Appendix I

Treatment Outcome of Multidrug-resistance Tuberculosis

(MDR-TB) in Nepal

TREATMENT OUTCOME OF MULTIDRUG-RESISTANT MYCOBACTERIUM TUBERCULOSIS (MDR-TB) IN NEPAL

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Abstract

The purpose of this study was to examine factors associated with treatment outcome of MDR–TB cases in Nepal. A retrospective analysis of MDR-TB cases by demographic determinants and treatment was conducted. A total of 494 MDR-TB cases were registered from years 2005 to 2008, with data obtained from the National Tuberculosis Center (NTC). Chi-squared tests were used to assess statistically the association between smear and culture conversion and treatment outcome. Determinants were analyzed with the use of Kaplan–Meier curves and Cox proportional-hazards models to generate estimates of the associations with the time to treatment outcome. Sputum conversion status and culture conversion status were positively associated with treatment outcome for MDR-TB. In a multiple Cox proportional-hazards regression model, no determinants were found to be associated with time to cure.

INTRODUCTION

Tuberculosis (TB) is the leading cause of mortality in adults due to an infectious agent, and kills approximately 2 million persons a year worldwide. The global epidemic of TB is growing. The spread of HIV/AIDS and the emergence of multidrug-resistant TB (MDR-TB) are contributing to the worsening impact of this disease. The impact of TB is particularly evident in Asia (especially in South-East Asia and the 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 live[1].

The prevalence of multidrug-resistant TB (MDR–TB) is also a problem in parts of Asia and the Western Pacific, impeding the effort to control and prevent TB in this region. Multidrug-resistance, defined as resistance to at least Isoniazid (H) and Rifampicin (R), requires prolonged treatment with agents that are more expensive and associated with higher rates of toxicity than first line anti-tuberculosis drugs. Despite improved treatment response rates, MDR-TB continues to have higher morbidity and mortality than drug sensitive TB. The World Health Organization (WHO) estimated 0.5 million new MDR-TB cases causing more than 1.3 million deaths in 2007[2]. For individuals diseased with multidrug-resistant strains of TB, the fatality rate is greater than 50 percent. The high prevalence of MDR-TB may be the result of inadequate treatment, irregular drug supplies, poor funding and functioning of TB programs,

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under diagnosis of TB cases, non-compliance on the part of the patient and widespread over-the counter availability of anti-tuberculosis drugs[3, 4].

TB is one of the foremost public health problems in Nepal, causing a significant burden of morbidity and mortality. The estimated mortality rate is 5,000-7,000 deaths per year[5, 6, 7]. Emerging MDR-TB is posing a new threat to TB control in Nepal, with current estimates 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[8, 9]. High incidence of MDR-TB in Nepal is associated with poor compliance of previous treatment history of TB, HIV infection and contact with drug resistant cases. In addition, the incidence of drug-resistant TB is facilitated by poor treatment regimens that are often prescribed by doctors who have failed to follow national treatment guidelines[10]. The lengthy and more complex treatment processes to get cured make it difficult for patients to adhere to treatment through to its completion[11].

In Nepal, the MDR-TB management program started in September 2005 with WHO Green Light Committee approval, and has since been diagnosing and treating MDR-TB patients under a GLC-approved DOTS-Plus project, using a standardized treatment regimen. Treatment progress is monitored with sputum culture examination every month during the intensive phase (first 8 to 12 months) and bimonthly during the continuation phase (9 to 24/32 months). The treatment program has been expanded to all five regions of the country. By 2008, the National Tuberculosis Center (NTC) had registered 494 MDR-TB cases for treatment[5].

Many studies have investigated the outcome of MDR-TB treatment worldwide. A recent study in Nepal among 175 MDR-TB patients showed a treatment success rate of 70 percent[12]. Reported rates of treatment success of MDR-TB ranged from less than 60 percent in Indonesia[13] and Taiwan[14] to just over 80 percent in Hong Kong[15], Korea[16], and Turkey[17].

Various studies have attempted to identify determinants for MDR-TB. Patient characteristics including age and human immunodeficiency virus (HIV) infection are also believed to influence the dynamics of transmission of drug-resistant organisms. However, information available on some of these issues is limited, controversial and prompts further studies.

The aim of this study was to investigate the treatment outcome of MDR-TB cases in Nepal and its associated factors from 2005 to 2008.

MATERIALS AND METHODS

The study population included MDR-TB cases in Nepal under a GLC-approved DOTS-Plus project reported from 2005 to 2008. The data were obtained from NTC, a specific information system managed by the NTC coordination team, working for prevention and control of TB and HIV/AIDS in the region. Information obtained from individuals contains demographic characteristics including age, sex, caste, religion and region. In addition, the final results of smear conversion and culture conversion at the end of the intensive phase (first 8 to 12 months) or at the end of the treatment or continuation phase (9 to 24/32 months) were reviewed. TB treatment outcomes were classified by standard definitions: cure, treatment completion, treatment failure, default, transferred out, still on treatment and death.

DEFINITIONS

For this analysis, we applied multidrug-resistant TB treatment and outcome definitions developed by NTC, Nepal, as follows.

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

Cured MDR-TB: A patient starting DOTS-PLUS treatment who completed treatment, was smear and culture negative in the last month of treatment (from months 24-32), and had been culture/smear negative during the preceding 12 months of treatment 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 persistent positive cultures continuously after 16 months.

Transferred out: A patient who was transferred to another reporting unit with unknown treatment results.

MDR-TB registration groups: Patients were categorized into four groups according to the registration groups used by the Nepal NTC[4].

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

The treatment regimens used by NTP are: Table 1 Treatment Regimens for TB

	Types of patients	TB Treatment Regimens	
		Initial Phase	Continuation Phase
Category 1 (CAT 1)	New sputum smear positive Seriously ill new sputum smear negative	Isoniazid, Rifampin, Pyrazinamide and Ethambutol for 2 months	Isoniazid and Rifampin for 4 months Isoniazid and Ethambutol daily for 6 months
Category 2 (CAT 2)	Retreatment TB cases including failures, relapses and return after default	Isoniazid, Rifampin, Pyrazinamide, Ethambutol and Streptomycin for 2 months followed by Isoniazid, Rifampin, Pyrazinamide and Ethambutol for 1 month	Isoniazid, Rifampin and Ethambutol for 5 months

Figure 1 shows a path diagram of the study. The determinants considered were the demographic factors (including region) and MDR-TB registration group. The outcomes were the final results of sputum smear and culture conversion status and disease outcome.
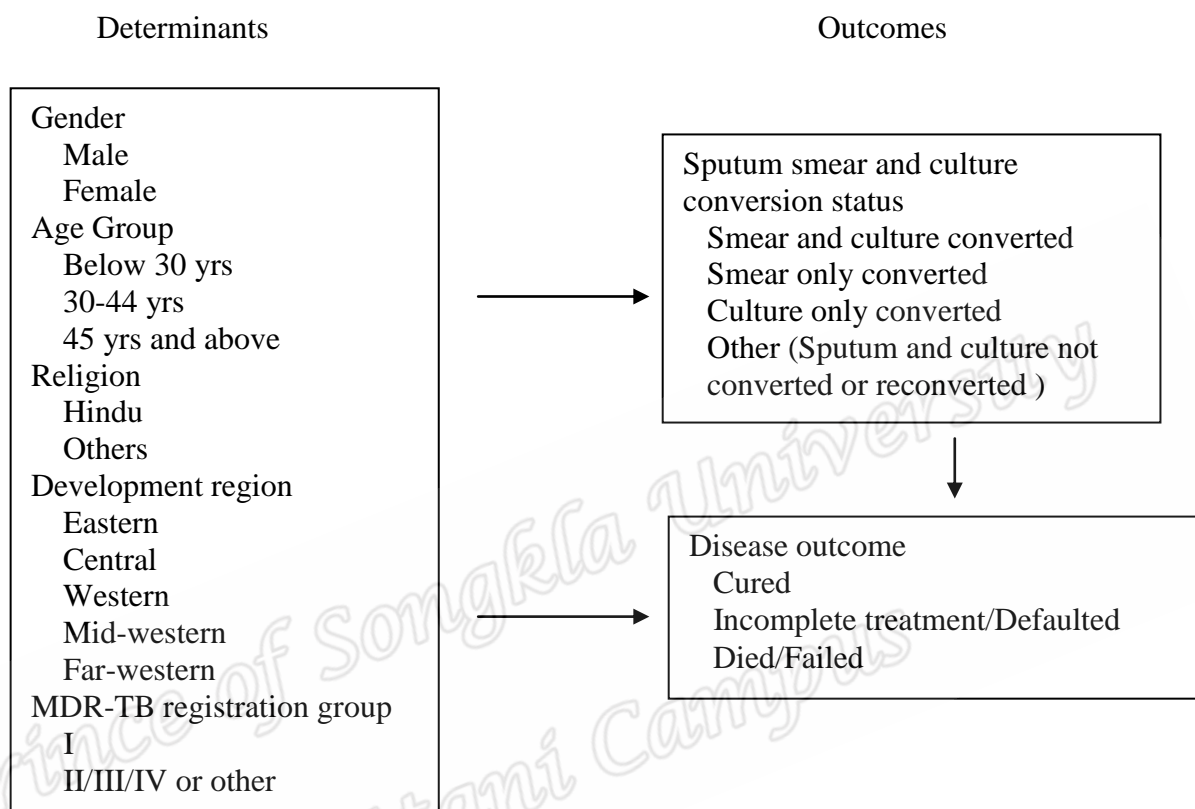
Determinants   Outcomes

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┌─────────────────────────┐
│ Gender                  │
│    Male                 │        ┌────────────────────────────────┐
│    Female               │        │ Sputum smear and culture       │
│ Age Group               │        │ conversion status              │
│    Below 30 yrs         │        │    Smear and culture converted │
│    30-44 yrs            │───────▶│    Smear only converted        │
│    45 yrs and above     │        │    Culture only converted      │
│ Religion                │        │    Other (Sputum and culture not│
│    Hindu                │        │    converted or reconverted )  │
│    Others               │        └────────────────────────────────┘
│ Development region      │                        │
│    Eastern              │                        ▼
│    Central              │        ┌────────────────────────────────┐
│    Western              │        │ Disease outcome                │
│    Mid-western          │───────▶│    Cured                       │
│    Far-western          │        │    Incomplete treatment/Defaulted│
│ MDR-TB registration group│        │    Died/Failed                 │
│    I                    │        └────────────────────────────────┘
│    II/III/IV or other   │
└─────────────────────────┘
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Figure 1 Path diagram of study variables

Statistical analysis

Preliminary statistical analysis involved examining the frequency distributions of the determinants and outcomes. Pearson's chi-squared tests were used to assess the association between the outcomes. Kaplan-Meier survival analysis was used to determine overall times to sputum smear conversion, cure, and failed/died, respectively, with other outcomes classified in each case as censored data. The log-rank test was used to assess the significance of differences between survival curves. Both univariate and multivariate Cox proportional hazards models were used to generate estimates of the associations between demographic factors and treatment and the time to cure, with other outcomes censored.

The results were obtained using the R program[18].

RESULTS

Of the 494 MDR-TB cases, 17 had missing treatment records. The remaining 477 MDR-TB were included in the analysis. Table 2 shows the demographic characteristics of the MDR-TB cases from 2005 to 2008. Most cases were males (65%), aged 15-44 years (71%) and Hindu (64%). The castes of most of the

respondents were Gurung/Magar/Lama followed by Brahmin and Chhetri. Most cases were observed in the years 2006 (35%) and 2007 (27%). The majority of cases were from the Central Region (58%), with 15 percent of cases from the Western region and 12 percent from the Eastern region.

Table 2 Demographic characteristics of MDR-TB cases

Characteristics	Number of cases (N=477)	Percent
Gender		
Male	310	65.0
Female	167	35.0
Age (in years)		
15 – 24 yrs	98	20.9
25 – 34 yrs	149	31.2
35 – 44 yrs	90	18.9
45 – 54 yrs	80	16.8
55 – 64 yrs	38	8.0
≥65 yrs	22	4.6
Religion		
Hindu	305	63.9
Buddhist	172	36.1
Caste		
Brahmin/Chhetri	150	31.4
Newars	59	12.4
Gurung/Magar/Lama	175	36.7
Terai	30	6.3
Dalits	63	13.2
Year		
2005	83	17.4
2006	165	34.6
2007	130	27.3
2008	99	20.8
Region		
Eastern	57	11.9
Central	279	58.5
Western	70	14.7
Mid western	38	8.0
Far western	33	6.9

Table 3 shows the clinical characteristics of the MDR-TB cases. Most MDR-TB cases were due to failures of CAT 2 (89%) followed by CAT 1 failure with culture and DST confirmed MDR-TB (6%). About 79 percent of cases had smear converted and 57 percent of cases had culture converted when last observed. The treatment outcomes of MDR-TB cases comprised 43 percent still on treatment, 32 percent completed treatment, 13 percent defaulted, 7 percent died and 3 percent failed.

Table 3 Clinical characteristics of MDR-TB cases

Characteristics	Number of cases (N=477)	Percent
MDR-TB registration group		
I	424	88.9
II	28	5.9
III	5	1.0
IV	20	4.2
Culture Status		
None	83	17.4
Not converted	101	21.2
Converted	271	56.8
Reconverted	22	4.6
Sputum Smear Status		
Negative	377	79.0
Scanty	3	0.6
Weakly positive	29	6.1
Moderate positive	25	5.2
Strong positive	43	9.0
Outcome		
Cured	155	32.5
Defaulted	62	13.0
Died	36	7.5
Failed	15	3.0
Transferred out	2	0.4
Still on treatment	208	43.4

Preliminary analysis showed only five cases with only culture converted status, so culture converted status was aggregated with smear converted status as "either smear or culture converted". For univariate analysis, three groups were defined, namely, "both converted", "either smear or culture converted" and "other".

Table 4 shows the association between this conversion outcome and treatment outcome. Cures occurred to a greater extent in cases where both smear and culture were converted (χ^2 = 155.18 with 4 df, p-value < 0.001).

Table 4 Association between culture conversion status and smear conversion status

Sputum smear and culture conversion status	Treatment outcome			
	Cured	On treatment/ Defaulted	Died/Failed	Total
Both converted	137	125	4	266
One converted	17	86	13	116
Other	1	61	33	95

For survival analysis, three age groups were used: < 30 years, 31-44 years and ≥ 45 years, and religion was grouped into "Hindu" and "Buddhist". Similarly, MDR-TB registration group was classified into two groups as "I" and "other" aggregating II, III and IV.

Table 5 reports the associations between each determinant and the time to cure. For each factor the reference category is the largest group and is indicated with hazard ratio 1. No factors were found to be significantly associated with time to cure.

Table 5 Factors associated with cure of MDR-TB in univariate and multivariate analysis

Characteristics	Number of cured	Person time in months	Univariate hazard ratio	P-value	Multivariate hazard ratio	P-value
Gender						
Male	103	4220	1		1	
Female	52	2513	0.72	0.06	0.76	0.12
Age						
< 30	68	2915	1		1	
30-44	45	2039	1.10	0.61	1.02	0.91
45 and above	42	1775	0.98	0.92	0.95	0.83
Religion						
Hindu	96	4200	1		1	
Budhhist	59	2533	0.77	0.12	0.86	0.41
Region						
Eastern	14	773	0.77	0.38	0.80	0.46
Central	98	4160	1		1	
Western	15	799	1.21	0.48	1.21	0.48
Mid western	16	521	1.59	0.08	1.48	0.16
Far western	12	480	1.02	0.92	0.88	0.70
MDR-TB registration group						
I	136	5875	1		1	
II/III/IV or other	19	858	1.07	0.77	0.97	0.90

Figure 2 shows Kaplan-Meier survival curves for time to smear conversion with respect to MDR-TB registration group. There was no significant difference in time to sputum smear conversion between the two MDR-TB groups (p-value=0.64).
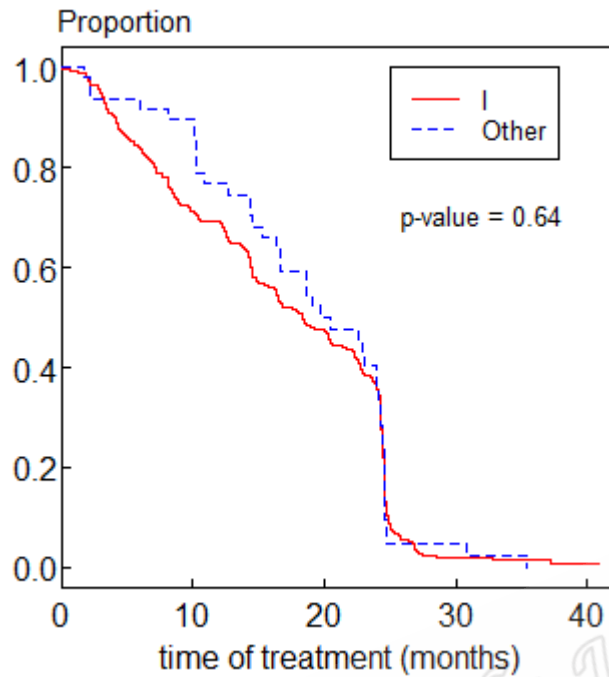
Figure 2 Kaplan-Meier survival curves for time to smear conversion

Figure 3 shows Kaplan-Meier survival curves for time to cure with respect to MDR-TB registration group. No significant difference in time to cure between the two MDR-TB groups was observed (p-value=0.78). The median time to cure for both groups was 24 months and 15 days.
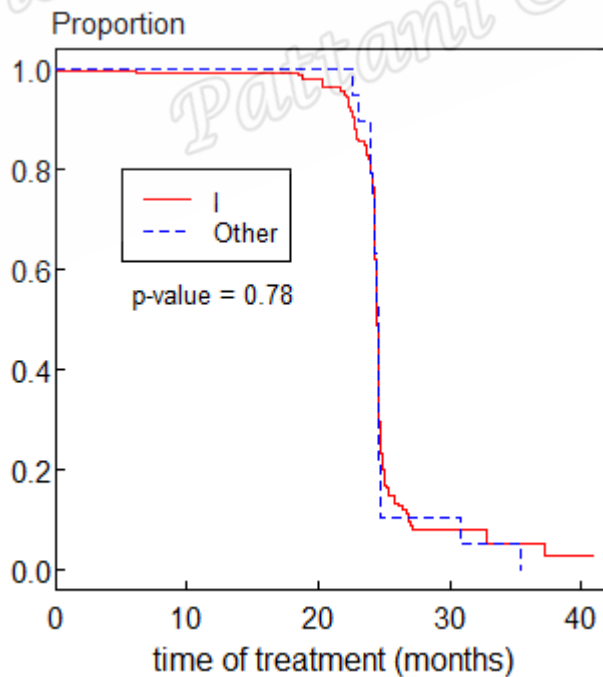

Figure 3 Kaplan-Meier survival curves for time to cure

Figure 4 shows the Kaplan-Meier survival curves for the time to treatment failure or death. There was no significant difference between the two MDR-TB groups (p-value=0.5).
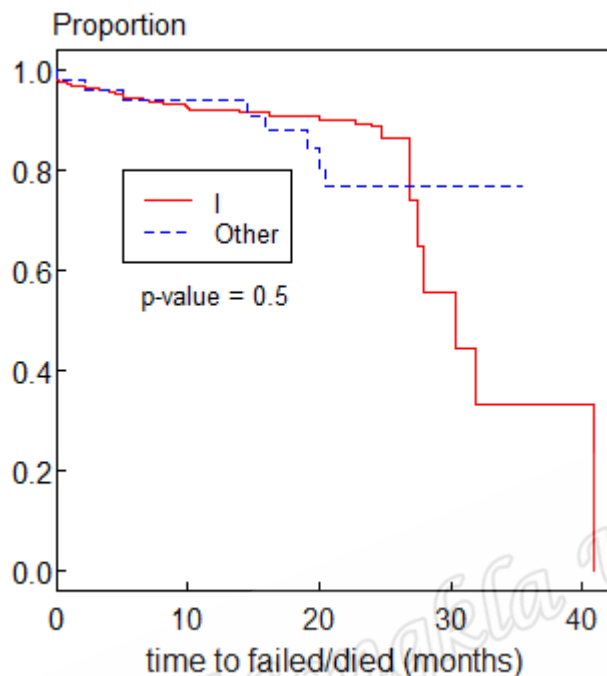
Figure 4 Kaplan-Meier survival curves for time to failure/death

DISCUSSION

We undertook a retrospective review of treatment outcome of MDR-TB cases and factors associated with treatment of MDR-TB cases in Nepal. The majority of the cases were male, as has been documented in other studies[19, 20]. Published studies have suggested higher risk of exposure to resistant strains together with poor compliance in males as contributory factors[21,22]. Drug resistance was higher in younger age groups. This is a matter of concern and should prompt further studies. There was little variation of MDR-TB cases over the four year period. The Central region accounted for more than half of the patients enrolled and has been the longest standing DOTS-Plus centre in the country.

About 79 percent of the patients had sputum smear converted and 57 percent of the cases had culture converted as the final results of sputum smear and culture test. Similarly 32 percent of the patients were cured over the four year period. However, the low cure rate is due to the fact that 43 percent of the cases had not completed their full course of treatment as the treatment requires 18 to 24 months.

Cures from MDR-TB tended to occur in cases when both sputum smear and culture were converted (Table 4). It should be noted that final treatment success is based on negative conversion of sputum and culture. In fact sputum culture conversion is an appropriate indicator of treatment outcome in patients with multidrug-resistant TB[23]. Sputum smear and culture conversion is used routinely as an indicator of the progress of treatment of multidrug-resistant TB and is an appropriate first goal of therapy.

Both univariate and multivariate Cox proportional hazards models were used to estimate relative risks between demographic factors and treatment and the time to cure. The models revealed no statistically significant associations between cure and age, gender and religion. These findings are consistent with other studies that have confirmed no differences in patient demographics and cure [3, 24]. However, patient education or socioeconomic determinants can lead to irregular medication intake that can contribute to resistance. Systemic problems such as inadequate public health resources and unpredictable drug supplies also play a role in treatment of MDR-TB[25]. These factors were not investigated in our study and further research in this area is needed. The survival analysis indicated that any treatment benefit was confined to the first 24 months.

This study was limited by its retrospective study design, as socio-demographic variables were abstracted from routine medical assessments conducted upon initiation of therapy. Besides this, we could not evaluate other factors known to be associated with drug resistant TB, such as HIV infection, previous TB treatment, number of drugs to which organisms' resistant, weight and prior hospitalization. However, plans to expand appropriate diagnostic and treatment services for patients with MDR-TB are urgently needed, particularly in regions where the burden of MDR-TB is greatest.

ACKNOWLEDGEMENTS

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Appendix II

Forecasting Tuberculosis (TB) Mortality in Thailand using

Multivariate Linear Regression

FORECASTING TUBERCULOSIS (TB) MORTALITY THAILAND USING MULTIVARIATE LINEAR REGRESSION

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Abstract

Tuberculosis (TB) is a major cause of morbidity, mortality, and disability worldwide. It is still a public health problem in Thailand. The objective of the study was to model and forecast TB mortality in Thailand using death certificate reports. A retrospective analysis of the TB mortality rate was conducted. Data were obtained from the national vital registration database for the 10-year period from 2000 to 2009, provided by the Ministry of the Interior and coded as cause-of-death using ICD-10 by the Ministry of Public Health. Multivariate linear regression was used for modeling and forecasting age-specific TB mortality rates in Thailand. Gender differences existed in TB mortality in Thailand with higher deaths occurring in males. TB mortality increased with increasing age for each sex and was also higher in the central and northern provinces. The trends of TB mortality decreased in most age groups and remained stable in others during ten-year period (2000 to 2009). The model forecast that the TB mortality will not increase over the 6-year period, and will actually decrease in most of age group and region for both sexes. The multivariate linear regression model can be used as a simpler method for forecasting TB morality. These findings provide information on forecasting for health authorities to help establish effective prevention programs in specific areas and groups where the TB mortality is relatively high.

Keywords: *mortality, Tuberculosis, modeling, forecasting, multivariate linear regression, Thailand*

INTRODUCTION

Tuberculosis (TB) remains a major cause of infectious disease mortality, with an estimated 8.8 million new cases and 1.6 million deaths annually [1,2]. It affects in particular low-income countries, with the highest case rates in Africa and the highest case numbers in Asia [1]. The enormous disparity and imbalance of TB globally is due to the underfunding of public health services, the spread of human immunodeficiency virus (HIV), and the emergence of multi-drug resistant TB (MDR-TB) [3]. It 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 cause of death among adults [1,2].

Thailand is one of the 22 WHO-designated high burden TB countries, with an estimated 90,000 TB cases occurring annually. 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 [1]. 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 [4]. Recent research based on National Tuberculosis Program (NTP) data from

2001 to 2005 shows that the rate of death from TB was more than two times higher in men than in women. Mortality was highest in persons 65 years and older and in persons aged 35-44 years [5].

Studies on TB mortality and forecasting were reviewed. Recent study compared mortality rates in TB/HIV co-infected individuals globally and by country using multivariate linear regression. The mortality rates of African countries were higher than non-African countries [7]. A study in United States developed multivariate Markov chain model to project TB incidence from 1980 to 2010. The projections of the model demonstrate an intermediate increase in TB incidence followed by continuing decline [6].

Long-term forecasts of mortality and disease burden are essential for setting current and future health system priorities. Better disease forecasting models would help public health officials to enhance the understanding of epidemic patterns in order to prepare for intervention measures in advance.

The objective of our study was to model and forecast TB (all forms) mortality in Thailand.

MATERIALS AND METHODS

Thailand is an independent country in Southeast Asia. It has four regions (Central, North-east, Northern and Southern) and 76 provinces [8].

Data for registered deaths due to TB were provided by the Bureau of Health Policy and Strategy, Ministry of Public Health. The data were collected from death certificates across the whole country. Deaths certificate are issued by a physician or nurse when death occurs in hospital and by head of village or health personnel when death occurs outside the hospital. This data is entered into the vital registration database that is maintained by Ministry of Interior. It is used by the Ministry of Public Health and coded cause of deaths using International Classification of Disease 10th edition (ICD-10). The resident population denominators used to compute mortality rates were obtained from the Population and Housing Census of 2010 undertaken by the National Statistics Office of Thailand.

Age, gender, residential area by region in Thailand and year were selected as the explanatory variables in studying the mortality rates of TB. Age was divided into seven groups (0-15, 15-24, 25-34, 35-44, 45-54, 55-64 and above 65+ yrs).

For each region and gender combination; multivariate linear regression model was used to investigate and forecast TB mortality by age group and year. This model is expressed as

$$\log(m_{xt}) = a_x + b_x t \qquad (1)$$

where m_{xt} is the central death rate (per 100,000) in age group x and year t for the specified gender and geographical region. The mortality rates generally have positively skewed distributions so it is conventional to transform them by taking logarithms. The factors a_x and b_x describe the level and annual increase, respectively of the age-specific mortality rate.

Since some cells or mortality in some age group and year had no reported cases, to allow log-transformation, we replaced zero counts by a suitably chosen small

constant, without changing any values of m_{xt} greater than 0. The multivariate linear regression estimates the same coefficients as one would obtain using separate univariate regression models [9]. This model has the additional advantage as it takes account of correlations between data in different age groups.

The R program, version 2.10 was used for all statistical analysis and creating graphs [10,11].

RESULTS

Preliminarily analysis

A total of 57259 death due to TB or during TB treatment for 10 year period (2000-2009) in Thailand. Among the deaths, 40,565 (70%) were males and 16,694 (30%) were females.

Statistical analysis

To log-transform the counts, we replaced zeros by 0.5 before fitting the model. The left panels of figure 1 show the TB mortality rates plotted by age group for each year; the right panels show the trends for 2000-2009 for each age group, together with the forecasts based on the model.
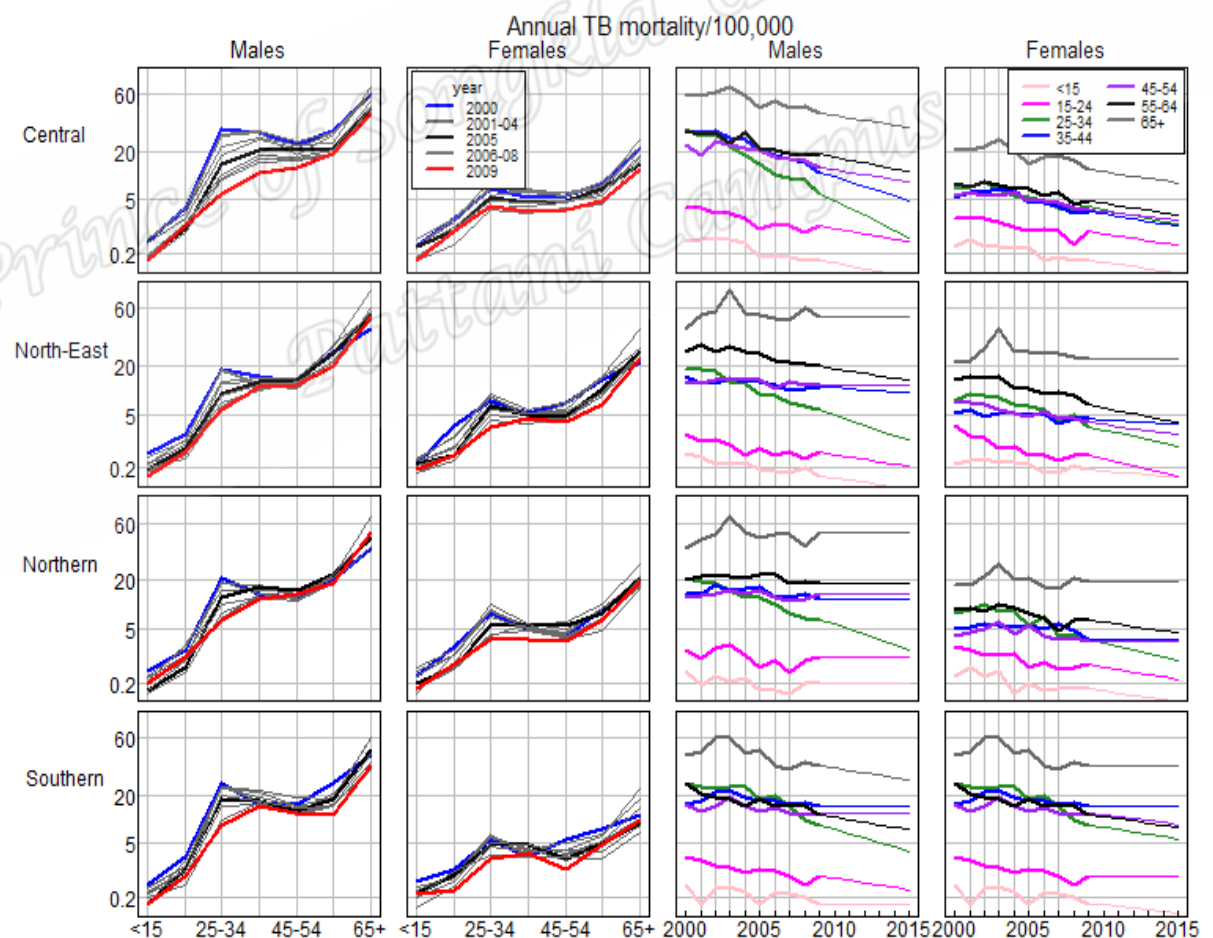
Figure 1 Plot of TB mortality rates by age group for each year (left panels) and trend with forecasts for each age group (right panels) for the four regions of Thailand

Figure 1 shows that mortality increased up to age group 25-34 years and decreased slightly before increasing in the higher age groups for both sexes. In all regions, age groups and years, males had higher mortality than females. In the central region, there was marked bulge in mortality among males between 25 and 55 years of age. However, there were fewer bulges in mortality in other provinces.

The time trends shown in the right panels indicate that the TB mortality decreases in most age groups and remained stable in others over the 10 year period. The model forecast that TB morality did not increase over the 6-year period, but decreased for 39 and remains steady for 17 of the 56 combinations of age group, gender and region.

The correlation varied substantially between age groups. Highest correlation was observed between 35-44 years and 45-54 years in females of the central region (0.88), followed by 55-64 years and above 65 years in female of north east region (0.69) and 35-44 years and 45-54 years in male in central region (0.66) (data not shown).

DISCUSSION AND CONCLUSION

In this paper, we applied multivariate linear regression to model and forecast the TB mortality in Thailand. The findings showed that gender differences existed in the mortality of TB; males had higher mortality rates than females in most age groups and regions, as consistent with TB mortality and gender patterns found in studies in Thailand [4,5]. However, in few age groups, mortality was higher in females than males.

Age has a major impact on TB mortality [12,13]. In our study, mortality was highest in age groups above 55 years for both sexes. Co-morbidity and decreased immune function are important factors in the increasing TB mortality among the elderly [12,13].

In the ten-year period (2000 to 2009), mortality decrease in most age groups and remained stable in others. The decreased in TB mortality may be attributed to successful TB control programmes in the country with the expansion of DOTS, case finding and treatment success in the recent years in Thailand [1,5]. The model demonstrates a gradually decreased in mortality for most combinations of age group, gender and region for 6-year period. Thus, the forecasting suggests that the morality rates of TB will now continue to decline or remain constant. Although TB mortality decrease and remain constant, the rates are high, indicating that TB is still endemic in most parts of Thailand, making TB a public health problem in Thailand.

There was pronounced bulge in mortality among males between 25 and 55 years of age in the Central region. Possible reasons for the bulge were not investigated in our study, but could be due to increased HIV incidence during 2001-2004, which attributed to higher incidence of TB [4,5].

Although the Lee-Carter model is often used for forecasting [14,15], this non-linear model cannot be fitted by ordinary regression methods, and thus does not routinely provide standard errors for estimated parameters. The multivariate linear regression has the additional advantage is that it takes account of correlations between data in different age groups. We recommend this method as an additional or alternative method to forecast disease mortality as it provide evidence of better disease forecasting.

The study had some limitations. Reliable data on TB mortality are unfortunately not available. Currently available data from the national vital registration and TB register or Hospital register in Thailand are an underestimate, as deaths occurring among defaulters are not included and the diagnosis of the disease is not done by public health people. Besides this, the general mortality from TB also includes deaths due to co-morbidities and other external causes. Ideally, TB mortality should include only deaths due to TB.

Further study is needed to investigate TB mortality in smaller regions, such as provinces or districts for detail investigation of mortality by specific location. The graphical method provides an informative display of the variation in mortality by gender, age group and region. Such graphs can be used by public health authorities for applying preventive measures to control TB mortality.

In conclusion, our study highlights the trend and forecasting of TB mortality by gender, age groups and location illustrated by a graph. These findings require further investigation, to assess the forecasted results with real data, but highlight the importance of selectively monitoring geographic locations and planning future intervention strategies according to prioritized risk groups.

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Appendix III

Spatial and Temporal Variations of Tuberculosis (TB) Incidence in

Nepal

SPATIAL AND TEMPORAL VARIATION OF TUBERCULOSIS (TB) INCIDENCE IN NEPAL

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Abstract

Tuberculosis (TB) is an important public health problem in Nepal. The aim of this study was to investigate the spatial and temporal variation of TB incidence in Nepal. TB cases collected from the National Tuberculosis Center (NTC) for an eight year period (2003-2010) were analyzed. The joint effects of gender-year and location on the TB incidence rates were modeled using linear regression on log-transformed incidence rates. Apart from a relatively small number of outliers, these models provided a good fit, as indicated by residual plots and the r-squared statistic (0.94). The overall incidence of TB was 1.31 cases per 1,000 populations with a male to female incidence rate ratio of 1.83. There were upward trends in incidence of TB in recent years for both sexes. There were marked spatial variations with higher rates occurring in the Terai region, and relatively moderate and low rates in the Hill and Mountain regions, respectively. TB incidence was also higher in capital city Kathmandu and other metropolitan cities. The log-linear regression model can be used as a simple method for modeling TB incidence rates that vary with location and year. These findings provide information for health authorities to help establish effective prevention programs in specific areas where the diseases burden is relatively high.

Keywords: *TB, TB incidence, spatial, temporal, log-linear models*

INTRODUCTION

Tuberculosis (TB) remains a major cause of infectious disease mortality, with an estimated 8.8 million new cases and 1.6 million deaths annually (WHO, 2009a). The global burden of TB is large, and is likely to remain high among public health problems in coming decades (Lopez *et al*, 2006). 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. 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 cause of death among adults (WHO, 2009a).

TB is one of the foremost public health problems in Nepal, causing a significant burden of morbidity and mortality. Every year approximately 30,000-40,000 people develop active TB; among them 20,000 have infectious (smear- positive) cases. These 20,000 are able to spread disease to others. Although TB is a curable disease, the mortality and incidence are high (DoHS, 2010; NTC, 2010). Moreover, the TB epidemic in Nepal has been worsened by the HIV/AIDs epidemic, population demographics, urbanization, changes in socio-economic standards and, more recently, emerging drug resistance TB that has fueled the high levels of disease in the country.

Several studies and the National Tuberculosis Center (NTC) annual report suggest

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marked regional differences in the incidence of TB in Nepal (Kakchapati *et al*, 2010; NTC 2010). The incidence rate of TB is generally higher in urban areas than in rural areas and in the Terai parts of the country, bordering to India. TB thus remains a major public health problem throughout Nepal, especially in the highly populated lowland Terai and in urban cities including the capital, Kathmandu.

The application of statistical models to TB was initiated in the 1960s, and since then these statistical models have been used to measure and understand strategies for control of TB (Legrand *et al*, 2008), joint epidemics of HIV and TB (Williams *et al*, 2005) and multi-drug resistance to TB (Dye *et al*, 1998). There are several studies that concentrate on spatial and temporal variation of TB incidence, for example, Kongchouy et al (2010) used log-transformed linear regression to examine the trend, seasonal and geographic effects on TB incidence in the fourteen southern provinces of Thailand, and identified the upper western and lower southern parts of the region as high TB risks. Kakchapati et al (2010) studied TB incidence rates in districts of Nepal from 2003 to 2008 using a negative binomial model and found spatial variations with higher rates occurring in the Terai region, followed by the Hill, and Mountain regions. Uthman (2008) applied Poisson regression models to determine the spatial and temporal variations in TB incidence in Africa and identified that southern, eastern and middle Africa experienced an upward trend in and suggested that 25 countries were at increased risk of TB.

Public health officials are often required to evaluate disease incidence in the country. They need to compare the standardized disease incidence rate within the area and time frame so that necessary actions can be taken. Thus, understanding their spatial and temporal distribution is helpful and essential for further refinement health intervention policies.

MATERIAL AND METHODS

Study Area and Data Source

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 is divided in 14 zones (75 districts), and has a current population of approximately 27.7 million and an annual population growth of 2.2% (World atlas, 2010). It is divided into three areas; Mountain, Hill and Terai, in order of decreasing altitude.

Data for TB were obtained from NTC for the 8-year period 2003-2010. These data are available in computer files for each year comprising characteristics of the disease, gender, location, and treatment status.

Since populations of districts in Nepal vary substantially, we computed the TB incidence rates in aggregated districts called "super-districts", defined as regions comprising contiguous districts in the same zone with a 2010 total population of above 140,000, as shown in Table 1. We thus obtained 64 super-districts listed in order of geographical location from far western to eastern (keeping districts within the same zone together).

Table 1: Definitions and populations of super-districts

Code	Super-district	Population	Code	Super-district	Population
1	Darchula	143,148	33	Rupandehi	857,291
2	Baitadi	273,219	34	Chitwan	568,495
3	Dadeldhura	148,217	35	Makwanpur	657,220
4	Kanchanpur	465,912	36	Parsa	599,199
5	Bajhang+ Bajura	323,202	37	Bara	675,072
6	Doti	244,907	38	Rautahat	654,723
7	Achham	269,504	39	Rasuwa+ Sindupalchowk	409,518
8	Kailali	761,652	40	Dhading	398,915
9	Karnali (zone)	975,186	41	Nuwakot	336,873
10	Dailekh	460,026	42	Kathmandu	1,363,512
11	Jajarkot	156,744	43	Kavre	451,595
12	Surkhet	344,237	44	Bhaktapur	270,107
13	Bardiya	466,702	45	Lalitpur	405,469
14	Banke	250,148	46	Dolkha	238,628
15	Rukum	221,859	47	Ramechhap	244,534
16	Salyan	249,442	48	Sindhuli	331,736
17	Rolpa	245,082	49	Mahottari	465,292
18	Pyuthan	245,503	50	Dhanusha	793,609
19	Dang	264,616	51	Sarlahi	759,631
20	Mustang+ Myagdi	149,599	52	Solukhumbu+ Okhaldunga	304,969
21	Baglung	312,830	53	Khotang	264,129
22	Parbat	181,277	54	Udaypur	344,588
23	Manang+ Lamjung	218,294	55	Siraha	677,957
24	Gorkha	334,022	56	Saptari	673,056
25	Kaski	455,559	57	Sankhuwasabha+ Tehrathum	313,791
26	Syangja	362,929	58	Bhojpur	228,983
27	Tanahu	368,194	59	Dhankuta	192,889
28	Gulmi	341,828	60	Sunsari	756,321
29	Arghakhanchi	242,159	61	Morang	1,000,114
30	Palpa	311,021	62	Taplejung+ Panchthar	390,466
31	Nawalparasi	672,760	63	Illam	334,376
32	Kapilvastu	576,769	64	Jhapa	801,041

Gender, residential area (by super-district) and year were selected as the explanatory variables in studying the incidence rates of TB. Gender and year were combined together to form sixteen gender-year groups. Age was not recorded.

Statistical methods

The additive log-linear model for incidence rates with normally distributed errors is

$$\ln\left(\frac{n_{ij}}{P_i}\right) = y_{ij} = \mu + \alpha_i + \beta_j \qquad (1)$$

In this model, P_i is the corresponding population at risk in 1000s and the terms α_i and β_j represent super-district and gender- year effects that sum to zero so that μ is a

constant encapsulating the overall incidence. The model fit is then assessed by the linearity in the plot of deviance residuals against normal quantiles.

The model also gives adjusted incidence rates for each factor of interest, obtained by replacing the parameters corresponding to the other factors by constants chosen to ensure that the total expected number of cases equals the observed number.

Sum contrasts (Venable and Ripley, 2002) were used to obtain confidence intervals for comparing the adjusted incidence rates within each factor with the overall incidence rate. Since the confidence intervals for factor-specific incidence rates obtained from the model divide naturally into three groups according to their location entirely above the mean, around the mean, or entirely below the mean, we used this trichotomy to create schematic maps of super-districts according to their estimated TB incidence rates.

The R program was used for all statistical analysis, graphs and maps (R Development Core Team, 2008).

RESULTS

Preliminary Analysis

A total of 271,873 TB cases were notified during the eight-year period (2003- 2010). Among the cases, 175,365 were males and 96,508 were females. Figure 1 shows the distribution of TB in Nepal by super-district ordered by increasing incidence rate. The dark lines represent years 2003 and 2010 and the light lines represent year 2004-09. Super-districts 53 and 14 had lowest and highest TB incidence, respectively. Males had proportionately higher incidence rates than females.
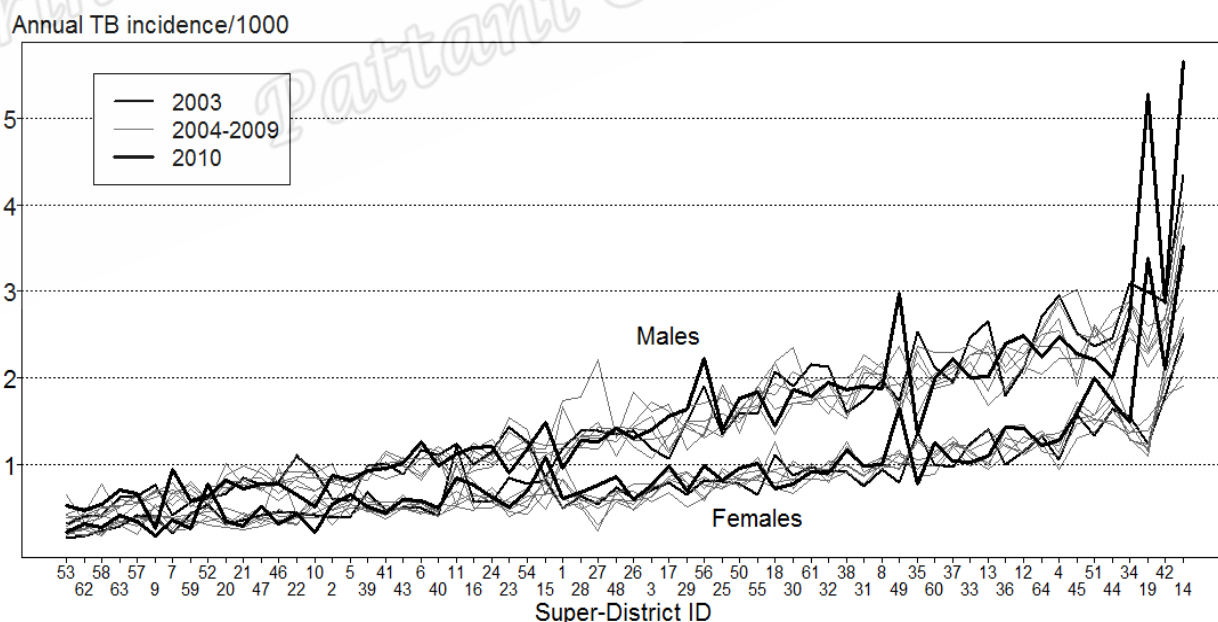

Figure 1: Distribution of TB incidence/1000 in Nepal by super-district 2003-2010

Statistical Analysis

While fitting the model, we detected outliers in the data. The residual plots before and after omitting 13 residuals greater than 3 in magnitude are shown in Figure 2. Seven of these outliers occurred in 2010. The gender, super-district ID and year of the 13 outliers are listed in the legend in the graph (left panel). The omission of outliers makes the normality assumption plausible.
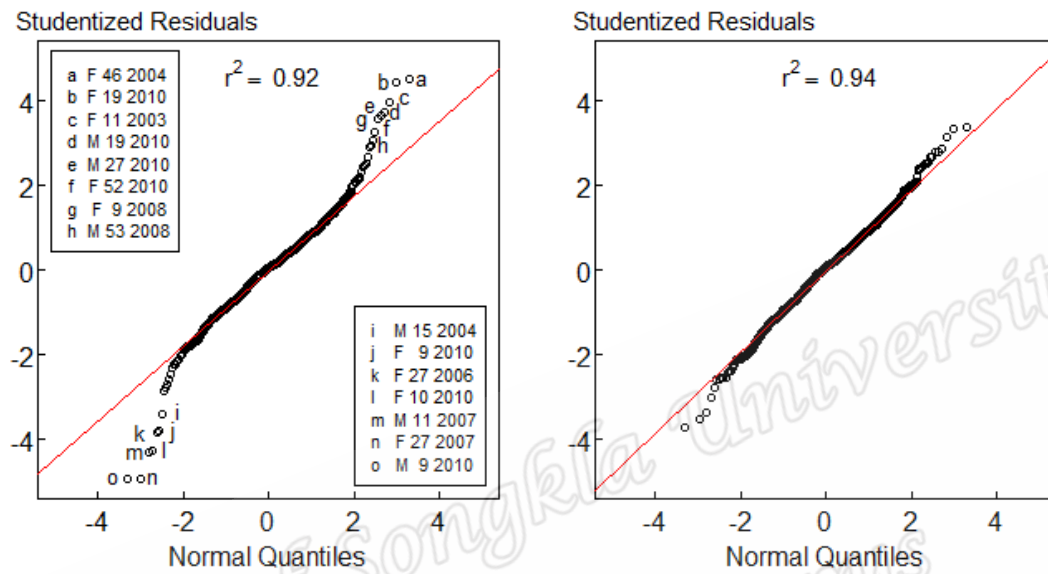

Figure 2: Diagnostic residual plots for log linear model before (left) and after omitting the outliers (right)

Figure 3 shows 95% confidence intervals for TB incidence rates by gender and year, adjusted for super-district. The horizontal dark lines denote mean incidence rates (1.70 per 1000 population for males) and (0.92 per 1000 population for females). For males, TB incidence showed a sharp increase for the year 2003-05, followed by a more moderate steady trend until 2008, when the increase again accelerated. For females, the trends of TB showed an increase for the year 2003-04, followed by downward trend until 2008, with a rise in recent years.
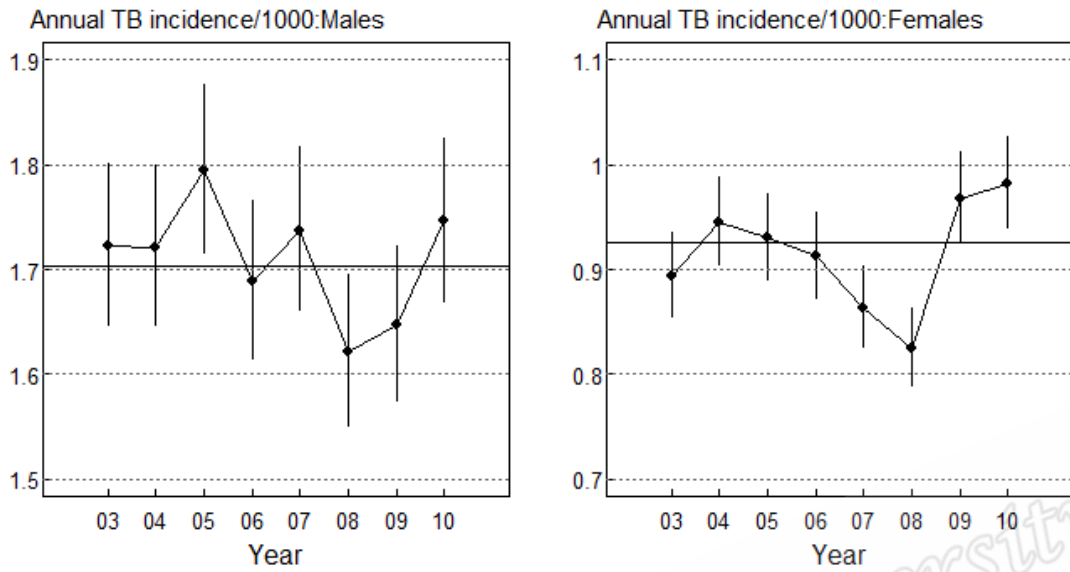
Figure 3: Annual TB incidence/1000 by gender and year, adjusted for super-district

Figure 4 shows 95% confidence intervals of annual TB incidence rates by super-district, adjusted for the effects of the gender and year. The vertical dotted lines represent the fourteen zones of Nepal and vertical lines represent the five development regions. The horizontal line denotes the mean incidence rate of TB for both sexes (1.31 per 1000 population).
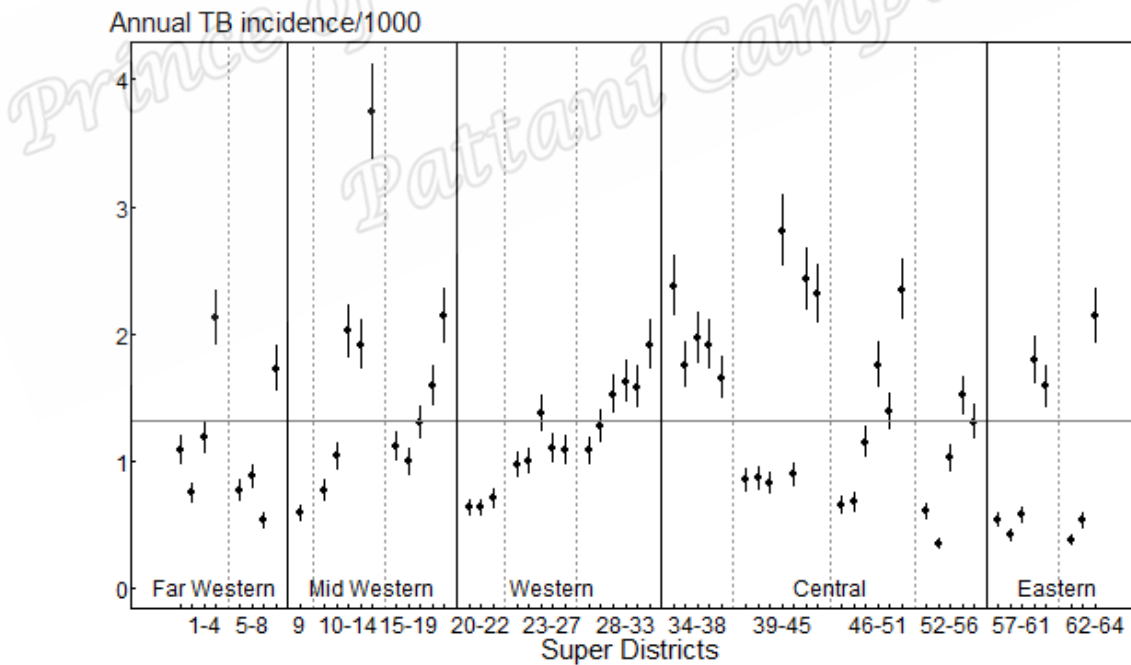

Figure 4: Annual TB incidence/1000 by super-district, adjusted for the gender/year

Super-districts with confidence intervals above the mean in Figure 4 were categorized as having a higher than average incidence (darkest shade), while districts with confidence intervals below the mean were categorized as having a lower than average

incidence (lightest shade) and super-districts with confidence intervals not evidently different from the mean were categorized as average (intermediate shade).

Figure 5 shows a thematic map based on this classification. The map shows a clear geographical pattern with the higher TB incidence occurring in most of the Terai region and some part of the Hill region.
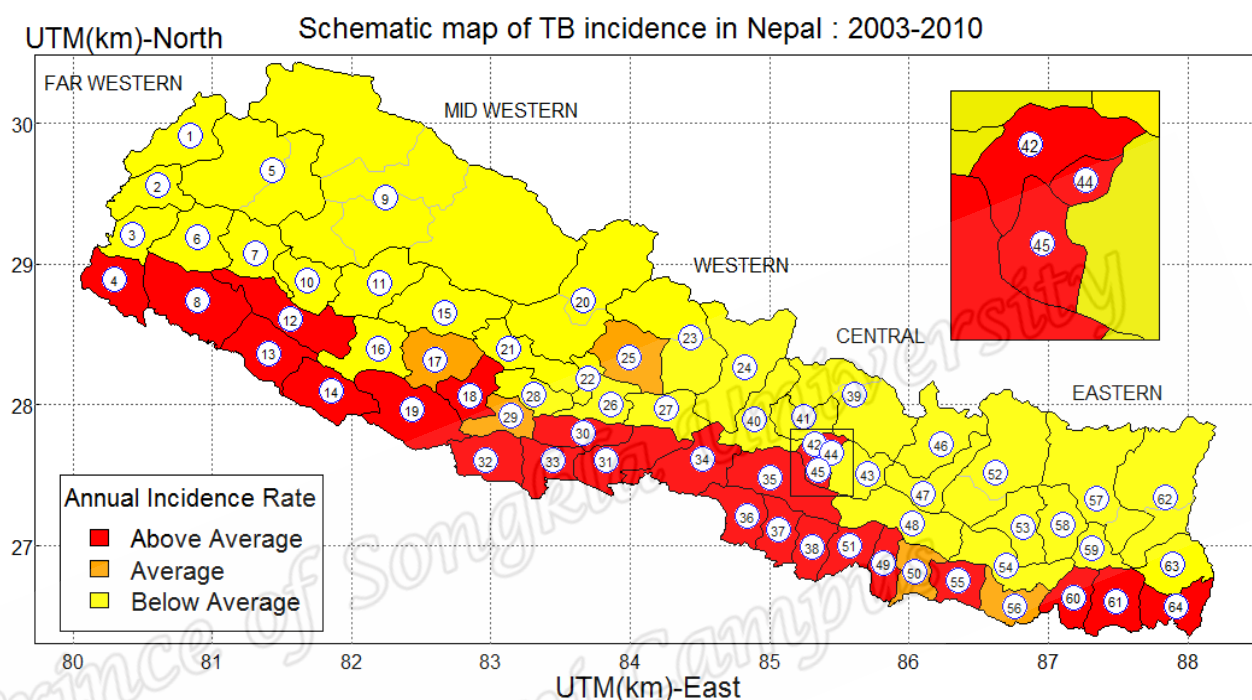

Figure 5: Schematic map of annual TB incidence rate in 64 super-districts in Nepal

DISCUSSION

The present study used statistical modeling to investigate the spatial and temporal variation of TB incidence in Nepal from 2003 to 2010. Linear regression models containing gender, year and super-district as factors were fitted to the log-transformed disease incidences. After omitting 13 outliers, this model provided an acceptable fit with an adjusted r-squared of 0.94. The overall incidence of TB was found to be 1.31 per 1,000 population. There existed marked gender difference in the incidence of TB; males had higher incidence rates than females. This is consistent with TB incidence and gender patterns found in recent studies in Nepal (Kakchapati *et al,* 2010) and also in accordance with other studies (Martinez *et al,* 2000; Borgdorff *et al,* 2000). Epidemiological findings and studies have reported that gender differentials in TB begin to appear between 10 and 16 years of age, and remain higher for males than females thereafter (WHO 2009b; Uplekar *et al*, 2001).

For the entire country, trends of TB incidence rate showed a sharp increase in years 2009-2010 for both sexes. The reasons for the increase were not investigated in our study, and could be due to an increase in HIV infection, multi drug resistance (MDR-TB) and the emergence of extensively drug-resistant TB in recent years (XDR-TB) (NTC 2010). Further research is needed to identify factors responsible for increased disease risk.

TB was distributed unevenly over Nepal: the higher incidence rates were found in the Terai regions. The high notification rate in the Terai region can be attributed to a combination of various factors such as medical, social and environmental factors. The Terai region is characterized by high temperatures, low socio-economic status, high population, malnutrition, high levels of poverty and social deprivation, all contributing to TB infection. There is also growing evidence that the reservoir of TB cases in the Terai has been inflated by people from neighbouring India crossing the border into Nepal to seek treatment. India occupies the first position on the World Health Organization's list of high burden countries (WHO, 2009a).

Besides this, TB incidences were found to be higher in highly populated metropolitan cities such as Kathmandu, Banke, Bhakthapur, Chitwan, Dang, Jhapa and others. The highest incidence was in Banke followed by the capital city Kathmandu. Several studies have indicated that urban centers had higher rates of TB than rural areas (Barr *et al*, 2001; Tupasi *et al,* 2000). Population density, migration, poverty and overcrowding appear to be major factors for disease transmission in these areas (Acevedo-Garcia, 2001).

There are some limitations in our study. It is based on secondary data and we could not include various risk factors for TB such as age due to unavailability of age-specific incidence data. Additional analyses are needed to evaluate the trends of TB using data for a longer study period, or more detailed incidence data (monthly, quarterly). However, the findings are illustrated by a thematic map showing the districts with high incidence rates. Such maps can be used by public health authorities for applying preventive measures to control TB outbreaks by focusing preventive measures according to priority in zones with high and increasing incidence.

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