Chapter 1

Introduction

Tuberculosis (TB) is a communicable disease that primarily spreads by the air borne route. Infection with tubercle bacilli is caused by three organisms including *Mycobacterium tuberculosis, Mycobacterium africanum, and Mycobacterium bovis.* They are the necessary causes of tuberculosis. *M. tuberculosis* is by far the most common. Thus, the risk of infection is strongly associated with the duration of intimate contact and the degree of infectiousness of the case. Crowding increases both the likelihood of coming into contact with a case and the closeness of the contact. (Comstock and Cauthen, 1993).

About one third of the world's population is infected by M. tuberculosis. In 1995, there were about nine million new cases of TB with three million deaths. Deaths from TB comprise 25% of all avoidable deaths in developing countries and 75% of TB cases are in the age group of 15-50 years (Maher, et al., 1997).

According to the third national tuberculosis survey in Thailand by the Tuberculosis Division during the 1991-1992 period, the infection rate among all age groups was found to be 29.5% (about 40.6% in the second survey in 1977). The prevalence rates were 1.01% and 0.24% based on x-ray examination and sputum examination, respectively. The number of tuberculosis patients registered for therapy increased from 43,000 in 1991 to 77,000 in 1995. The tuberculosis mortality rate (deaths per 100,000 population) declined during the 1990-1994 period, i.e., from 7.0 in 1990 to 5.9 in 1994. The highest death rate was found in the Northeast and the lowest in the South, being three times higher in males than females. The risk of death from tuberculosis was lowest (0.1 - 4.8%) for the population in the 0-24 age group and more than 75. Risks of 0.1 - 4.8% were found for those aged 25-49 and 70-74, and 11.3 - 2.1% for those aged 55-69 (Ministry of Public Health, 1996a).

Tuberculosis is the main complication of the hospitalized AIDS and ARC patients with an average proportion of around 40%, the highest proportion of above 60% has been found in Bangkok (Payanandana, 1995). An increase of HIV infection may impact on tuberculosis control, because the pathogenesis of tuberculosis infection and disease related directly to cell mediated immune system (CMI). The HIV infection that induced the CMI depletion leads to defective immunologic response to *M. tuberculosis* will change to pathogenesis of TB (Rattanadilok Na Bhuket, 1996a). Infection with HIV greatly increases the likelihood of reactivation of latent tuberculosis infection to active disease about 15-30 times (Aungsattapan and Rakrungtham, 1998). The closely relationships of TB and HIV co-infection lead to accompany epidemic.

The HIV epidemic has increased the burden of TB, especially in populations where the prevalence of TB infection is high among young adults. It is estimated that nearly two billion people world-wide are infected with *M. tuberculosis*, 16 million are HIV infected and five to six million are dually infected with *M. tuberculosis* and HIV. Seventy percent of dually infected TB/HIV people live in sub-Saharan Africa and 20% in Asia. HIV is the most powerful factor known to increase the risk of progression of TB infection to disease (Maher, et al., 1997).

One of the major public health problems in Thailand is tuberculosis, which has been compounded by the emergence of multi-drug resistant strains of *Mycobacterium tuberculosis* (MDR-TB) and increasing numbers of HIV infections. Single drug resistance and multi-drug resistant were observed in TB patients with HIV seropositive and the age group of lower 35 years (Rattanadilok Na Bhuket, 1996b). The number of AIDS patients increased from 448 in 1991 to 21,881 in 1996 (Kunanusol, 1998). It has revealed the great epidemic of HIV infection. It is clear that once the HIV seropositivity rate among new TB patients is another indicator reflecting the threat of HIV. Particularly in the upper Northern provinces of Thailand, new TB patients with HIV infection were found to increase from 5.4% in 1989 to 40.6% and 45.7% in 1994 and 1995, respectively (Ministry of Public Health, 1996b)

The prevalence of co-infection from HIV serosurveillance among newly diagnosed TB patients in Zonal TB Center 11, Nakhon Si Thammarat, dramatically

increased from 2.35% in 1992 to 20% in 1997 (Communicable Disease Control, regional 11 reports, 1994-1998). This situation clearly revealed the impact of HIV infection on tuberculosis control. Thus, global TB control should be strengthen in order to tackle TB problems in the situation of wide spreading of HIV. Furthermore, the discrimination of TB patients with and without HIV infection should be examined to obtain useful information that could be used for proper health management.

Objectives

The aim of this study is to investigate the differences in demographic factors, health status and behaviours, and disease characteristics of pulmonary tuberculosis patients between those with and without HIV infection. Many reports about HIV infection in TB patients did not clearly show the relationship between demographic factors (such as age, gender and occupation) and disease characteristics among TB patients and HIV infection. To strengthen the relationships, the investigation of demographic factors and disease characteristics should be conducted.

The investigation of HIV infection in laboratory is more effective, but we cannot examine individuals because of high cost of investigation. Thus, the relationships of demographic factors and disease characteristics of this study could be used as a characteristic diagnostic test for the investigation of HIV infected in pulmonary TB patients. The characteristic screening test is useful for the physicians' decision making to confirm HIV infection in laboratory.

The specific objectives are as follows.

1. To investigate the characteristics of pulmonary tuberculosis patients with and without HIV infection.

2. To develop a model to discriminate the probability of HIV infection in TB patients.

The research hypothesis is that the demographic factors, characteristics of disease, health status, and behaviours, of pulmonary tuberculosis patients with and without HIV infection are different.

Definition of Terms

A patient with pulmonary tuberculosis is a new patient who has a positive direct smear and/or an abnormal chest x-ray finding.

TB patient with HIV positive means a pulmonary TB patient who was investigated for HIV infection by the Elisa method and confirmed with Western Blot showing positive results.

Characteristics of disease comprise clinical signs and symptoms, chest x-ray finding and a degree of sputum.

- *Clinical signs and symptoms* are cough, haemoptysis, chest pain, dyspnea, fever, weakness, weight loss and other symptoms.
- *Chest x-ray finding* is an abnormal chest x-ray, classified into non-cavity, cavity and miliary.
- *Degree of sputum* is specified for acid fast bacilli positive in 4 grades as follows.

0 means acid fast bacilli could not be found.

1 means low density acid fast bacilli was found.

2 means moderate density acid fast bacilli was found.

3 means high density acid fast bacilli was found.

Health status and behaviours include receiving BCG, other diseases, smoking and drinking.

- *Receiving BCG* means that the patient received the BCG vaccine.

- *Other diseases* mean other current diseases accompanying pulmonary tuberculosis, such as diabetes mellitus, heart disease, hypertension and renal disease.

- *Smoking* means a personal habit, that is, current smoking or ever smoked and stopped less than 6 months ago.

- *Drinking* means a personal habit, that is, currently drinking some kind of alcoholic beverage, or past drinking and stopped less than 6 months ago.

Review of Literature

The review of the literature is divided into two sections as follows.

1. Tuberculosis and HIV infection.
2. Studies related to this study.

1. Tuberculosis and HIV Infection

1.1 Causes of tuberculosis infection and personal risk factors

The risk factors for becoming infected with tubercle bacilli are three related organisms *Mycobacterium tuberculosis, Mycobacterium africanum, and Mycobacterium bovis. M. tuberculosis* is by far the most common. M. africanum is rarely found outside of northwestern Africa. The diseases due to M. bovis are limited in developed countries by wide spread pasteurization of milk and in the developing world by the low consumption of milk along with the practice of boiling much that is consumed (Comstock and Cauthen, 1993).

There is some evidence that the risk of acquiring infection increases with age during the period from infancy to early adult life (Sutherland and Fayers, 1975), probably because of increasingly numerous contacts with other persons. Males are more likely to have been infected than females, again probably reflecting their opportunity for more and varied contacts in most societies. The personal risks of

developing tuberculosis are related to malnutrition, socioeconomic status, genetic susceptibility, low immune, psychosocial stress and institutional living.

1.2 Pathogenesis of tuberculosis infection

The infection of disease depends on the immunocompetence of the host. Tuberculosis infection and disease directly related to cell mediated immune system (CMI) especially CD4+ T lymphocytes, which involve in many aspects of the immune response to *M. tuberculosis*. Primary tuberculosis is most often a subclinical, or mild, self-limited illness. Although human primary tuberculosis is usually self-limited, the infection can progress locally or systemically when host defenses are inadequate. When tuberculosis infection occurs for the first time in adults, the disease resembles primary tuberculosis in childhood, with nonspecific lung infiltrates and lymphadenopathy, sometimes followed by tuberculosis pleuritis. An apical or subapical primary site, malnutrition, concomitant illness, immunosuppressive therapy, and most important, HIV co-infection are factors predisposing to progressive primary tuberculosis (Nardell, 1993).

1.3 Pathogenesis of tuberculosis in HIV infected persons

Tuberculosis develops by one of two pathogenetic sequences : (1) direct progression from recently acquired infection to disease; and (2) recrudescence of previously acquired, latent infection. Generally, in areas of low prevalence of tuberculosis, most cases arise from latent infection, because few new infections are occurring. However, because HIV impairs the mechanisms by which new tuberculous infection is contained, the risk of direct progression is much greater in the presence of HIV infection; thus more cases may be occurring by this sequence. The mechanisms of tuberculous infection are kept quiescent and are not well understood, but have been found to clearly involve in cell-mediated immunity. In the normal host, once the cell-mediated immune response to infection with *M. tuberculosis* develops, there is a likelihood of new exogenous infection being acquired. Infection with HIV greatly increases the likelihood of reactivation of the latent tuberculous infection, thereby leading to clinical tuberculosis. This cause has been found to be most common. However, because of the HIV-induced immune defect (CD4+ T lymphocyte), and

HIV-infected person who has been previously infected with *M. tuberculosis* may still be vulnerable to new infection.

It has been speculated that HIV infected patients are more likely to acquired tuberculous infection when exposed to *M. tuberculosis* (Daley, et al., 1992). It is clear that once the HIV-infected person becomes infected with *M. tuberculosis*, the infection can progress very rapidly to cause clinical disease (DiPerri, et al., 1989) In situations during which groups of HIV-infected persons are exposed to a patient with infectious tuberculosis, explosive outbreaks of tuberculosis may occur (Hopewell, 1993).

1.4 Clinical features

A patient with cavitary tuberculosis characteristically has persistent coughing and may have haemoptysis. Systemic symptoms of fever, weight loss, and anorexia are also associated with cavitary disease. The clinical manifestations of tuberculosis occurring in patients with HIV infection vary considerably, depending on the severity of the immunosuppression, because of the virulence of *M. tuberculosis*. Tuberculosis tends to occur earlier in the course of HIV infection.

In retrospective studies, a "typical" pulmonary tuberculosis is not the norm. Diffuse infiltrations commonly have been observed in the lower lung rather than the usual upper lobe involvement. Cavitation is unusual.

In prospective studies, the radiographic findings in patients with HIV infection are indistinguishable from those in patients who are HIV-seronegative. The findings include typical upper lobe infiltration, often with cavitation. A greater prevalence of atypical findings includes a higher frequency of adenopathy, diffuse or lower lobe infiltration and a lower frequency of cavitation, compared with HIV-seronegative patients. The prevalence of positive sputum smears and cultures is the same in TB patients with and without HIV infection (Nardell, 1993).

In HIV-infected patients, pulmonary TB is still the commonest form of TB. The presentation depends on the degree of immunosuppression. Table 1.1 shows how the clinical picture, sputum smear result and chest x-ray appearance often differ in early and late HIV infection (Maher, et al., 1997).

Table 1.1 Pulmonary TB features with stage of HIV infection

Features of pulmonary TB	Stage of HIV infection	
	Early	Late
Clinical picture	Often resembles post-primary pulmonary TB	Often resembles primary pulmonary TB
Sputum smear result	Often positive	Often negative
Chest x-ray appearance	Often cavities	Often infiltrates with no cavities

2. Studies Related to This Study

The studies related to this study are most simply described within each group of variables of interest, namely, demographic factors, characteristics of disease, health status and behaviours.

2.1 Demographic factors

Akksilp (1995) noted that the highest prevalence of HIV infection in tuberculosis patients and blood donors was found in the age group of 21-30 years.

Taweepvoradaj (1996) reported that the prevalence of HIV infection in TB patients in Takhli hospital was 7.2%. Most of them were observed in the age group of 20-39 years.

Hussain (1995) reported that demographic factors such as age, sex, marital status, occupation and geographic area, showed a significant relationship with HIV seropositivity in TB patients at a chest clinic center, in Bangkok. Among HIV seropositivity, 75% were in the age group of 25-44 years, 90% were males, 56% were unmarried and 52% were employed (as laborers). Educational status and monthly family income of the patients were also related to HIV seropositivity in TB patients. (PSU cd-rom network : 1998a).

Wangmanee, et al. (1995) found that the factor most significantly associated with initial drug resistance of *M. tuberculosis* in new patients at the Central chest clinic was a history of TB in the family.

2.2 Characteristics of disease

Al-Ghazzi (1995) reported that fever, cough, haemoptysis, lymphadenopathy, and signs of extrapulmonary tuberculosis were statistically different between TB patients with and without HIV infection, while generalized weakness, dyspnea and plural effusion were not statistically different in TB patients at Ratchaburi hospital. Chest x-ray findings and laboratory results were significantly different between TB patients with and without HIV infection. TB patients with HIV infection were more common in males in younger age groups, among single persons, those with higher levels of education, higher income, no history of previous diseases, and IV drug users. Residential area, smoking, alcohol consumption, and history of old TB were not significantly different between TB patients with and without HIV infection (PSU cd-rom network : 1998b).

Veerapand (1997) reported that patients with HIV infection usually have abnormal chest x-rays. Co-infection of HIV and tuberculosis, and chest x-ray findings were classified into three categories, based on stage of HIV infection or the levels of cellular mediated immunity (CMI). First, the reactive form or post-primary tuberculosis or typical form was found in the patients who have slightly lower resistance. They were found with the localized reticulonodular infiltration or mixed infiltration on upper lobe or superior segment of lower lobe and properly with cavity. Second, the atypical form was usually found in patients who have low resistance or late stage. The alveolar infiltration pattern was found on the middle or lower lobe. Cavity was rarely found because it occurred due to the interaction of hypersensitivity of cell-mediated immunity (CMI). When CMI decreases it reduces the cavity. The disseminated form is usually found in fine or coarse interstitial infiltration. Finally, normal chest x-rays are found in early diagnosis. Furthermore, the pathogenesis could be found in endobronchial tuberculosis.

2.3 Health status and behaviours

Montoya and Patricia (1997) reported a matched case-control study in Medillin and Cali, Colombia, where persons infected with and without HIV had low levels of protection against TB by BCG. The protective effect of BCG did not vary among HIV positive subjects. When the protective effect was determined against extrapulmonary forms of TB, the level of protection was 47% among the HIV negative individuals, which was statistically significant. In contrast, among the HIV positive individuals no protective effect was found. The interaction of HIV infection in the effect of the BCG against extrapulmonary TB was statistically significant. The presence of HIV infection modifies the protective effect of the BCG vaccine against extrapulmonary TB. (PSU cd-rom network : 1998c).

Wechakit (1997) investigated risk factors and rates of HIV infection among women attending Bangrak hospital, Bangkok, and found that the major risk factors of HIV infection among housewives were domiciliary place, education, consorting with a driver, drinker or smoker, and low or no condom use. For sex workers, the risk factors were alcohol drinking, smoking and low or no condom use.

From these findings, the following conceptual schematic diagram of HIV infection in TB patients is suggested as shown in Figure 1.1.

Figure 1.1 Schematic diagrams representation of HIV status in pulmonary TB patients