CHAPTER II

LITERATURE REVIEW

1. The TB Epidemic

TB is a contagious bacterial disease caused by *Mycobacterium tuberculosis*. Like the common cold, TB is spread through the air. The main source of infection is a person with TB of the lungs (pulmonary TB) who coughs, sneezes or spits, and spreads infectious droplets containing the bacteria into the air (WHO, 1999).

Once infected with *M. tuberculosis*, a person stays infected for many years, and often for life. The vast majority (90 percent) of people infected with *M. tuberculosis* do not develop the disease of tuberculosis. Active disease occurs in an average of 10 percent of those who are infected. Various physical or emotional stresses trigger progression from infection to disease. Any weakening of the immune system—for example, by malnutrition or HIV infection—increases the chances for disease to develop. Left untreated, a person with active TB will infect on average 10 to 15 persons a year (WHO, 1999).

An estimated one third of the world's population is already infected by Mycobacterium tuberculosis. Each year an estimated 8.4 million new cases are produced from this reservoir of infection, and 1.9 million people die of the disease (WHO, 2002). TB kills more young people and adults than any other single infectious

agent in the world today. The developing world is the worst affected claiming 95 % of all TB cases and 98 % of TB deaths. Additionally, 75 % of all TB patients in developing countries are among those in their most economically productive years (15-45) (WHO, 1999).

Thailand is one of the 22 TB high countries which includes the set of countries which account for 80 % of the world's burden of TB. The estimated annual numbers of cases and death are 38,000 (sputum smear–positive TB disease), 86,000 (total incidence of TB disease) and 13,000 (deaths from TB disease) (WHO, 2004).

The most effective approach to TB control is the identification and cure of these infectious cases. Proper treatment of infectious cases quickly makes them non-infectious so that they can no longer spread TB to others. Effective treatment breaks the cycle of transmission. Therefore. cure is the best prevention. This is even more important because of the emergence of drug-resistant TB (WHO, 2002).

Drug-resistant TB is a human-made phenomenon caused by inconsistent or partial treatment, when TB bacilli become resistant to the most common anti-TB drugs. This happens when doctors or health workers prescribe the wrong drugs or the wrong combination of drugs, the drug supply is unreliable, or patients do not take all their medicines regularly for the required period of time. Once the bacilli become resistant to one or more anti-TB drugs, the infected person can go on to infect others with the same drug-resistant strain. Multidrug-resistant TB is more difficult and more expensive to treat, and more likely to be fatal (WHO, 1999).

2. Situation of Tuberculosis Control

The forty-fourth World Health Assembly (1991) recognized the growing importance of Tuberculosis (TB) as a public health problem and the potential for cost-effective control using currently available tools (WHO, 1991). This led to a reassessment of ongoing TB control efforts. The persistence of TB has been due chiefly to the neglect of TB control efforts by governments, poorly managed TB control Programs, poverty, population growth and migration, and a significant rise of TB cases in HIV endemic areas. To address the situation, a new framework for effective TB control was then developed and a global strategy called DOTS was introduced (WHO, 2002).

DOTS (Directly Observed Treatment, Short-course) is known to be the most effective strategy available for controlling the TB epidemic today, and is composed of five key elements (WHO, 1999);

- Government commitment to sustained TB control activities.

- Case detection by sputum smear microscopy among symptomatic patients self- reporting to health services.

- Standardized treatment regimen of six to eight months for at least all confirmed sputum smear positive cases, with directly observed treatment (DOT) for at least the initial two months.

- A regular, uninterrupted supply of all essential anti-TB drugs.

- A standardized recording and reporting system that allows assessment of treatment results for each patient and of the TB control program overall.

This cost-effective strategy was developed from the collective best practices, clinical trials and programmatic operations of TB control over the past two decades.

Government commitment to sustained TB control is essential for the other four components to be implemented and sustained. This commitment must first translate into policy formulation, and then into the financial and human resources and administrative support necessary to ensure that TB control is an essential part of health services (WHO, 1999).

An important feature of DOTS is the basic management unit—usually covering a population of 100,000 to 150,000—that has the staff and resources to diagnose, initiate treatment, record and report patient treatment progress, and manage supplies. This basic management unit must operate successfully within existing general health services, which is critical for the full integration and effectiveness of TB control services in the primary health care network, particularly during this era of health sector reform (WHO, 1999).

Another important feature is a recording and reporting system used by health care workers to systematically monitor patient progress and TB program performance. This results-oriented system enables quality assurance of program implementation and treatment and cure of TB patients. Data collected as part of TB management can be a useful indicator of access to and quality of the general health system (WHO, 1999).

The therapeutic regimens recommended by WHO have been shown to be highly effective for both preventing and treating TB. However, poor adherence to anti TB treatment is a major barrier to its global control. Tuberculosis is a communicable disease, thus poor adherence to a prescribed treatment increases the risks of morbidity ,mortality and drug resistance at both the individual and community level (WHO, 2003).

3.   Poor Adherence to Tuberculosis Treatment

For several decades patients' non-compliance with treatment has been recognized as the most significant problem facing the Tuberculosis control program (Nagamvithayapong, 1998). Patients' non-compliance is the cause of treatment failure, relapse, and increase in drug resistance (Monie et al., 1982). Combs et al. (1987), Personne (2005) and WHO (1996) mentioned that the most serious problem hindering TB treatment and control is non-compliance of patients, which is believed to delay sputum conversion to smear negative, increase the relapse rates by 5-6 times, and help the emergence of resistant mutant strains.

A WHO report indicated in 2001 that the average default rate among smear positive cases in 22 high burden countries under DOTS strategy was 6.2 % while 10 % among non-DOTS cases (WHO, 2004). Gad et al. (1997) noted that in Alexandria, Egypt, 65.1 % of the sample studied of TB patients were compliant with the prescribed regimen. About one third of the patients were non-compliant, which may result in treatment failure. Pronab et al. (2003) mentioned that, under the India's national Tuberculosis program, treatment complete rate of only 30 % could be achieved, and

ultimately program did not make a significant dent into the problem. This was mainly due to treatment default which remains a serious problem in therapy.

According to the report from National TB program on the treatment outcome from 1999 to 2003, default rate was 19 % in Bangkok. The review of the National TB Program in Thailand conducted by WHO in 2003 highlighted that in Bangkok and the central region of the Thailand, the default rate is unacceptably high and needs to be investigated (WHO, 2004).

As such, treatment default has remained as the most significant problem challenging TB control program throughout the world especially in developing countries.

4. Definition of TB Treatment Default

Measuring the treatment adherence behavior of TB patients serves as a corner stone of any successful TB control. Great emphasis should be placed on assessing TB control program in terms of high levels of adherence among registered patients which in turn lead to the high cure rates, less resistances and complication and effective eradication (John, 2000).

Adherence may be measured using either process-oriented or outcome oriented definition. Outcome oriented definitions use the end-result of treatment ,e.g. cure rate, as an indicator of success. Process oriented indicators make use of intermediate variables such as appointment keeping or pill accounts to measure adherence (WHO, 2003).

Both definition of treatment default have been applied, depending on each program situation. For instance, according to the parameters described in the IUATLD, non-adherent TB cases were categorized into three groups, patients who interrupted treatment more than twice for more than a month with positive sputum smear status were called chronic interrupter, patients who interrupted treatment with positive smear status once in a month were called moderately interrupter, and those who interrupted treatment only one with negative sputum smear status were called slightly interrupter. Some countries like Pakistan followed IUATLD to define the interrupted TB patients (John, 2000).

However, from the perspective of TB control program management ,WHO defines an interrupted treatment (defaulted) patient as someone who did not collect drugs continuously for 2 months or more at any time after registration(WHO, 2004). Most of the countries including Thailand are following WHO guideline for the definition of TB treatment default in their TB control program.

5.   Factors that Affect TB Treatment Default

Many factors have been known to be associated with patient default. These factor have been gathered from a great number of studies undertaken throughout the world. The range of study to determine the factors contributing to the defaulting behavior of the patients includes socio economic status of the patients, patient characteristics, the relationship between health care provider and patient, the treatment regimen and health care setting.

Socio-economic factors

Socio demographic factors of TB patients has been illustrated as determinants associated with treatment default.

The age of the patients was reported to be associated with treatment default but detailed findings were varied among different researchers. Mamboya (2002) noted that defaulters were younger than non-defaulter (p-value ; 0.039) and also Singh et al (1976) found the highest default rate at the 21-30 years of age. However, Sivaraman (1990) reported that defaulting had shown peak levels at ages 40-49. On the other hand, some studies reported non-association between age and treatment default (Gad et al., 1997 & Chee et al., 2000).

Santa et al (2003) found that the male gender was significantly associated with high default rate. But some researchers reported that gender was not significantly associated with default (Gad et al., 1997 & Chee et al., 2000).

Chee et al. (2000) and Gad (1997) reported that occupation were not associated with treatment default.

Socio economic status of the patients seems to be important since patients' decision on whether they will continue treatment is likely to be affected by their social environment and economical status. It was reported that "three socio-economic variables, i.e. the monthly income per capita in a family, the type of house, and the monthly income" were the major determinants of adherence to treatment (WHO, 2004).

Lack of effective social support networks and unstable living circumstances are additional factors that create an unfavorable environment for adherence to treatment (WHO, 2003).

Patient related factors

Patient related factors are the important ones because the adherence is most dependent on the behavior of the people who receive treatment. It is said that, as far as the dynamics of TB therapy are concerned, a patient should be the central focus (WHO, 2003).

Conditions, circumstances and behavior of the patient have a strong relationship either to be adherent or non-adherent (John, 2000).

Since chemotherapy for TB patients takes more than 6 months, even in the short course regimen containing highly efficacious anti-TB drugs such as Isoniazid and rifampicin, it can be assumed that the continuous intention and motivation of the patients by themselves based on their knowledge and perception of the disease seem to be playing the fundamental role in order to complete the prescribed regimen without defaulting.

A study by John (2000) said that the complex perception of the patients, enormous traditional barriers and psycho-social conditions greatly interfere with the sustainability of the treatment.

Knowledge about TB has been known to be significantly associated with treatment defaulting among TB patients by many research results (Gad et al., 1997, OR=8.57), and Stewart (1984) mentioned that when patients know about the natural history of TB, its complications and the importance of complying with drug therapy, their adherence to the prescribed regimen was improved. In a similar study in India in 1992, the authors found that there was an association between compliance behavior of patients and their knowledge of specific aspects of the disease (Barnhoorn et al., 1992). Dick et al. (1997) said that knowledge about TB and a belief in the efficacy of the medication would influence whether or not a patient chose to complete treatment.

On the contrary, there was a finding that correlation between patient's understanding of etiology of tuberculosis and adherence to their treatment was not significant (WHO, 2004). Dick said in 1996 that patients with TB apparently fluctuate in the intensity of their motivation to complete their treatment and admit to considering defaulting many times during their long course of therapy.

In some TB patient, altered mental states caused by substance abuse, depression, and psychological stress may also play a role in their adherence behavior(WHO, 2003). Santha et al. (2003) noted that higher default rates were associated with alcoholism.

A variety of other reasons have been stated by other workers, such as family events, carelessness and forgetfulness, lack of time etc (Singh, 1972 & Mandoki, 1982 & Kashyap, 1977 & Chartterjee, 1977 & Khana, 1977).

Although treatment under direct supervision (DOT) might eliminate an element of "forgetfulness", "carelessness" and so on, feasibility of applying DOT for every patients who are under different circumstances could be challenging issue (WHO, 2004).

Disease related factors

It can be assumed that the demand for health care increases if people suffer from the disease more severely. Also improvement in disease symptoms may make patients relax and therefore likely to be non-adherent to the further treatment.

In this sense, features of the disease are potential determinants of compliance. Some strong determinants of adherence are those related to the severity of symptoms, rate of progress and severity of the disease, and the availability of effective treatment (WHO, 2003). Patients with active disease and those with severe symptoms are more compliant. Haynes (1979) and Gad et al. (1997) said that patients who experienced more cough, haemoptysis and sweating generally complied more to the treatment. These patients may have been more convinced of the severity of their disease.

On the other hand, it is a common problem in TB therapy that many patients stop taking anti-TB drugs if they feel better after initiation of chemotherapy (WHO, 2004).

Regimen related factors

Given the fact that the latest short course chemotherapy for TB lasts for 6 months, regimen related factors should also be taken into consideration.

The number of tablets that need to be taken, as well as their toxicity and other side effects associated with their use have been reported to act as deterrents to continuing treatment (WHO, 2003).

According to the result of research conducted by National TB control program of Egypt, the most important causes of defaulting were a patient's feeling of improvement, long duration of treatment, and fear of side effect (Tolba et al., 1995).

It was reported that even lack of inject able medications in a standard regimen might be perceived by some patients as a wrong treatment hence leading to their treatment default. One researcher was confronted by patients demanding changes in their treatment regimens merely because in their opinion oral medications were not "strong" enough to cure them (WHO, 2004).

Intolerance to drugs and temporary illness caused defaulting in some patients. Tuberculosis patients with other associated chronic diseases, e.g. diabetes or ischaemic heart disease, who receive other drugs on a daily basis, were less likely to comply with anti-tuberculosis treatment. This may be attributed to the complexity of compliance with too many drugs, especially for less educated people, in addition to the increased cost (Mandok, 1982 & Kahsyap, 1977).

Cator (2002) said that HIV positive status among TB patients was risk factor which were independently associated with default.

In contrast to these findings, Wong (1995) reported that associated disease did not contribute to non-compliance in his study.

Health care provider and service related factors

Currently there is a strong voice that patient is an active collaborator in the treatment process not a passive, acquiescent recipient of health professional's advice. The participants at the WHO Adherence meeting in 2001 noted that the relationship between the patient and health care provider must be a partnership that draws the abilities of each in a way of creating an atmosphere in which alternative therapeutic means are explored, the regimen is negotiated, adherence is discussed and follow-up is planned (WHO, 2004).

Pronab et al. (2000) undertook a comparative evaluation to determine the influence of organizational set-up on the defaulting behavior of tuberculosis patients in the States of West Bengal, Jharrkhand and Arunachal Pradesh. In this study, the defaulting pattern was analyzed in four centers, one of which was a private hospital, one an NGO and the other two were government institutions. Of the different types of organizations, government organizations showed higher rates of default (TB center, 38.1 % and District TB center, 29.3%) compared to the NGO (20%) and private hospital (10.78%).

This study did not investigate in detail the reason of high or relatively low default rate in certain health service setting, but did however show that organizational set-up of an institution was also a determinant for defaulting behavior of tuberculosis patients .

In 1995, Egypt TB Control Program conducted a study on the institutional factors contributing to TB patients defaulting through interviews with health workers considering the default problem from the health service provider's perspective. The study found that improper distribution of health providers among clinics, importance of training in improving knowledge of health providers, importance of health education for patients, significance of financial incentive, work environment and training as staff motivation management elements were institutional factors affecting health care seeking behavior of TB patients (Tolba et. al., 1995).

WHO (2003) said that poor developed health services ; health care providers who are untrained, overworked, inadequately supervised in their tasks ; inability to predict potentially non-adherent patients ; availability of expertise and flexibility in the hours of operation of treatment centers were health care team /health system-related factors affecting treatment default of the patients.

One analytical study in the UK reported that provision of financial incentives for health workers may give a better outcome particularly for the treatment of infectious disease like TB (Giuffrida et. al., 1997).

The literature describes over 200 variables associated with patients who default on treatment. Many of the cited determinants of default are unalterable, and the demographic, social and other patients characteristics often relate poorly to the intention or motivation and do not explain why some TB patients adhere to treatment despite having several unfavorable characteristics. After all, dealing with the treatment default in TB patients appears to be very complicated issue, which do not have concrete answer to remedy the situation of high default rate being reported everywhere under global TB control program (WHO, 2003).

Therefore, more dedicated efforts are needed to explore the answers to solve the serious problem faced in the area of adherence to TB treatment. A variety of research questions ranging from social and anthropological to clinical and programmatic studies still need to be raised.