CLINICAL OUTCOMES AND ECONOMIC BURDEN OF PATIENTS HAVING DIABETES MELLITUS AND TUBERCULOSIS IN THREE HOSPITALS IN MALAYSIA

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CLINICAL OUTCOMES AND ECONOMIC BURDEN OF PATIENTS HAVING DIABETES MELLITUS AND TUBERCULOSIS IN THREE HOSPITALS IN MALAYSIA

By

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This thesis is dedicated to...

To my mother (Mariam), my Father (Ishaq), my elder brother (Mohammed Rashad), my wife (Fardosa), and my children.

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In the name of Allah

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LIST OF ABBREVIATIONS

AFB	Acid Fast Bacilli
ACE	Angiotensin Converting Enzyme
AIDS	Acquired Immune Deficiency Syndrome
BCG	Bacille Calmette Guerin Vaccination
BMI	Body Mass Index
BOD	Burden of disease
CO	Central Obesity
COPD	Chronic Obstructive Pulmonary Disease
DFU	Diabetic Foot Ulcer
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DM-TB	Patients with combined diabetes mellitus and tuberculosis
DOTS	Directly Observed Treatment Short-course
EPTB	Extra Pulmonary Tuberculosis
ESRD	End Stage Renal Disease
GHPP	General Hospital Plu Penang
HbA1c	Glycated Haemoglobin
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HTN	Hypertension
HUSM	Hospital Universiti Sains Malaysia
IDDM	Insulin Dependent Diabetes Mellitus
INH	Isoniazid
LDL	Low Density Lipoprotein

MDRTB	Multiple Drug Resistant Tuberculosis
MS	Metabolic syndrome
MTB	*Mycobacterium tuberculosis*
NAAT	Nucleic Acid Amplification Test
NHMS III	Malaysian Third National Health and Morbidity Survey
NIDDM	Noninsulin Dependent Diabetes Mellitus
NTM	Nontuberculous *Mycobacterium*
PML	Polymorphonuclear leukocyte
PN	Peripheral Neuropathy
PTB	Pulmonary tuberculosis
PVD	Peripheral Vascular Disease
SLE	Systemic Lupus Erythematosus
TB	Tuberculosis
UMMC	Universiti Malaya Medical Centre
USM	Universiti Sains Malaysia
UKN	Unknown
WHO	World Health Organization

DAPATAN KLINIKAL DAN BEBANAN EKONOMI PESAKIT YANG MENGALAMI DIABETES MELLITUS DAN TUBERKULOSIS DI TIGA BUAH HOSPITAL DI MALAYSIA

ABSTRAK

Prevalens diabetes mellitus (DM) di Malaysia telah berkembang ke tahap epidemik. Sejak sekian lamanya peningkatan suseptibiliti pesakit diabetes terhadap penyakit berjangkit termasuk tuberkulosis (TB) telah dilaporkan. Jenis kajian adalah kohort berasaskan prevalens. Pesakit dalam kajian ini dibahagikan kepada tiga (3) kumpulan: Pesakit TB sahaja; Pesakit dengan DM sahaja; Pesakit yang mengalami DM dan TB. Setiap kumpulan terdiri daripada 200 orang subjek. Pesakit diabetes distratakan ke dalam tiga kategori umur. Pada awalnya, pesakit dikenal pasti secara rentas silang (cross-sectional) selama dua tahun. Dalam tempoh kajian, iaitu Mac 2005 – Mac 2008, setiap fail perubatan pesakit diteliti sekurang-kurangnya dua kali: pada awal kajian dan selepas dua tahun

Borang pengumpulan data yang memberikan maklumat tentang demografi dan klinikal pesakit digunakan. Pesakit TB dikelaskan berdasarkan penyakit: pulmonari, ekstrapulmonari, dan gabungan pulmonari dan ekstrapulmonari TB. Prevalens DM dan HIV dalam kalangan pesakit TB dinilai. Dapatan rawatan TB, komplikasi berkaitan dengan TB, dan jangkamasa jangkitan TB di nilai. Keutamaan diabetes dan TB dalam kalangan pesakit DM-TB ditentukan. Pesakit diabetes di bahagikan dalam tiga kategori umur. Jangkamasa hipertensi dan diabetes dikaji untuk menentukan yang mana didapati lebih utama. Untuk semua kumpulan, jumlah penyakit kronik dan komorbiditi yang terhasil sewaktu kajian ini dinilaikan. Selepas pengenalpastian sumber dan rawatan perubatan yang digunakan oleh pesakit, maka

kos bagi rawatan tersebut dinilai. Prevalens DM dan HIV dalam kalangan pesakit TB adalah 7.7 dan 29.9% masing-masing. Secara demografik, dalam kalangan kumpulan DM-TB terdapat lebih ramai lelaki(72%) dan merokok (45.5%) berbanding dengan 58.3% dan 33.5% masing masing dalam kalangan kumpulan TB. Prevalens TB pulmonary didapati lebih ramai dalam kalangan Cina(83.7%) dan India (75.5%) berbanding dengan 66.7% dalam kalangan pesakit Melayu. Wanita melayu lebih prevalens dalam kalangan pesakit DM sahaja.Perokok adalah lebih prevalens dalam kalangan pesakit Cina sementara pesakit India lebih kerap mengambil alkohol. Pesakit melayu juga didapati lebih prevalens dalam kalangan kumpulan TB sahaja. Secara klinikal 74% dari kalangan pesakit DM-TB mempunyai sputum yang positif berbanding dengan 51% dalam kalangan TB sahaja. Lebih kurang 87% dalam kalangan DM-TB yang mempunyai TB pulmonary berbanding dengan 59.% dalam kalangan TB sahaja. Kumpulan DM-TB juga mempunyai kadar mortality yang tinggi (15 kes) berbanding dengan 2 kes dalam kalangan TB sahaja. Kumpalan TB mempunyai pesakit yang lebih muda (purata 44.4 tahun) dan yang kurang berat badan (purata 49.3 kg) berbanding dengan purata 55.1 tahun dan 56.1kg masing masing dalam kalangan TB sahaja. Kumpulan TB sahaja juga terdapat pembedahan yang lebih tinggi (43%) berbanding dengan 17% dalam kumpulan DM-TB. Jangkamasa simptom TB didapati lebih panjang dalam kalangan kumpulan TB sahaja (4.5 bulan) berbanding dengan 2.6 bulan dalam kalangan TB sahaja. Dengan pengecualian pada COPD, semua penyakit kronik yang wujud bersama-sama adalah lebih prevalens dalam kalangan wanita. Kumpulan Diabetes mempunyai lebih banyak komorbiditi dan jangkamasa diabetes dan hipertensi yang lebih lama. Diabetes terjadi lebih awal berbanding hipertensi dan tuberculosis iaitu selama 4 tahun. Secara ekonomik, kos total kumpulan DM-TB adalah RM 4530 berbanding

RM 3082.8 dalam kalangan TB sahaja dan RM 6945.26 dalam kumpulan DM sahaja. Kos untuk penggunaan ubat ubatan secara kronik adalah RM 1663.5 untuk kumpulan DM-TB berbanding RM 631.7 untuk kumpulan TB sahaja dan RM 5160 untuk DM sahaja.

Kata kunci: Tuberkulosis, Bebanan Penyakit, Diabetes Mellitus, Kos, Mortaliti, Malaysia.

CLINICAL OUTCOMES AND ECONOMIC BURDEN OF PATIENTS HAVING DIABETES MELLITUS AND TUBERCULOSIS IN THREE HOSPITALS IN MALAYSIA

ABSTRACT

The prevalence of diabetes mellitus (DM) in Malaysia is growing to the epidemic level. Since a long time increased susceptibility of diabetic patient to wide range infectious diseases including tuberculosis (TB) has been reported. This study was intended to assess the clinical outcomes and economic burden of combined DM-TB condition. The type of this study is prevalence based prospective cohort. Study patients were divided into three groups: patients with TB infection only; patients with DM only; patients with coexistence of DM and TB. Each group included 200 subjects. Cases (DM-TB) were compared separately with DM only and TB only groups. Patients were first identified as cross-sectional and followed for a minimum of two years. During study period, March 2005-May 2008, each patient's medical file was reviewed at the beginning of the study and at the end of the study. Data collection forms containing required demographic, cost, and clinical information were used. TB patients were classified into pulmonary, extrapulmonary, and patients having both pulmonary and extrapulmonary TB. Prevalence of DM and HIV and other TB risk factors were studied. TB treatment outcome, TB related complications, and TB infectivity period were studied. Durations of hypertension, DM and TB were assessed. Diabetic patients were stratified into three age categories. Prevalence of chronic diseases was studied. A cost of health care resource utilization was studied. The prevalence of HIV and DM among TB patients was 7.7 and 29.9% respectively. Demographically, DM-TB group had more male gender (72%) and smokers (45.5%) compared to 58.3% and 33.5% respectively in TB group. Prevalence of pulmonary TB was more in Chinese (83.7%) and Indians (75.5%) compared to 66.7% in

Malays. Smokers were more prevalent in Chinese race, while Indians were more prevalent in alcoholics. Clinically, 74% of DM-TB patients were sputum positive compare to 51% in TB only. About 87% of DM-TB subjects had pulmonary TB compared to 59.5% in TB only group. DM-TB subjects also had more mortality rate (15 cases) compared to 2 cases in TB only group. TB only group had younger (44.4 years) and underweight subjects (49.3Kg) compared to 55.1 years and 56.1 Kg respectively in DM-TB group. Also TB only group showed more surgical operations (43%) compared to 17% in DM-TB group. TB symptom period was longer in TB only group (average of 4.5 months) compared to average of 2.6 months in DM-TB subjects. With the exception of COPD, all coexisting chronic diseases were more prevalent in females. Females were also more prevalent in DM only group. DM group had more comorbid, and longer history of diabetes mellitus and hypertension. Diabetes antedated hypertension and tuberculosis nearly for 4 years. The total cost of DM-TB group during the two years of study period was RM4530 compared to RM 3082.8 in TB only and RM 6945.26 in DM only group. Cost of chronic medicines during the two years of study was RM1663.5 for DM-TB group compared to RM 631.7 for TB only group and RM 5160 for DM only subjects. In conclusion, compared to TB only, DM-TB group showed more severe condition, higher mortality, and higher cost of treatment. DM only group showed higher number of comorbidity and cost of treatment.

Keywords: Tuberculosis, Diseases Burden, Diabetes Mellitus, Cost, Outcomes, Mortality, Malaysia.

CHAPTER ONE

INTRODUCTION

1.1 Background

Tuberculosis (TB) is bacterial infectious disease caused by *Mycobacterium tuberculosis*. The disease is the leading cause of death among infectious diseases, and around 2 million people died from TB in 2008 (WHO, 2011). Although fast increasing incidence of HIV diverted the world's concentration on the other infectious diseases, TB remained, especially in developing countries, as an important threat to the human health. As stated by Iseman (2000), tuberculosis has probably killed 100 million people over the past 100 years, although a cure was available in second half of the 20th century (Thomas *et al.*, 2003).

A strong correlation between illiteracy and poverty on one side, and tuberculosis on the other side is well documented. TB mainly affects disadvantaged-lower class people. Even within rich countries, TB mainly affects categories with lower level of education and income (Baker *et al*, 2008). The load of TB is overwhelmed with the increasing rate of HIV coexistence, multiple drug resistant TB, and homelessness. In 1993, the World Health Organization took an unprecedented step of declaring tuberculosis a global emergency (Ho, 2004).

Although an appropriate combination of antibiotics could cure 95 percent of tuberculosis and the widespread application of the only currently available vaccine, Bacille Calmette Guerin (BCG), tuberculosis is still out of control in certain areas of the world (WHO 2011). The disease that appeared to have been conquered in

developed countries in the twentieth century by biomedicine armed with powerful antibiotics began to reverse in the late 1980s.

There are numerous social and medical risk factors for tuberculosis. These risk factors are varied among different regions and social categories. Among well-documented TB risk factors are poverty, illiteracy, HIV, DM, and silicosis (Boucot 1957, Concato and Rom, 1994, Gandy & Zumla, 2002).

Diabetes mellitus (DM) is well documented as a medical risk factor for TB. Although the reason is not yet well elucidated, diabetic patients are more susceptible to infectious disease including tuberculosis than are non diabetic subjects (Boucot 1957, Masoodi et al, 2006).

Recently, as a result of economics and health services reforms in many countries and increased demand of health related technology, health economics studies are revolutionized. Economics of all chronic diseases and specifically diabetes became a matter of great interest because of increased life expectance, changes in priorities of the health care services that took place in many countries, and the advance that was made about the knowledge in prevalence, complications, and the intensive diabetic therapy. The more market-oriented approach to health services has sharply affected the rational distribution of the health care services (Gandy & Zumla, 2002). In Vietnam, during economic reforms, low income categories who could not pay according to the market cost suffered from inequality of health services (Dao *et al*., 2008).

1.2 Research Problem: Clinical Outcomes and Economic Burden of Patients Having Diabetes Mellitus and Tuberculosis in Three Hospitals in Malaysia

Resurgence of TB in the late 80s was attributed to numerous risk factors such as HIV, low TB project funding, migration from TB epidemic area, drug-abuse, and others. However, the role of diabetes mellitus was not highlighted. The burden of disease (BOD) in study includes epidemiology, morbidity, mortality and costs associated with the disease. The incidence and/or prevalence of disease are first studied and the percentage of people affected is reported. After stating the portion of a society affected by any disease, it is common to evaluate how far is the severity of the disease on affected people (morbidity), and if there are any complications that may result from the disease as well as the mortality attributable to the disease. Finally, the cost of the disease at different levels including the person affected, health care providers, and whole society is evaluated. Although BOD is sometimes expressed in the terms of cost of illness, however, more components are encompassed by BOD. BOD is measured by prevalence of the disease, morbidity, mortality, cost of illness as well as the disability adjusted life years (DALY) (Nahin, 2005). The burden of illness is first identified through epidemiological study, and then, the burden is translated into monetary unit.

1.3 Rationale for the Study

Although Malaysia is an Asian country with intermediate burden of TB, and is close to high TB burden countries; however, studies related to TB risk factors in the region are lacking. After searching through English medical literature, no studies related to the burden of DM-TB were done in Malaysia or other neighbouring countries, or even globally. Studies assessing complications of DM-TB are limited,

and require more details. High percentage of TB patients is diabetic, and implication of DM on TB is not well elucidated. The majority of the studies were cross-sectional diagnosis based estimates from population, or projection from previous studies and involve only a part of direct medical costs. Individualized studies like this research with reasonable follow-up time and assessing outcomes and complications related to the TB are time consuming and expensive, but reliable.

1.4 Hypothesis

The clinicians and researcher in Malaysia feel the significance of coexistence of DM and TB, and as a result there are two hypotheses in this study:

- Is the DM a leading risk factor for TB in Malaysia compared to other factors like HIV, multiple drug resistant TB, and drug-abuse?.
- Is the coexistence of DM and TB has impact on complications and treatment expenditure compared to DM only or TB only conditions?.

Null hypothesis: DM is not a leading TB risk factor in Malaysia, and comorbidity of DM and TB has no impact on the complications and cost of treatment of TB patient.

1.5 Significance of the Study

The study is highlighting the importance of diabetes as a TB risk factor. Although it is known that DM patients are more susceptible to TB infection than is the general population, however, this awareness is poor, and if DM is mentioned in the medical literature as a risk factor for tuberculosis, it is mentioned at the end of a long list of risk factors with low priority. This is while, according to the hypothesis of this study, DM is the first Malaysian medical risk factor for tuberculosis.

On completion of this study, it is hoped that it would be able to improve the information related to the preventive measures for both diabetic patient and society against tuberculosis through:

- a better understanding about the nature of DM-TB patient with respect to TB dispersion, and highlighting complications and economic burden of DM-TB,
- the study may suggest addition of preventive measures for DM patients, and
- highlighting the magnitude of diabetes as a risk factor for tuberculosis which may encourage clinicians and researchers to conduct further studies aimed to reduce the progression of TB among DM patients.

1.6 Aims

Generally the aim of this study is to assess the impact of combined DM-TB condition on the affected person, society as well as the resources of the country.

1.6.1 Objectives

Specifically, the objectives of this research are

- To determine the prevalence of diabetes and other TB risk factors among TB patients in Malaysia.
- To assess the association between DM and TB in the terms of complications and cost of illness.
- To assess differences of TB care in different hospitals and relation of this differences to the TB outcome.
- To highlight the severity of the combined DM-TB condition on the affected patients and the general population.

1.7 Theoretical and Conceptual Frame Works

Theoretically, DM patients suffer from immune dysfunction which negatively affects natural body's defence mechanism against infectious diseases like TB. The immune dysfunction and other factors like smoking and poverty may accelerate opportunistic infection with the resultant severe pathogenic status (see Fig 1.1). Conceptual frame work of the study and its steps is shown in Fig 1.2.

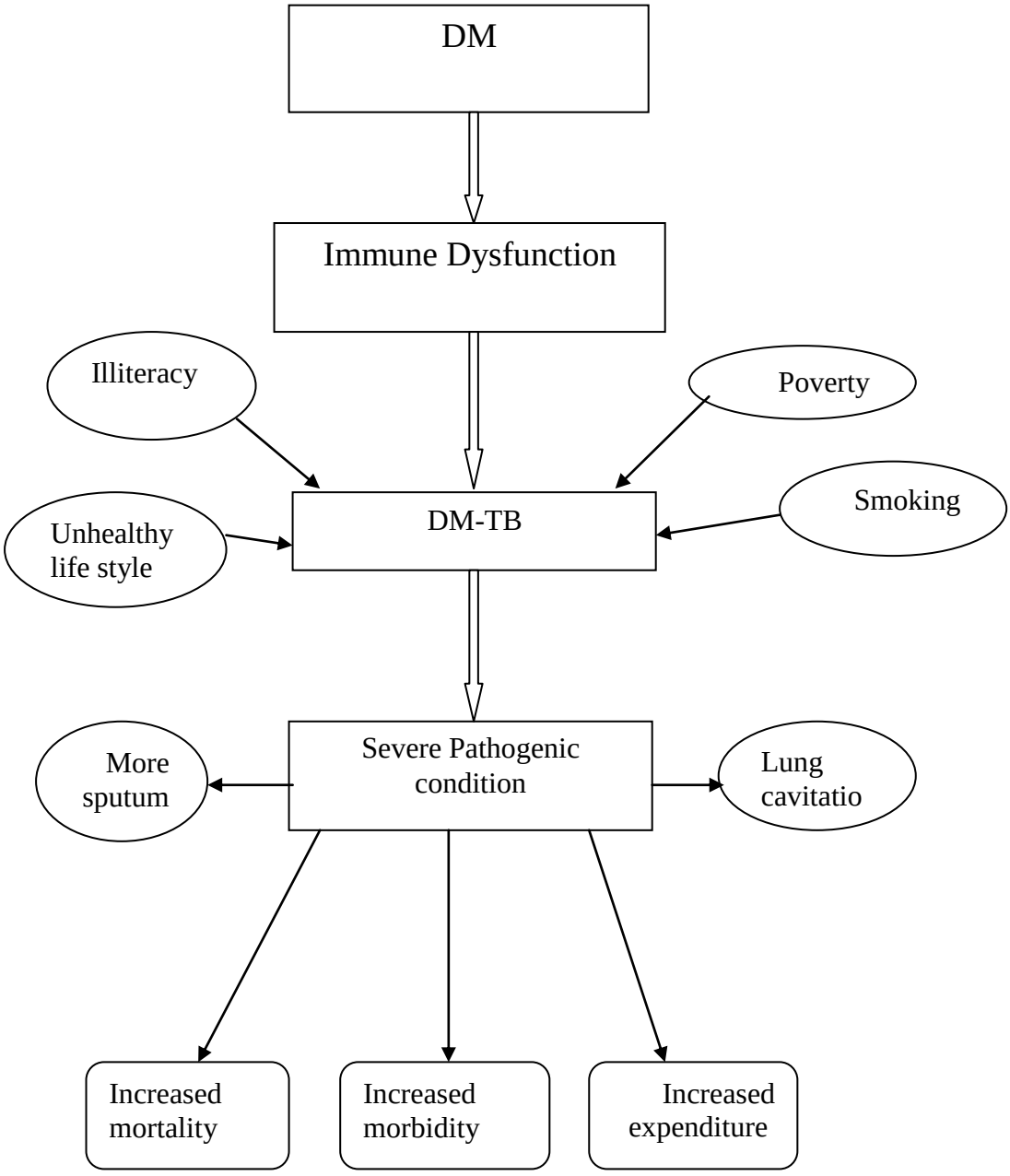

Figure 1.1: Theoretical Frame Work

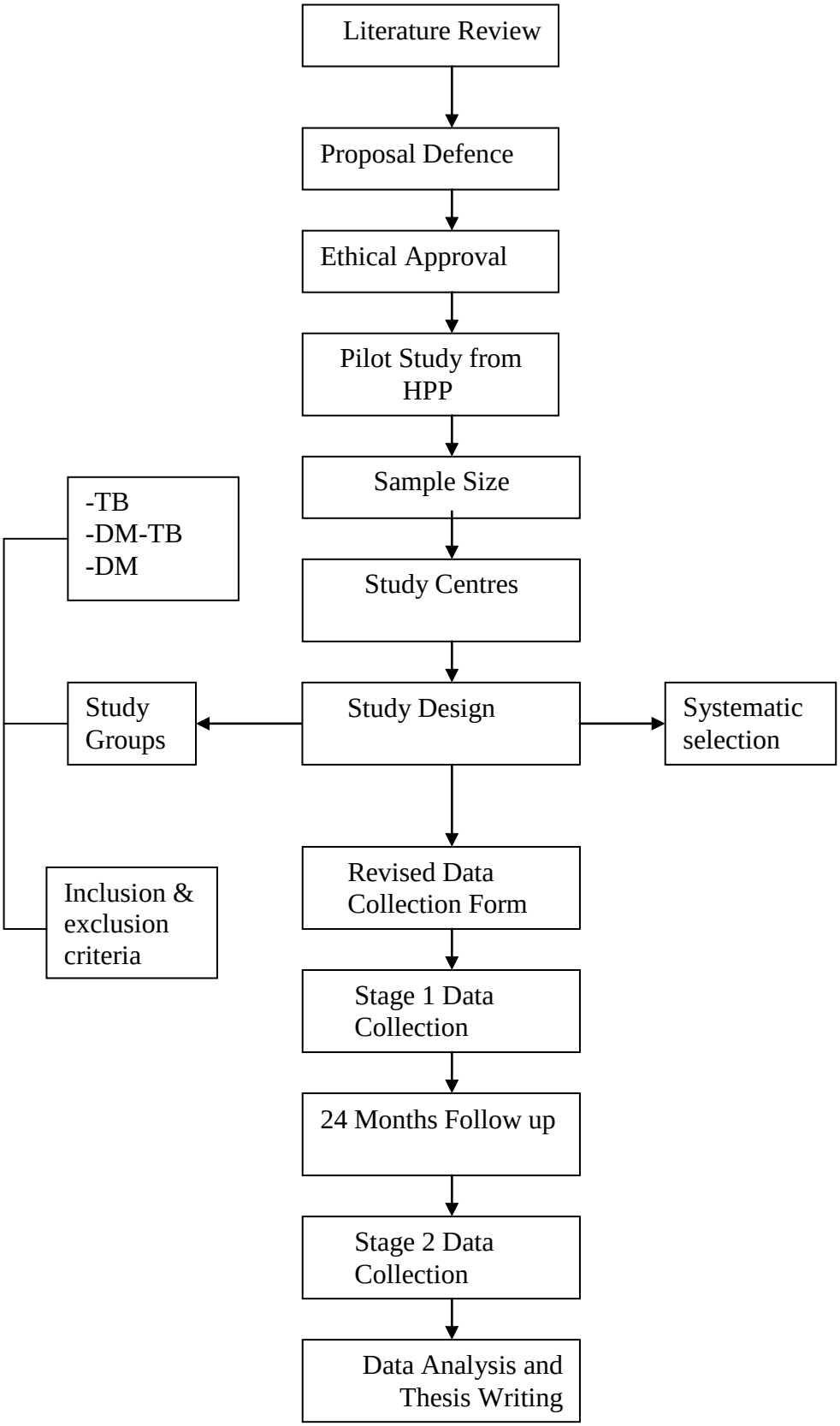

Figure 1.1: Conceptual Framework

CHAPTER TWO

LITERATURE REVIEW

2.1 Tuberculosis

2.1.1 Epidemiology of tuberculosis

Estimation and assessment of TB burden is difficult especially in those countries with poor infrastructure (Begum et al., 2007). However, after AIDS, tuberculosis is the world's commonest cause of death from infectious diseases (Thomas *et al*., 2003). Around one third of the world's human population has been infected by *Mycobacterium tuberculosis* (WHO, 2011). In 2008, there were around 11 million active TB cases including 9.4 million new cases. Only 5.7 million were detected including 2.7 million sputum-smear positive cases (WHO, 2011). TB causes the death of millions of people each year including 100,000 children under the age of 5 (Gandy & Zumla, 2002). Although mortality from TB disease has substantially declined in the developed countries, the situation in the developing countries has been totally different. TB disease remained, especially in poor countries one of the most feared and stigmatized disease (Saunderson, 1995). There is growing recognition that the conquest of this disease cannot be achieved by medical advances alone. The disease is a complex interplay between political, social, economic, cultural, and biological factors. The emergency of drug resistant strains of TB, the prevalence of coinfection with HIV and social and economic factors are the main contributory factors of the disease.

Geographically, prevalence of TB varies. In Malaysia, TB notified cases per 100,000 people were 80, 64.7, and 48 in 1977, 2000, and 2006 respectively (Iyawoo,

2004, NHMS III, 2006). In US, since the middle of the19th century, the disease has been following a decreasing trend of mortality rates from 194.4 per 100,000 in 1900 to 9.0 per 100,000 in 1955 (Boucot, 1957). Currently, incidence of TB ranges from 8 per 100,000 populations in rich countries like North America and Western Europe to 410 per 100,000 in low income countries (WHO, 2011). In rich countries, the disease is the disease of the inner city and urban population where socially lower classes reside. According to the New York City Department of Health, the incidence of TB in New York was 3 times higher than the national rate (Bashar *et al*. 2001). Within New York, the incidence was 10 times higher in the inner city compared to the other parts of the city. Although in earlier decades TB had been a disease of the general population, later on by the 1980s, TB had become primarily the disease of disadvantaged people.

Although Sub-Saharan Africa has the highest incidence rate, China and India have the largest world-wide case loads. India, China, Indonesia, Bangladesh, and Pakistan together account for more than half the global burden. Around 80% of new cases occur in 22 high-burden countries. However, as per Ministry of Public Health (1990), the prevalence of TB was declining in China since 1979 (796 per 100,000) to 138 per 100,000 in 2010 (China Tuberculosis Control Collaboration, 2004; WHO 2011). Because of economic reforms, certain countries like members of the former Soviet Union have increased case load for the last decade.

The incidence of TB is increasing in many parts of the world due to the unfortunate coexistence with human immunodeficiency virus (HIV) infection, poor living condition, and multiple drug resistance (McMurray, 2003; Ho, 2004; Needham

et al., 2004). People with dual infection, TB and HIV, have a higher mortality rate of 2.5 fold. In addition to HIV infection, resurgence of TB is mainly due to drug abuse, and poor living conditions (Blanc-Perez *et al*., 1998). In America, HIV is the main risk factor. In a 1993 report of one of the hospitals in Atlanta, USA, about 40% of newly diagnosed TB was HIV positive. A similar result was reported in US metropolitan areas (McGowan & Blumberg, 1995).

Economic factor was highlighted in earlier times when the TB disease was concentrated in the lower socioeconomic classes as a result of malnutrition and large dosage of infection due to crowding (Boucot, 1957). Poverty, infrastructural decay, and declining health services have facilitated the spread of TB. The more market-oriented approach to the health care services has sharply affected the rational distribution of the health care services. Even in the developed countries such as UK, the current increase of the disease can be attributed to widening the social inequality. The funding of the TB control is lower than other infectious diseases such as malaria, leprosy, and AIDS. Poverty and malnutrition, gender inequality, and inadequacy of medical services are central elements of the disease resurgence. Fear from stigma is a cultural factor (Gandy and Zumla, 2002). Occasionally, active tuberculosis may occur at higher socioeconomic levels due to the massive exposure as in case of health workers or as a result of comorbid with other special disease (Boucot, 1957).

In the general population, tuberculosis increases with increasing age. However, age factor is dependent on the region. In developed countries, the disease mainly affects the elder population; while on the other hand, the disease mostly

affects people in their productive ages in developing countries (Boucot, 1957, Iyawoo, 2004).

By sex, tuberculosis is more frequent among men than among women. Once infected, women in their reproductive age are more sensitive to develop TB than the men of the similar ages. TB is the third leading cause of death worldwide among women aged 15-44 (WHO, 2011).

2.1.2 Diagnosis

Diagnosis of TB depends on the likelihood that someone is susceptible to the infection; the state of the disease whether it is latent infection or active tuberculosis; anatomical site of infection, whether it is pulmonary or extrapulmonary; diagnostic tools, whether it is clinical, laboratory, and X-ray; screening modality, whether it is detected through active, passive or other ways of screening; and geographical areas. Diagnosis of probable TB requires at least one of three elements: positive sputum smear for AFB, strong clinical suggestions, and chest x-ray suggesting TB. However, each of these elements is relatively insensitive and non-specific (Centres for Disease Control and Prevention, 2011).

2.1.2(a) Physical evaluations

Clinical manifestation of the disease partially depends on the anatomical organ involved and can be classified into systemic and organ related symptoms. Low grade of fever, weight loss, and loss of appetite are relatively non-specific systemic symptoms (Sepkowitz, 2001). Early tuberculosis may be asymptomatic or there may be vague complaints of fatigue, anorexia, low-grade fever or slight cough. On the

other hand, haemoptysis may be the first strong symptom. Haemoptysis may sometimes accompany the cough. Locally, acute pleuritic pain, high fever, sweats, rapid weight loss, and racking cough are manifestations of advanced pulmonary TB. However, the clinical manifestation of TB may be obscured by coexisting diseases such as HIV, DM, cancer and others. Cough which is the most common feature of pulmonary tuberculosis is initially non-productive, which subsequently, as a result of inflammation, progresses to productive (American Thoracic Society, 2000).

Extra-pulmonary tuberculosis is problematic in terms of diagnosis, and costly because of its non-specific clinical manifestation. It is one of the challenges to physicians especially in those countries with low TB load. Disseminated tuberculosis which is also known as milliary TB results because of inadequacy of the host defences in containing tuberculous infection and involvement of the infection in multiple body organs. Because of pulmonary involvement, cough may accompany disseminated TB. Lymph node tuberculosis is the most frequently encountered extra-pulmonary TB. It is characterized as a painless swelling of one or more lymph nodes. Supraclavicular fossa and posterior or anterior cervical chain are the most commonly involved sites. In children, intra-thoracic adenopathy that compresses bronchi is common. Fever and pleuretic pain are the manifestation of pleural TB. Effusion, cough and dyspnoea may also occur. Skeletal tuberculosis is characterized by skeletal pain, swelling of affected joints and limitation of movement. In case of delayed diagnosis, vertebral tuberculosis may result in compression of the spinal cord with severe neurological consequences (Turgut, 2001). TB meningitis can result from direct meningeal invasion during a tuberculosis bacillemia at the initial infection or at the time of occurrence of breakdown of old pulmonary and/or

parameningeal foci. Headache, decreased level of consciousness, and neck stiffness are indications of meningeal TB. Symptoms of GIT TB are not specific and require differential diagnosis to exclude rectal carcinoma and appendicitis (Das *et al.,* 1996).

2.1.2(b) Laboratory investigations

Microbiological diagnosis of TB depends on area's prevalence rate, the type of laboratory equipments, and personnel qualification. Specimens that are required for TB diagnosis include sputum, gastric aspirates, urine, cerebrospinal fluids, pleural fluid, bronchial washings, biopsy of suspected tissues, bone marrow, and others. The diagnosis of active pulmonary tuberculosis is based on adequate bacteriologic or tissue proof. Investigations like fine needle aspiration cytology, biopsy from affected lymph node or pleural ascetic are helpful for extrapulmonary cases (Tripalthy, 2003). At least two out of the three sputum smear should be acid-fast bacillus positive to label the patient smear positive. Three sputum samples need to be taken from each person with suspected TB; one spot specimen and two early morning specimens. One positive sputum report is unreliable. If only one smear is positive, but the patient has radiological abnormalities, the case is diagnosed as an active pulmonary TB. In the presence of radiological abnormalities with persistent TB symptoms, the patient is also considered as a case of pulmonary TB, regardless of the result of sputum test outcomewhether it is positive or negative. When sputum is available, several specimens should be examined by smear and confirmed by culture. In the absence of sputum, cultures of gastric washing are indicated. Because of the possible false smear positive result due to the presence of nontuberculous acid-fast bacilli, care should be exercised for samples taken from gastric contents. Detection of acid fast bacilli (AFB) through sputum stained smears under microscope

is considered as the first indication of *Mycobacterium* presence in a specimen. The process is very quick, easy, and inexpensive. It provides preliminary information about the diagnosis of TB. Because detection of AFB is not specific, differentiation of tuberculous and nontuberculous *Mycobacterium* should be performed (American Thoracic Society, 2000).

Because of negative sputum result, bronchoscopy may be considered. If bronchoscopy is indicated, bronchial secretions rather than gastric washings should be studied. Bronchial secretions have the virtue of being aspirated directly from the suspected portion of the bronchial tree.

Culture is more sensitive than microscopy. However, diagnosis of *Mycobacterium tuberculosis* in children is not that reliable bacteriologically as in the case of adult TB patient. TB confirmation bacteriologically is not more than 28% in children compared to 90% in adults. Identification of *Mycobacterium tuberculosis* through culture and subsequent drug susceptibility are requested for treatment of TB.

On December 8, 2010, WHO endorsed a new test which is considered a major milestone for global TB diagnosis and care. Nucleic acid amplification test (NAAT) is considered very quick and accurate test compared with currently available tests (WHO, 2011).

The erythrocyte sedimentation rate may be elevated in active tuberculosis, but a normal sedimentation rate is not necessarily excluding the disease. Anaemia is the commonest haematological abnormality being more evident in the disseminated

forms of TB. The use of genetic-based tests may be helpful for further classification of patients with AFB smear positive disease. However, it is not practical for routine screening (Sepkowitz, 2001). Nucleic acid amplification technique and cultivation of *Mycobacterium* are helpful. Polymerase chain reaction and serologic tests are expensive with low-proven values especially for poor countries (Gandy & Zumla, 2002).

2.1.2(c) Radiology investigation

Chest X-ray findings are helpful although it is non-specific; because as per FitzGerald *et al*. (1991) report, 10% of pulmonary TB patients have normal chest X-rays (Sepkowitz, 2001). Changes in the roentgenogram may precede symptoms. Serial films are always more helpful than single radiology report. X-ray findings should be compared and interpreted with physical signs. The absence of abnormal findings cannot rule out tuberculosis. The presence of abnormal signs may not also necessarily mean tuberculosis. Cavitations, formation of scar with loss lung parenchyma volume and calcifications may be considered as indications of tuberculosis (China TB Control Collaboration, 2004). The extent of disease on X-ray was graded into 4 categories: normal, minimal, moderately advanced, and far advanced (Guwatudde, 2003).

2.1.2(d) Tuberculin Skin Test

Mantoux test is to diagnose TB infection for subjects who are at risk of TB infection. In the past, tuberculin test was of special importance for all practical purposes of TB diagnosis, except for the first three to seven weeks after infection. Failure to react to intracutaneous tuberculin was used to rule out active tuberculosis.

Recent tuberculin positive conversion after serial tests with negative results is of great value. If illness or X-ray changes occur, converters may be treated as tuberculous with confidence. Currently tuberculosis skin test using purified protein derivative (PPD) is used for the identification of latent TB infection. However, there is no reliable method of distinguishing tuberculin reactions caused by vaccination with BCG from those caused by natural *Mycobacterium* infection. PPD is not routinely applicable for poor countries (Gandy & Zumla, 2002). Low sensitivity in immune-compromised patient, cross reactivity with BCG vaccine and environmental *Mycobacterium*, the longer time required for the result of the test (48-72 hours), and the interpretation of the result are limitations of tuberculin skin test according to Huebner *et al*., 1993 (Thomas *et al*., 2003). Interpretation of tuberculin skin test depends on the prevalence of TB in specific geographical areas, the likelihood of TB infection, and comorbidity with other diseases.

In certain countries, especially those with low rate of TB, any test above 5-mm is considered as infection. In countries like China, the test is considered positive if, induration of 10 mm or higher was noted during 72 hours (Tuberculosis Control, China, 2004). However, in other countries with high TB burden and where a large proportion of adults and children have been immunized, the definition of positive skin test may be different. In subjects with BCG scar, it is impossible to distinguish between infection and immunization (Zangger *et al*., 2001). An increase in size by 5 mm between first and second test is considered to be suggestive of primary infection. In certain cases, like HIV patients, subjects with close contacts of infectious cases, and cases with fibrotic lesions on chest radiography, a reaction of 5 mm and upward is considered as positive. For subjects who are at risk, 10 mm and higher tuberculin

reaction is considered positive. By any means, reaction of 15 mm and above, the test is considered as a positive.

2.1.2(e) Biopsy

Fine needle aspiration cytology and other operations are used for suspected TB cases when other investigations could not finalize the diagnosis. Lymph node biopsy is an example of these procedures.

2.1.2(f) Other Diagnostic Measures

Patients with abnormal X-ray are treated with antibiotics as a diagnostic tool to differentiate tuberculosis from chest infection due to other bacterial species. Those not improved with antibiotics indicate more intense suspicion of TB infection.

2.1.3 TB Diagnoses and Resources

In general, diagnosis of TB is economic resources dependent. In countries with high prevalence of tuberculosis, possibility that direct smear positivity is due to *Mycobacterium* TB is more than 95%. Sputum cultures and individual drug susceptibility testing are expensive for poor countries and not necessary. For low resource countries, WHO recommends sputum microscopy and staining for acid fast bacilli. Higher resource countries, chest x-ray, sputum culture and susceptibility testing are used.

2.1.4 Classification of TB Diagnoses

TB cases are classified (according to the final labelling) into definite TB infection if culture results confirm TB; probable TB, when smear is positive, and

clinical presentation consistent with TB or moderate chest X-ray abnormality and response to anti-TB regimen. The possible TB is diagnosed if clinical presentation is consistent with TB; otherwise it is unlikely tuberculosis.

2.1.5 Non Tuberculous *Mycobacterium*

Differentiation of TB from other nontuberculous *Mycobacterium* is important for the final diagnosis of TB. Introduction of new technology in laboratory that can easily recognize nontuberculous *Mycobacterium* (NTM) and improvement in health services in many countries helped the isolation of NTM (Martin-Casabona, 2004).

2.1.6 Pathogenesis of Tuberculosis

TB is a member of bacterial groups known as *Mycobacterium* which contain *M. tuberculosis, M. bovis, M. africanum, M. microti, and M. canetti. M. tuberculosis* is transmitted via airborne from human to human, and there no known animal reservoir. The disease is transmitted from one person to another through the air. Air droplet nuclei are produced when the person with TB infection is singing, laughing, or talking. The droplets that contain germs of bacteria are suspended in the air; when someone breathes in the droplets of air containing TB germs, he becomes infected with TB. The size of the particles generated is important. Air droplets with particle size 1-5 microns in diameter are capable of inducing infection, because such particles are small and they penetrate the alveoli of the lungs. Also, these small air droplets can spread in the air easily and can be kept airborne for long time. Larger particles that are produced by TB patients, although they contain numerous bacilli, do not serve as effective media for disease transmission. These particles do not remain airborne, and if inhaled, do not reach alveoli. The airborne droplet containing *M. tuberculosis* remains the source of infection for minutes to hours after expectoration.

Once inhaled, the air droplet nucleus containing *M. tuberculosis* is transported through bronchial tree and deposited on a respiratory bronchiole or alveolus. The bacterium is then taken up by alveolar macrophages which is the starting point of struggle between exposed person immune system and the infection with the resultant of either successful containment of the bacteria or progression to active TB.

The risk of the TB infection is dependent on the duration of contact, and the extent of exposure. Infection with TB usually requires repeated, close, and long time contact. Transmission of *M. tuberculosis* is governed by the number and concentration of organisms expelled into the air, and the virulence of the organism. In the terms of proximity, TB cases among family members and close friends are considered first contact group, while classmate and teachers are classified as second contact group. *M. tuberculosis* grows shortly over 2-12 weeks until they reach 1000-10000 in number which is sufficient to provoke cellular immune interaction with tuberculin skin test. At this stage there is no sign of TB infection and a positive tuberculin skin test is the only indication for the presence of *M. tuberculosis*. Tubercle bacilli first spread through lymphatics to the hilar lymph nodes and then through blood stream to more distant sites. The host immune system like activated T cells and macrophages from granulomas limit the growth and the spread of tuberculosis. However, granulomas may contain only a few viable bacilli. The risk of developing TB is greatest during the first two years. Even if someone becomes infected with TB, the body defence mechanisms contain the infection and the person does not become sick easily. About 10% of infected persons with TB may develop tuberculosis in their life time. The remaining 90% will never get sick from TB

infection. Infection with TB is different from becoming sick with TB infection. The former is known as latent infection, while the latter is known as tuberculosis.

Tuberculosis may result from latent infection or from direct contact of active tuberculous patient. Someone who has been infected with TB for years gets change in health condition, body defence becomes weak, and the hidden latent infection becomes overt. In other ways, someone may first get tuberculosis by breathing in the TB germs directly from a sick patient, and the body is unable to protect itself against the disease. Adult patients with pulmonary TB may infect people in their environment because of their ability to produce sputum and transmit the germs than children do. Although transmission is possible, children and adolescents are rarely contagious (Zangger *et al*., 2001). Patients with acid fast bacilli (AFB) smear positive are more infectious, and each of these patients may go on to infect 10-15 persons per year if they are not treated. Sputum-smear positive cases are not only more infectious than smear negative case, but have higher fatality cases. Coexisting diseases such as HIV, diabetes, silicosis, treatment with steroids increase the chance of tuberculosis disease.

2.1.7 Tuberculous Related Complications

Tuberculosis related complications are documented for both pulmonary and extra-pulmonary TB. Tuberculosis is a bacterial infectious disease that usually attacks the lung, but it can affect any other parts of the body too. Anatomically, tuberculosis infection is divided into pulmonary and extra-pulmonary. The ratio of pulmonary to nonpulmonary depends on numerous factors such as geographical, and other coexisting diseases such as HIV and diabetes mellitus (American Thoracic

Association, 2000). The main site of the clinical manifestation is the lung. The lymph mode is the anatomical site that is affected mainly by extra-pulmonary TB. Tuberculosis lymphadenitis can be primary or postprimary.

Primary tuberculosis lymphadenitis that occurred as a complication after vaccination with BCG vaccine has been reported (Jakubikovå *et al*., 1996). Haematological complications were noted by numerous workers in pulmonary, disseminated, and pleural TB cases. In a Malaysian study, thrombocytosis and lymphocytopenia in TB patients were reported (Aweis *et al*., 2010). Lymphocytosis was observed in 69% of paediatric patients with abdominal TB (Veeragandham, 1996). Increased erythro-sedimentation rate, anaemia, leukocytosis, neutrophilia, severe lymphocytopenia, leucopenia, monocytosis, thrombocytosis, thrombocytopenia, and lymphocytosis were reported (Kony *et al*., 2000; Onarati, 2001; Singh, 2001). In addition to anaemia, thrombocytosis and hypercoagulable states that disappear 30 days after anti TB drugs initiation have been reported. This hyper-coagulable state may affect negatively patients with deep venous thrombosis (Turken *et al*., 2002).

Acute respiratory distress due to airway narrowing caused by enlarged tuberculous mediastinal lymph nodes was reported by Worthington *et al*. (1993). These respiratory complications developed or progressed soon after the initiation of anti-TB drugs. New or worsening of lymphadenopathy, fever, cerebral tuberculosis, and pleural effusion have also been noted. As suggested by Fisman *et al*. (2000), these reactions were linked to possible improved cell mediated immune function that might be secondary to damage of alveolar capillary membranes (Akira, 2001). Acute

respiratory distress resulting from mediastinal lymph node enlargement with critical compression of major airways requiring thoracic surgery in paediatric subjects with pulmonary TB was reported (Awad, 2002).

Respiratory failure is one of the complications of extra pulmonary TB. Respiratory failure secondary to extrinsic compression on the airways by enlarged lymph nodes is managed by decompressing the lymph by incision and not by excision. All these procedures require early intervention by multidisciplinary involvement and careful joint management (Awad, 2002).

Complication of TB can affect any part of gastrointestinal tract (GIT), from the oesophagus to the anal canal. Tuberculosis of GIT can be secondary to a primary focus in any part of the body or can develop primarily within intestinal tract. It is difficult to distinguish it from malignancy, Crohn's disease, appendicitis, and ulcerative colitis. Even in endemic areas the accuracy of clinical diagnosis is poor. Rectal tuberculosis is rare and accounts for 4.5% of the GIT tuberculosis. Because of its similarity to carcinoma its diagnosis is difficult. Diagnosis of oesophageal tuberculosis is difficult and requires a combination of different diagnostic methods. Dysphagia, cough related to the meals and chest pain as a result of esophageal fistulas were reported by Rämö *et al*. (1996).

Multiple drug resistant (MDRTB) is one component of TB complications. Although chemotherapy is the mainstay of all TB cases, surgery is reserved for the diagnosis or for the management of certain complicated cases like MDRTB. The rationale for considering operation is to excise specific areas where the TB bacilli

can hide itself from the effects of host defence mechanism and anti-TB drug therapy. Usually these areas are the gross cavitations where the nature of these areas can provide protection for the TB organisms. By ablation of cavitations, there is a possibility that the protective nature of cavitations is reduced and the organisms come in direct contact with the host defence system and chemotherapy.

Patients who remain smear/culture positive, despite adequate drug therapy containing appropriate drugs to which the resistant *Mycobacterium* TB strains are sensitive, are considered as candidates for the operation. It is not easy to specifically diagnose the area (reservoir) of resistant bacilli. A higher percentage of nonconversion rates among lobectomies (partial resection) compared to pneumnectomies was reported (Leuven *et al*., 1997).

Pneumothorax as a complication of TB has been reported and about 58.3% of pneumothorax cases were correlated with tuberculosis. Combined pneumothorax and active TB showed severe clinical conditions, demanding for more operative procedures like thoractomy, longer catheter aspirations and hospital stay (Blanco-Perez *et al*., 1993). Surgical operation is necessary for tuberculosis fistulas of the oesophagus for safety and more rapid recovery than by medical management alone and for diagnostic reason. Rectal TB responds very well with drug treatment. However, if the stenosis (stricture) persists for 3-6 months post chemotherapy, surgery is recommended for both treatment and diagnosis of possible coexisting malignancy (Das, 1996).

2.1.8 Treatment of TB

The hope to overcome TB disease is dependent on socio-political commitment that includes appropriate fund allocation with especial emphasis on society and health professional education, case detection and proper diagnosis, treatment with appropriate drugs, good supervision, and reduction of the patient's sufferance and financial load. Many patients have no realistic access to health facilities. The coexistence of HIV and TB is a complex matter that makes treatment difficult. The injectable drug, streptomycin, can become a source of HIV transmission if multiple uses of syringes applied. Stigmas that result from HIV and TB, is one of the obstacles for the eradication of TB (Saunderson, 1995).

Ensuring the completion of treatment for patients with TB is the most important issue of TB control. The ultimate elimination of tuberculosis requires an organized and smoothly functioning network of primary referral services based on cooperation between clinicians and public health programs. To ensure that the disease is treated appropriately, understanding the patients' perspective is important (Needham *et al*., 2003). TB treatment outcome is dependent on the structure and the managing team (Lin *et al*., 2006). In Taiwan, improved compliance with the treatment as a result of incentives paid to the patients was reported (Tsai *et al*., 2010). The newer short-course regimen is very cost effective. Cure rate of up to 86% was documented in Tanzania, the first country that implemented short-course chemotherapy regimen (Wyss *et al*., 2001).