic second line drugs and remain infectious for longer than in the case with patients infected with drug-sensitive strains. It is estimated that there were 0.5 million new MDR-TB cases causing more than 1.3 million deaths in 2007 (WHO 2009). The implications are profound: for individuals infected with multidrug-resistant strains of TB, the fatality rate is greater than 50 percent. The burden of MDR-TB in many settings is the result of inadequate treatment, irregular drug supplies, poor funding and functioning of TB programmes, under-diagnosis of TB cases, non-compliance to treatment instructions on the part of the patient and widespread over-the-counter availability of anti-tuberculosis drugs (Espinal et al 2001).

1.2 TB in Thailand

Thailand is an independent country in Southeast Asia, bordered to the north by Burma and Laos, to the east by Laos and Cambodia, to the south by the Gulf of Thailand and Malaysia, and to the west by the Andaman Sea and the southern extremity of Burma. It is the world's 50th largest country and the 21st most-populous, with approximately 65 million people. The country is divided into 76 provinces, which are gathered into four regions by location, namely central, north, northeast and south (World atlas 2010).

TB is a serious public health problem in Thailand. The country is ranked 18th on the list of 22 high TB-burden countries. Every year 90,000 TB cases occurred, and of them about 15,000 or 16.5 percent, are in Bangkok and younger than 45 years. The prevalence of TB was estimated to be 192 per 100,000 population for all forms in 2007, with an incidence rate of 62 new smear-positive cases per 100,000 population and a mortality rate of 19 per 100,000 (WHO 2009). Recent research based on

National Tuberculosis Program (NTP) surveillance data from 2001 to 2005 shows that the rate of death from TB was more than two times higher in men than in women. Morality was highest in persons 65 years and older and in persons aged 35-44 years (Jittimanee et al 2009).

The Thailand Health Profile Report indicates that the number of TB cases declined between 1985 and 1989 but increased slightly from 1990 to 2005 due to an explosive HIV epidemic in the 1990s that resulted in a sudden increase in TB cases. The prevalence of TB has risen by 2 percent each year during the past five years and there was no tendency to decline during the period 1995-2002 (Wibulpolprasert 2007). The major contributor is HIV-associated TB, which accounted for an estimated 20 percent of all TB cases in Thailand (WHO 2009). Overall, for the entire country for over 10 years, the co-infection prevalence increased from 14.5 percent in 1989 to 28.7 percent in 2005.

Several studies and the Thailand Health Profile suggest that there exist noticeable regional differences in incidence of TB. The highest numbers of TB cases occurred in some provinces of the central and northern region of Thailand (Jittimanee et al 2009, Wibulpolprasert 2007). TB remains a major infectious disease in Thailand.

1.3 TB in Nepal

Nepal, officially the Federal Democratic Republic of Nepal, is a landlocked country in South Asia and is the world's youngest republic. It is bordered to the north by the People's Republic of China, and to the south, east, and west by the Republic of India. It has five development regions (eastern, central, western, mid western and far western), 14 zones and 75 districts (www.worldatlas.com). It is divided into three

distinct geographical areas, listed in decreasing altitude: Mountain (7% of the population), Hill (43%) and Terai (50%).

TB is one of the foremost public health problems in Nepal, causing a significant burden of morbidity and mortality. About 45% of the total population is infected with TB, out of which 60 percent are of reproductive age group (DoHS 2008, NTC 2010). It is the most common cause of death in the most economically productive age group, comprising adults aged 15 to 49 years (Harries et al 1998). The reported incidence of all forms of TB amongst the general population was 176 per 100,000 in 2006 with mortality (including HIV) 23 cases per 100,000 (WHO 2009). As in other countries, TB epidemic in Nepal can be traced in part to poor working and living conditions. Many of these conditions persist to this day, and along with the MDR-TB and HIV/AIDS epidemic, have fueled the current high levels of TB in the country.

Several studies and NTC annual report provides evidence that the magnitude of TB infection across the country is alarming and varies across locations. The reported caseload was extremely heavy in the Terai and in many urban areas (DoHS 2008, NTC 2010, Kakchapati et al 2010). Thus TB remains a major public health problem, especially in the highly populated lowland Terai and the metropolitan cities including the capital, Kathmandu.

MDR-TB is an emerging threat to TB control in Nepal. The current estimate is 2.9 percent (95% CI: 1.8-3.2%) among new cases and 11.7 percent (95% CI: 7.1-18.3%) among previously treated cases in 2007 (Wright et al 2009, Malla et al 2009). High incidence of MDR-TB in Nepal is associated with poor compliance to recommended

treatment, previous treatment history of TB, poor treatment regimens that are often prescribed by doctors and contact with drug resistant cases (Hurtig et al 2000).

1.4 Rationale of the study

Incidence and mortality are direct indicators of the burden of TB, indicating the number of people suffering from the disease at a given point in time and the number dying each year. Furthermore, incidence and mortality respond quickly to improvements in control, as timely and effective treatment reduce the average duration of the disease (thus decreasing incidence) and the likelihood of dying from the disease (thus reducing disease-specific mortality). Moreover, public health officials are often required to evaluate the impact of disease in a region. They need to compare the standardized status of disease within the area, time frame and risk groups so that necessary actions can be taken.

Statistical modeling may provide the necessary quantitative framework for investigating key issues related to disease. The models have been used to understand disease transmission dynamics and to predict the effects of different interventions and to study disease epidemics. Models can be used to examine the disease incidence, disease prevalence, disease specific mortality rates, or the percentage of patients completing treatment and best predict the health of population over time.

There are a number of related studies on the application of statistical modeling to TB, for example the impact of TB control strategies on TB (Legrand et al 2008), HIV and TB joint epidemic (Williams et al 2005, Bacaër 2008) and spatial and temporal variation of TB incidence (Uthman 2008, Nunes 2007). Besides this, models have been developed to describe the TB transmission dynamics and the impact of

interventions on TB, including drug sensitive TB (Blower et al 1996, Vynnycky and Fine 1997, Dye et al 2002) and drug-resistant TB (Blower and Gerderding 1998, Dye et al 1998, Dye and Williams 2000). These models address these issues and allow public health officials to make the best use of available epidemiologic data.

Investigating the regional and temporal pattern of TB can indicate areas with problems and possibly predict periods of likely disease epidemics. Information on future mortality trends is essential for population forecasts, public health policy, actuarial studies, and many other purposes. Long-term forecasts of mortality are used for setting current and future health system priorities. Better disease forecasting models would help public health officials to prepare for intervention measures in advance. Similarly, treatment outcomes of MDR-TB have varied among studies, and data on long-term survival are still scarce. So there is need to assess the burden, clinical characteristics and treatment outcomes of MDR-TB.

1.5 Definitions of terms

Some definitions that are used in this thesis and paper are as follows:

TB case: A patient in whom TB has been bacteriologically confirmed with 2 sputum smears positive for AFB and who is suppose to discharging Tubercle bacilli should be designated as the “Tuberculosis case” .

TB mortality: TB cases dying during treatment, regardless of the cause.

MDR-TB case: A patient who had TB resistant to both isoniazid and rifampicin, with or without resistance to any other antituberculosis drugs.

Cured MDR-TB: A patient who had negative smears and cultures throughout treatment for at least 18 months (or 24 months, in the absence of first-line drugs)

Defaulted MDR-TB: A patient, who had not collected drugs for two months or more after registration.

Failed MDR-TB: A patient who had persistence positive smears or cultures despite treatment for at least 18 or 24 months.

Died MDR-TB: Death from tuberculosis or complications of treatment.

Transferred out: A patient who was transferred to another reporting unit with treatment results not known.

Treatment success: A patient who was cured after completing treatment.

Clinical treatment failure: A patient who defaulted, failed, died or transferred out.

MDR-TB registration groups: Patients were categorized into four groups according to the registration groups used by the Nepal NTP.

I. Smear positive CAT 2 (Category 2 treatment regime) failure
II. CAT 1 (Category 1 treatment regime) failure with culture and Drug Sensitivity Testing (DST) confirmed MDR-TB
III. Any MDR-TB Patient household contact, who is smear positive, with culture and DST confirmed MDR-TB
IV. An MDR-TB patient who was smear positive, with culture and DST confirmed MDR-TB

1.6 Literature Review

Various literatures relevant to these studies are reviewed, including application of statistical methods for spatial and temporal variations on TB, TB mortality and forecasting and treatment outcome of MDR-TB.

1.6.1 Application of statistical methods to TB

Several studies focus on analyzing spatial and temporal variations of TB incidence worldwide.

Uthman (2008) applied Poisson regression models to determine the spatial and temporal variations in TB incidence in Africa from 1991-2005 to test for evidence of global and local spatial clustering. The study identified that southern, eastern and middle Africa experienced an upward trend in the number of TB cases and suggested that 25 countries were at increased risk of TB, and ten countries could be grouped as "hot spots" for TB.

Kistemann et al (2002) investigated spatial patterns of TB in Cologne (Germany) using GIS and Poisson regression models. The study indicated a strong positive association between TB incidence and immigration for the entire population. The economic conditions, immigration variables, the deprivation of certain ethnicities rather were inferred to be significant to TB level.

Kongchouy et al (2010) used log-transformed linear regression to examine the trend, seasonal and geographic effects on TB in the fourteen southern provinces of Thailand. Differences in gender-specific rates were noted in cases aged 25 year or more, with the highest rate noted in patients aged 65 years or over. There was no evidence of a trend in the annual incidence of TB during 1999-2004, but the incidence has a

significant season variation with peaks in the first quarter (January to March) over the six year period. The high risk areas were in upper western and lower southern parts of the region.

Kakchapati et al (2010) studied on TB incidence rates in districts of Nepal from 2003 to 2008 using negative binomial model. TB incidence showed a steady decreasing trend, but the number of cases was still very high. Gender differences existed in TB incidence in Nepal, with higher rates in males. There were pronounced spatial variations with higher rates occurring in the Terai region and urban areas.

Karim (2007) determined the temporal trend and high risks areas of TB in Bangladesh. Age-period-cohort (APC) analysis was conducted using generalized linear models for Poisson and negative binomial contributions to delineate the trends of TB incidence. The findings showed that higher risks were in 40-44 yrs and the trends of TB incidence were decreasing for both males and females. The highest relative risks were in capital city Dhaka and other metropolitan cities.

Nunes (2007) studied on TB incidence in Portugal used spatial scan statistics to identify the spatiotemporal clusters. TB incidence presents clear spatial patterns: a significant high incidence rate space-time clusters were identified in three areas of Portugal (between 2000 and 2004) and a purely temporal cluster was identified covering the whole country, during 2002.

Uthman et al (2009) investigated the spatial and temporal distribution of TB-HIV deaths in Africa for 16-year study period from 1990 to 2005 using multilevel Poisson growth curve models. Evidence shows that there is no decline in growth in TB deaths among HIV positive in most Africa countries. Spatial clustering suggested that 13

countries were at increased risk of TB-HIV deaths, and six countries could be grouped as "hot spots".

Williams et al (2005) used a mathematical model to describe the spatial and temporal variations in TB and HIV in India. The model predicted that without the Revised National TB Control Program (RNTCP), HIV would increase TB prevalence (by 1%), incidence (by 12%) and morality rates (by 33%), between 1990 and 2015.

Bacaër et al (2008) present a mathematical model with six compartments for the interaction between HIV and TB epidemics in South African Townships. The study identifies that various control measures such as condom promotion, increased TB detection and TB preventive therapy have a clear positive effect.

Au-Yeung et al (2011) compare mortality rates in TB/HIV co-infected individuals globally and by countries using multivariate linear regression. An estimated 13 TB/HIV deaths occurred per 100,000 population globally with the African region having the highest death rate at 86 per 100,000 population, followed by Eastern European Region in 2008. The mortality rates of African countries were higher than non-African countries.

Kourbatova et al (2006) determined risk factors for mortality among newly diagnosed TB in Samara (Russia) using multivariate logistic regression modeling. Advanced TB disease at the time of diagnosis (as demonstrated by having bilateral lung involvement, cavitary disease, symptoms month, and anemia) were associated with increased TB mortality in Samara.

Kolappan et al (2006) measure the mortality rate among a cohort of TB case treated in Chennai, India. Young age, male sex, smear positivity, treatment default, treatment

failure and the combination of smoking and alcoholism were identified as risk factors for TB mortality.

Lubart et al (2007) determined the mortality rate and predictors of mortality among patients hospitalized with TB in Israel. The mortality rate was relatively low and the predictors of mortality were older age, ischemic heart disease and other diseases.

Barnes et al (2011) described long-term trends in TB mortality and compare trends estimated from two different sources of public health surveillance data. Trends and changes in trend were estimated by join-point regression. Comparisons between data sets were made by fitting a Poisson regression model. Estimates of trends in TB mortality vary by data source; one data set showed a sustained improvement in the control of TB since the early 1990s whereas the other indicated that the rate of TB mortality was no longer declining.

Holtgrave et al (2004) applied multivariate linear regression to examine the state-level relationship between social capital, poverty, income inequality, and TB case rates. Poverty, income inequality, and social capital were all significantly correlated with TB case rates with social capital being the strongest predictor variable.

Dye et al (2009) used regression analysis to explore the associations between TB trends and various aspects of development in 134 countries from 1997 to 2006. TB incidence rate changed annually within a range of 10 percent over the study period in the 134 countries examined, and its average value declined in 93 countries. The rate was declining in countries that had a higher human development index, lower child mortality, low HIV infection rates, access to improved sanitation, greater health expenditure, high-income countries and lower immigration.

Similarly, several statistical models have been used for disease analysis and forecasting.

Debanne et al (2000) developed a multivariate Markov chain model to project TB incidence in the United States from 1980 to 2010. The projections of the model demonstrate an intermediate increase in TB incidence (similar to that which actually occurred) followed by continuing decline. The rate of decline depends strongly on geographic, racial, and ethnic characteristics.

The non-linear Lee-Carter approach (Lee and Carter 1992) is widely used in both the academic literature and practical applications for disease forecasting. It has become the leading statistical model of forecasting in the demographic literature (Deaton and Paxson 2004). There have been several extensions of the Lee-Carter method such as non-parametric smoothing, Kalman filtering, and multiple principle components.

Cesare and Murphy (2009) analyses trends and forecasts mortality rates for three major causes of death - lung cancer, influenza-pneumonia-bronchitis, and motor vehicle accidents - using Lee-Carter, Booth-Maindonald-Smith, Age-Period-Cohort, and Bayesian models to assess how far different causes of death need different forecasting methods. The results show major differences between the different forecasting techniques**.**

Kiliemana and Roslanb (2009) forecast TB in Terengganu region by applying linear trend, quadratic trend, simple moving average, simple exponential smoothing and Holt's trend corrected exponential smoothing. The study shows that Holt's trend corrected exponential smoothing is the best forecasting model, followed by the quadratic trend model. The results also show that people aged between 35–44 years

old, male, Malay and unemployed were in a high risk group of TB and suggest increased in TB cases in subsequent years.

Löytönen et al (1998) produce a short-term forecast of the spatial development of MDR-TB epidemic in Finland. The method applied is a chorological multistep procedure using statistical and geographical methods and a simulation technique. The simulated 6 year cumulative distribution of new MDR-TB cases showed a marked concentration of cases in the capital region and in a cluster of municipalities along the west coast.

1.6.2 Treatment outcome of MDR-TB

The increasing worldwide incidence of MDR-TB has emerged as a threat to public health and TB control. Several studies investigating the outcome of MDR-TB treatment worldwide and treatment outcomes have varied among studies.

In an early study of the treatment of MDR-TB, Hadiato et al (1996) reported an overall cure rate of less than 60 percent in Indonesia. The cure rates have been higher in more recent studies. In a study of patients in Turkey, the rate of successful treatment was 77 percent (Tahaoglu et al 2001), and a report from Korea cited a treatment success rate of 83 percent (Park et al 1998). In Nepal, Malla et al (2009) describe the outcomes of MDR-TB patients who received treatment during the first 12-months of the MDR-TB treatment programme in Nepal. Cure was reported among 70 percent of patients (range 38%–93% by Region), 8 percent died, 5 percent failed treatment, and 17 percent defaulted.

Various factors such as patient demographics, previous treatment history, HIV infection, number of drugs to which organisms were resistant, duration of treatment,

weight and prior hospitalization are believed to influence the treatment outcome of MDR-TB. However, studies by Espinal et al (2001) and Mirsaeidi et al (2005) showed no association between patients' demographics and cure rate of MDR-TB. A recent study in Nepal by Malla et al (2009) showed that cure was inversely associated with body weight.

Kliiman et al (2009) identified HIV infection, previous TB treatment and positive acid-fast bacilli (AFB) smear at the start of treatment were risk factors for poor treatment outcome in MDR-TB in high HIV prevalence setting in Southern Africa. However, many important variables, including patients' HIV status, were inconsistently reported between studies. Previous reviews of MDR-TB reported no individual patient or programme characteristic was associated with a significantly greater proportion of patients achieving treatment success (Mukherjee et al 2004, Caminero 2006). Studies that incorporated both treatments for longer than 18 months and directly observed therapy (DOT) throughout the entire treatment period had a significantly greater proportion of patients achieving treatment success than all other studies (Orenstein 2009). In addition, Holtz et al (2006) concluded that sputum culture conversion and time to sputum culture conversion is considered the most important interim indicator for treatment success in patients with MDR-TB.

Issues such as logistics, programme resources, transportation, food assistance, and social support that are accounted for in different ways by different programmes but often not reported in published studies may have affected the proportion of treatment success (Orenstein 2009). For example, an innovative community-based treatment model that involved social and nutritional support, twice-daily directly observed

treatment and early empiric use of second-line TB drugs was successful in reducing mortality of MDR-TB patients in Lesotho (Seung et al 2009).

1.7 The studies

The data structure for the first study was follow up data to determine overall times of treatment outcome, with other outcomes classified as censored data, whereas the data structure for remaining studies were essentially the same in each case, with the outcome defined as an incidence rate or morality rate based on cells classified by categorical determinant variables, and other continuous or categorical determinants defined on the same cells.

Statistical methods were applied to three outcomes:

(1) treatment outcome of MDR-TB (2) mortality of TB and (3) incidence of TB.

The path diagrams for the studies are shown in Figure 1, Figure 2 and Figure 3.

Study I: Treatment Outcome of MDR-TB in Nepal

Path Diagram

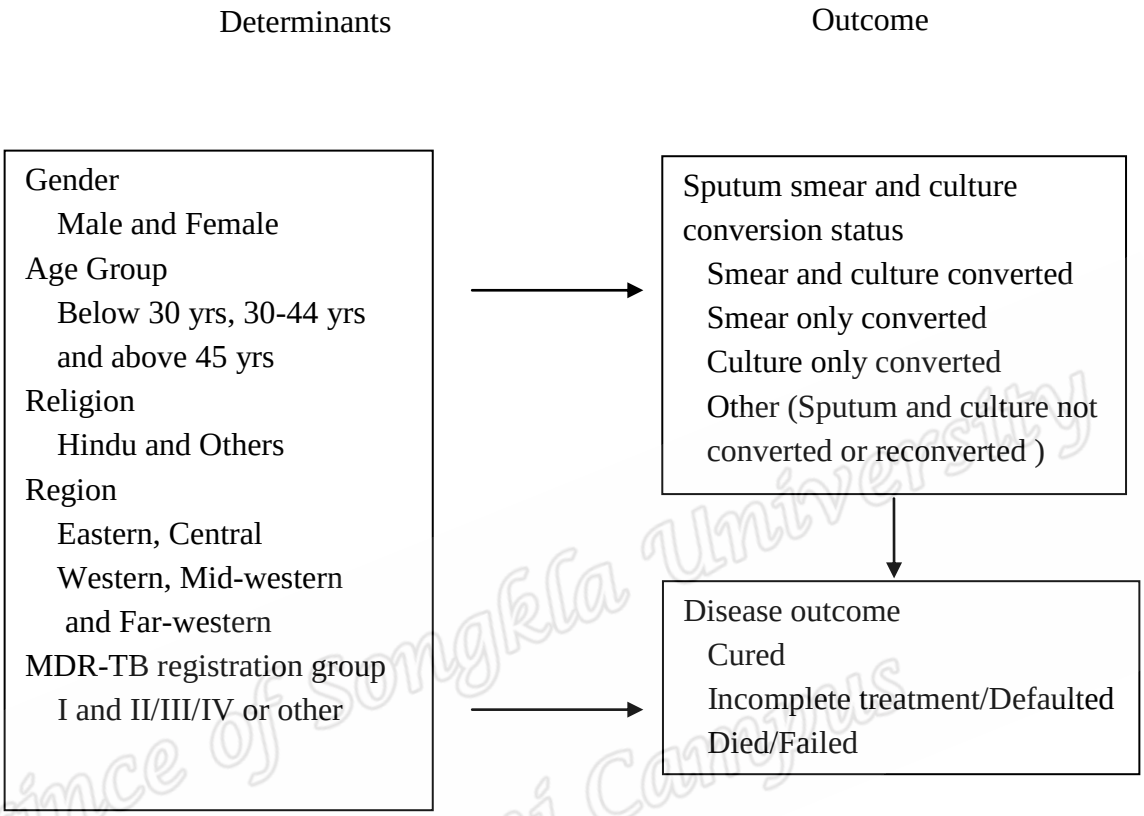


Figure 1.2: Path diagram for variables used in the first study

Study II: Forecasting TB Mortality in Thailand using Multivariate Linear Regression

Path Diagram

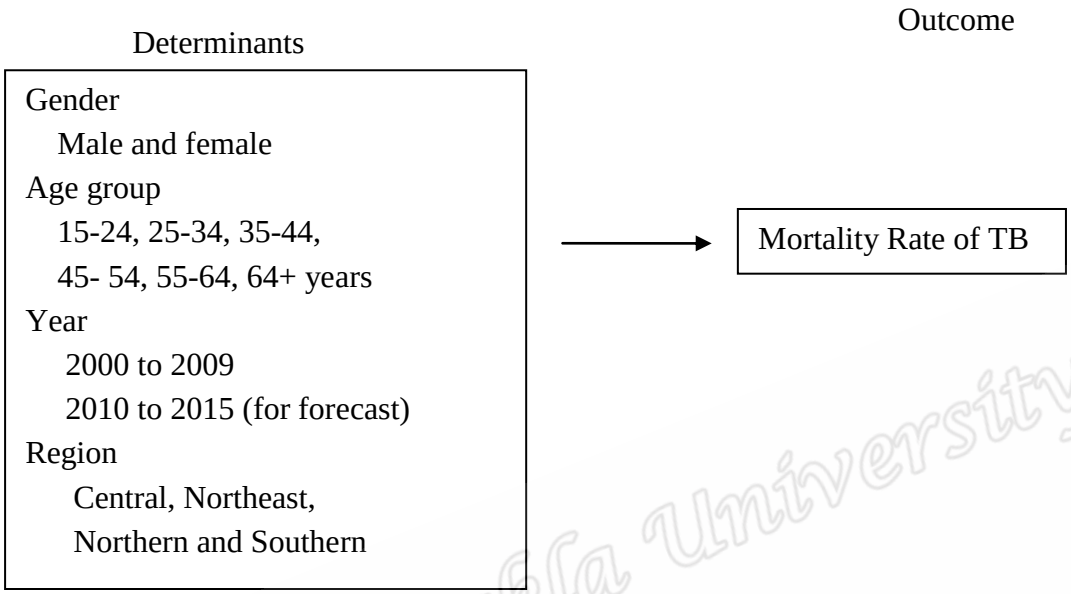


Figure 1.3: Path diagram for variables used in the second study

Study III: Spatial and Temporal Variations of TB Incidence in Nepal

Path Diagram

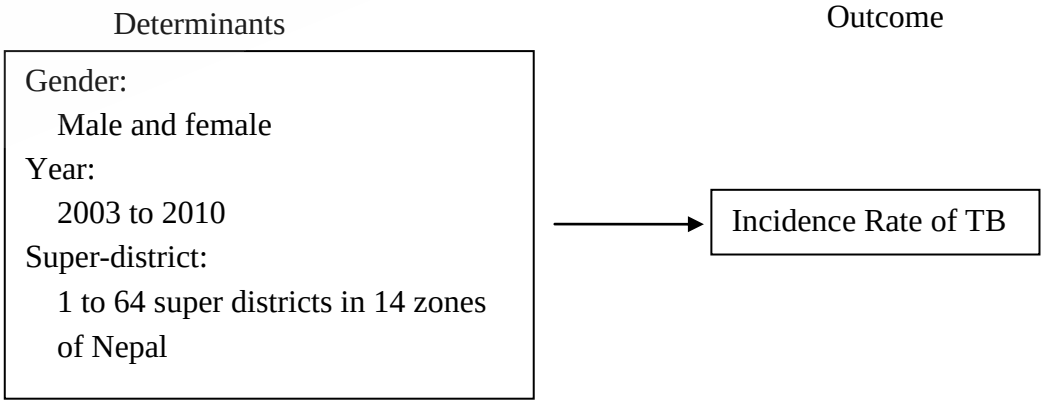


Figure 1.4: Path diagram for variables used in the third study

1.8 Objectives and plan of thesis

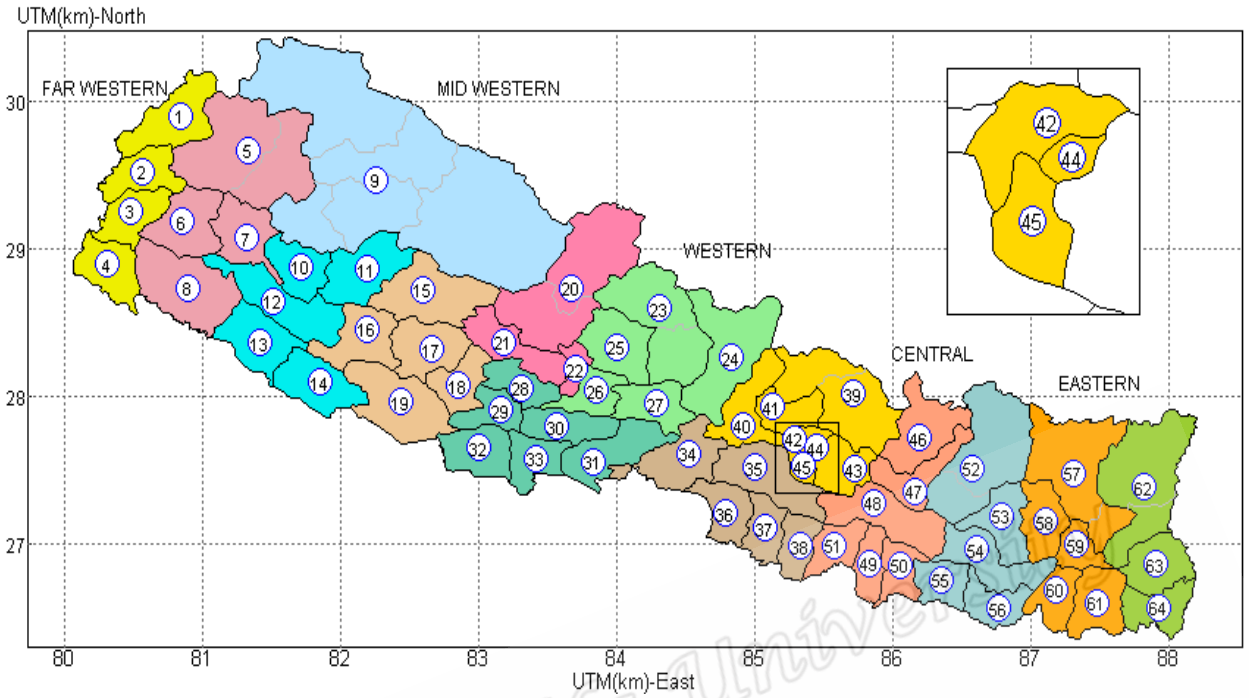
Appropriate statistical models are used to model treatment outcome, TB mortality rates and incidence rates. Kaplan-Meier Curves and Cox proportional hazards were used to assess statistically significant factors for treatment outcome of MDR-TB. Multivariate linear regression and Log transformed linear regression were applied to identify the associations between demographic factors (location, season, age, and gender) and data outcomes (mortality and incidence rates).

The objectives of studies were thus as follows:

1. To investigate the treatment outcome of multidrug-resistant TB (MDR–TB) in Nepal from 2005 to 2008.
2. To forecast TB mortality in Thailand using multivariate linear regression.
3. To examine spatial and temporal variations of TB incidence in Nepal from 2003 to 2010.

1.9 Road map of the thesis

This thesis contains four chapters. The introductory chapter discusses the introduction, rationale and also includes a review of some relevant literature. Chapter 2 provides a description of the methodology including an overview of the statistical methods for data analysis. Chapter 3 shows preliminary analysis of the studies. Chapter 4 states the summaries and general conclusions. Suggestions for further research are also provided in this chapter.



1 Darchula	17 Rolpa	33 Rupandehi	49 Mahottari
2 Baitadi	18 Pyuthan	34 Chitwan	50 Dhanusha
3 Dadeldhura	19 Dang	35 Makwanpur	51 Sarlahi
4 Kanchanpur	20 Mustang+ Myagdi	36 Parsa	52 Solukhumbu+ Okhaldunga
5 Bajhang+ Bajura	21 Baglung	37 Bara	53 Khotang
6 Doti	22 Parbat	38 Rautahat	54 Udaypur
7 Achham	23 Manang+ Lamjung	39 Rasuwa+ Sindupalchowk	55 Siraha
8 Kailali	24 Gorkha	40 Dhading	56 Saptari
9 Karnali (zone)	25 Kaski	41 Nuwakot	57 Sankhuwasabha+ Tehrathum
10 Dailekh	26 Syangja	42 Kathmandu	58 Bhojpur
11 Jajarkot	27 Tanahu	43 Kavre	59 Dhankuta
12 Surkhet	28 Gulmi	44 Bhaktapur	60 Sunsari
13 Bardiya	29 Arghakhanchi	45 Lalitpur	61 Morang
14 Banke	30 Palpa	46 Dolkha	62 Taplejung+ Panchthar
15 Rukum	31 Nawalparasi	47 Ramechhap	63 Illam
16 Salyan	32 Kapilvastu	48 Sindhuli	64 Jhapa

Figure 1.5: Map of Nepal with 64 super-districts