Chapter 4

Conclusions and Discussion

This chapter includes the main results of three papers included in Chapter 3. The first section of this chapter summarizes the overall findings and statistical methods used in the studies. The second section discusses the implications of the studies. Moreover, limitations and recommendations are given in the last section.

4.1 Overall findings

Treatment Outcome of Multidrug-resistance Tuberculosis (MDR-TB) in Nepal

The aim of this study was to investigate the treatment outcome of 494 MDR-TB cases in Nepal from 2005 to 2008. 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. 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. It can be concluded 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 multidrug-resistant TB (Holtz et al 2006). The univariate and multivariate Cox proportional hazards models revealed no statistically significant associations between cure and age, gender and religion, confirming findings from other studies (Espinal et al 2000, Mirsaeid et al 2005). The survival analysis show time to sputum smear conversion and time to cure was found to be 24 months so it indicated that any treatment benefit was confined to the first 24 months. Studies revealed that the proportion of patients treated successfully improved when treatment duration was at least 18 months, and if patients received DOT throughout treatment (Orenstein 2009).

Forecasting Tuberculosis (TB) Mortality in Thailand using Multivariate Linear Regression

The objective of the study was to model and forecast TB mortality in Thailand using death certificate reports. Multivariate linear regression was used for modeling and forecasting age-specific TB mortality rates in Thailand. Age, gender, residential area by region in Thailand and year were selected as the explanatory variables in studying the mortality rates of TB. A total of 57,259 deaths occurred due to TB for 10-year period (2000-2009) in Thailand. Gender differences existed in the mortality of TB; males had higher mortality rates than females in most age groups and regions. This is reasonably consistent with TB mortality and gender patterns found in studies in Thailand (Jittimanee et al 2009).

Mortality was highest in age groups above 55 years for both sexes which could be due to the fact that co-morbidity and decreased immune function are important factors causing TB mortality among the elderly population (Dutt and Stead 1993, Salvado et al 2010). It can be noted that TB had the greatest impact on youth and adults and has become cause of death among adults (WHO 2008). The time trends indicate that the

TB mortality decrease in most age groups and remained stable in others 10-year period (2000-2009). Furthermore, the model also forecast that TB mortality gradually decreased for most combinations of age group, gender and region for 6-year period (2010-2015).

Spatial and Temporal Variations of Tuberculosis (TB) Incidence in Nepal

The objective for this study was to examine regional and temporal patterns of TB incidence in Nepal to determine the districts and gender groups with high disease risk. We used a log-transformed linear regression model containing additive effects associated with the gender-year and location. However, a diagnostic plot of residuals from this model indicated 13 outliers in the study. After omission of the outliers, these models provided a good fit, as indicated by residual plots and the r-squared statistic (0.94).

The findings showed marked gender difference in the incidence of TB; male had higher incidence than female, consistent 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 demonstrate that in most settings, TB incidence rates are higher for males, at all ages except in childhood, when they are higher for females. Studies have reported that sex differentials in prevalence rates begin to appear between 10 and 16 years of age, and remain higher for males than females thereafter (WHO 2003).

As for the entire country, trends of TB incidence rate showed a sharp increase in recent years (2009-2010) for both sexes. The reasons for the increase of TB cases were not investigate in our study, and could be due to increase in HIV infection and multi drug resistance (MDR-TB) and emergence of extensively drug-resistant TB (XDR-TB) which contributes to high incidence of TB in Nepal in recent years (NTC 2010).

TB was distributed unevenly over Nepal: the higher incidence rates were found in super-districts of the Terai and urban areas. 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, malnutrition, high levels of poverty and social deprivation, all contributing to TB infection. However, TB cases in the Terai, has been inflated by people from the neighboring country 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 2010).

However the lower incidence rates of TB in mountain area are consistent with the studies from Kenya (Mansoer et al 1999) and Mexico (Vargus et al 2004), which reported that the TB incidence decreases strongly with increasing altitude. The cause of the close inverse relationship of altitude and TB incidence might be related to the well known changes in alveolar oxygen pressure at different altitudes. The progressive decline of the barometric pressure as altitude decreases leads to lower alveolar oxygen pressure, which in turn inhibits the development of TB lesions.

Besides this, TB incidences were found to be highest in metropolitan cities such as Kathmandu, Bhakthapur, Chitwan, Dang, Jhapa and others. 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, Holtgrave et al 2004).

4.2 Statistical methods used

The reasons for selecting the statistical methods used for last two studies are discussed in this section.

The second study used multivariate linear regression to model TB mortality by age group and year, with forecasts based on fitting multivariate regression models for each sex and region. Multivariate linear regression is a logical extension of the multiple regression concepts to allow for mutually correlated response (dependent) variables. Multivariate regression estimates the same coefficients as one would obtain using separate univariate regression models and furthermore, the multivariate method also gives the covariances between the estimated parameters. The correlation should be taken into account when forecasting the age groups. If there is high correlation in age groups, it should be reduced to factors. In our study, the correlation varied substantially between age groups. So the multivariate linear regression is extended to factor analysis model by involving the weight sum of factors to data covariance matrix and minimizing the correlations between the factors for specified number of factors. Thus we obtained three factors (aggregations of mortality rates for data within the age groups defined by the factors) from seven age groups and use these combined rates for forecasting.

Furthermore, the advantage of the models is that they give standard errors for the estimated coefficients of the additional components and thus provide a basis for statistical inference on the patterns found. Although the Lee-Carter model is often used for forecasting (Lee and Carter 1992, Lee and Miller 2001), this non-linear model cannot be fitted by ordinary regression methods, and thus does not routinely provide standard errors for estimated parameters. So multivariate linear regression can be used an additional or alternative method to forecast disease mortality as it provides evidence of better forecasting as illustrated in our study.

The third study examined the spatial and temporal variation of TB incidence in Nepal from 2003 to 2010. The log-transformed linear model were fitted to joint effects of gender-year and location on the TB incidence rates and provided a good fit, as indicated by residual plots and the r-squared statistic (0.94). It can be noted that the log-transformed linear model provided alternative method for examining incidence rates. This model had been applied successfully in various studies and provided a superior method for data analysis to the alternative negative binomial model (Ardkeaw and Tongkumchum 2009, Kongchouy et al 2010). The advantage of these model is that confidence intervals for adjusted rates within each factor were computed in such a way that they could be compared with the overall mean. These confidence intervals depend on the standard errors from sum contrasts (Venables and Ripley 2002). A further advantage of these confidence intervals is that they provide a simple criterion for classifying levels of a factor into three groups according to whether each corresponding confidence interval exceeds, crosses, or is below the overall mean (Kongchouy 2010). For patterns of location effects, they can been shown on a thematic map with just three colours.

4.3 Implication of the results

The first study highlights the treatment outcome of MDR-TB in Nepal. Information from the study will be useful for setting up health policies for preventing, controlling and planning responses to MDR-TB in Nepal.

The second study presents insights into the mortality of TB by gender, year and location. The statistical modeling with graphic illustration provides a practical example to present the forecasting TB for six-year period. These graphs can be used by public health authorities for applying preventive measures to control TB mortality by focusing on groups at high risk. We recommend this multivariate linear regression method as an additional or alternative method to forecast disease mortality.

The third study should reflect the relative patterns of TB incidence with respect to demographic, spatial and temporal variations in Nepal. The findings are illustrated by a thematic map showing the districts with high incidence rates. There is urgent need of TB control measures on a sustained and long term basis on high TB burden areas of Nepal. The log-linear regression model could be used as a simple method for modeling disease incidence rates.

4.4 Limitations of the study

With respect to the first study, it was not possible to 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, duration of treatment, weight and prior hospitalization. Besides this, patient education or socioeconomic determinants can lead to incomplete treatment that can cause to resistance. Inadequate public health resources and unpredictable drug supplies also play a role in treatment of MDR-TB. These factors were not investigated in our study.

The second study had some limitations. The currently available data from the national vital registration 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. Moreover, the general mortality from TB also includes deaths due to co-morbidities and other external causes. So, reliable data on TB mortality are lacking.

The third study analyzed for short period (from 2003 to 2010). Additional analyses are needed to evaluate the trends of TB using data for a longer study period, or more detailed incidence data (monthly, quarterly). Second, we could not incorporate age, which is considered as one of the risk factors for TB, due to unavailability of age-specific incidence data.

4.5 Recommendations

Further research in this area is needed to determine other factors known to be associated with drug resistant TB, such as HIV infection, previous TB treatment, duration of treatment, weight and prior hospitalization. However, patient education or socioeconomic determinants and inadequate public health resources and unpredictable drug supplies also need to be assessed.

Further study is needed to investigate TB mortality in smaller regions, such as provinces or districts. Similarly, it would be useful to apply the multivariate linear regression method to additional examples of forecasting and modeling diseases.

Further research is needed to identify factors responsible for increased TB incidence in Nepal in recent years. Moreover, studies are needed to evaluate the trends of TB in high incidence areas using data for a longer time period.