EPIDEMIOLOGICAL AND CLINICAL OUTCOMES OF TUBERCULOSIS WITH ITS CO-MORBIDITIES IN GENERAL POPULATION AND IN PRISONS IN MALAYSIA

by

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DEDICATION

Words cannot repay the dedication, heroic efforts and not only financial as well as moral support of my father Mr. Umar Hayat Khan. This Research work is dedicated to my father Umar Hayat Khan, my mother Bukhari Begum, my brothers, my wife Nosheen Amer, our sons Zakir Hayat Khan and Umair Hayat Khan, my (late) uncle Ali Sher Khan and aunty Sakhi Jana Begum (late).

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Amer Hayat Khan

TABLE OF CONTENTS

Chapter 4: DISCUSSION

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND SYMBOLS

ABC	Abacavir
ADA	American diabetes association
ADR	Adverse drug reaction
AFB	Acid-fast bacilli
AIDS	Acquired immune deficiency syndrome
ARVT	Antiretroviral Therapy
ATAS	Anti Tuberculosis Association Sarawak
ATS	American thoracic society
ATT	Anti Tubercular Therapy
AZT	Zidovudine
AZT/3TC	Combivir
BCG	Bacillus Calmette-Guérin
CD4	Cluster of differentiation 4
CDC	Centers for disease control
COPD	Chronic obstructive pulmonary disease
CRC	Clinical Research Centre
CS	Cycloserine
CT-SCAN	Computed tomography
CXR	Chest x-ray
DDi	Didanosine
DIV	Delavirdine
dl	Deciliter
DM	Diabetes Mellitus
DNA	Deoxyribonucleic acid
DOTS	Directly observed treatment shortcourse
DRC	Drug rehabilitation centers
EFV	Efavirenz

ELISA	Enzyme-linked immunosorbent assay
EMB	Ethambutol
ESAT	Early secreted antigenic target
ETA	Ethionamide
FBG	Fasting blood glucose
FDC	Fixed dose combination
FNA	Fine needle aspiration
HAART	Highly active anti retroviral therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immune deficiency virus
IDF	International Diabetes Federation
IHD	Ischemic heart disease
INH	Isoniazid
IUATLD	International union against tuberculosis and lung disease
IVDU	Intravenous drug user
kg	Kilogram
LOA	Loss of appetite
LOW	Loss of weight
LPAs	Lymphocyte proliferation assays
LTBI	Latent tuberculosis infection
MDR	Multiple drug resistance
mg	Milligram
ml	Milliliter
MRI	Magnetic resonance imaging
MTB	*Mycobectirium tuberculosis*
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRC	National reference centre
NRTIs	Nucleoside reverse transcriptase inhibitors

NTP	National tuberculosis control programme
NVP	Nevirapine
OD	Odd ratio
OHA	Oral hypo glycemic agent
PA	Particle agglutination
PAS	Para amino salicylic acid
PCR	Polymerase chain reaction
PI	Protease inhibitor
PPD	Purified protein derivatives
PPD	Purified Protein Derivative
PZA	Pyrazinamide
RIF	Rifampicin
RNA	Ribonucleic acid
SM	Streptomycin
SOB	Shortening of Breathing
SSM	Sputum Smear Microscopy
STI	Sexually transmitted infection
TB	Tuberculosis
TST	Tuberculin skin test
TST	Tuberculin Skin Test
USA	United States of America
USAID	United States Agency for International Development
UTI	Urinary tract infection
WHO	World Health Organization
XDR	Extensive drug resistance
XDR-TB	Extensively drug-resistant tuberculosis
ZN	Ziehl-Neelsen staining
µL	Micron liter
µm	Micron meter

LIST OF APPENDICES

List of Presentations and Publications

Publications

1. Khan AH, Sulaiman SAS, Muttalif AR, Hassali MA, Khan TM: Tuberculous Lymphadenitis at Penang General Hospital, Malaysia. *Med Princ Pract* 2011; 20:80-84.

2. Amer H. Khan, Syed A. Sulaiman, Abdul R. Muttalif, Mohamed A.Hassali,. Anti-Tubercular Chemotherapy and Drug Induced Hepatitis. *HealthMed.* 2010; VOL 4, NO 3, 536-544.

3. **Amer Hayat Khan**, Syed Azhar Syed Sulaiman, Abdul Razak Muttalif, Mohamed Azmi Hassali & Ridhwan Abdullah. Gender differences in the prevalence of Tuberculous Lymphadenitis at the State of Penang, Malaysia: Findings from a cross-sectional study. *Archives of Pharmacy Practice*. Vol. 1, Issue 1, 2010.

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2. Syed Azhar Syed Sulaiman, Amer Hayat Khan, Abdul Razak Muttalif, M. Azmi A. Hassali. (2009). Epidemiological evaluation of TB among Diabetic Patient in three Malaysian states. International TB symposium & exhibition held at Pulau Penang, Malaysia. 18-19 March, Pp. 51.

3. Syed Azhar Syed Sulaiman, Amer Hayat Khan, Abdul Razak Muttalif, M. Azmi A. Hassali. (2009). Sustainable Health Evaluation of Tuberculosis in a Prison: Malaysian Experience. The 9th Asian Conference on Clinical Pharmacy held at CEOX, Seoul, Korea. 26 – 28 September, Pp. 21-22.

4. Abdul Razak Muttalif, Amer Hayat Khan, Syed Azhar Syed Sulaiman, M. Azmi A. Hassali. (2009). Outbreak of Tuberculosis in Pening Prison, Malaysia. Malaysian Thoracic Society, 11th Annual Congress held Kuala Lumpur, Malaysia.24th to 26th July, Pp. 33. **"Awarded 3rd Prize"**

5. Amer Hayat Khan, Syed Azhar Syed Sulaiman, Abdul Razak Muttalif, M. Azmi A. Hassali, Muhammad Abdul Hadi. (2008). Incidence of Tuberculosis among Diabetic Patients. The 8th Asian Conference on Clinical Pharmacy held at Surabaya, Indonesia. 1 – 4 July, Pp. 291.

6. Amer Hayat Khan, Syed Azhar Syed Sulaiman, Abdul Razak Muttalif, M. Azmi A. Hassali, Muhammad Abdul Hadi. (2008). Epidemiological Evaluation of Tuberculosis in the state of Penang: Malaysia: A retrospective analysis of year 2006. The 8th Asian Conference on Clinical Pharmacy held at Surabaya, Indonesia. 1 – 4 July, Pp. 146.

7. Amer Hayat Khan, Syed Azhar Syed Sulaiman, Abdul Razak Muttalif, M. Azmi A. Hassali, Muhammad Abdul Hadi. (2008). Incidence of Tuberculosis in a State Prison: The Preliminary Findings. Malaysian Thoracic Society, 10th Annual Congress held Kuantan, Pahang, Malaysia.18th to 20th July, Pp. 51.

KAJIAN EPIDIOMOLOGI DAN PENILAIAN KLINIKAL TUBERKULOSIS BESERTA DENGAN STATUS KO-MORBIDITI DI KALANGAN POPULASI UMUM DAN PENGHUNI PENJARA DI MALAYSIA

ABSTRAK

Ancaman penyakit tuberkulosis (TB) menunjukkan peningkatan yang ketara dengan ancaman kematian kepada kombinasi TB dengan status komobiditi seperti Virus Kurang Daya Tahan Penyakit (HIV)-Sindrom Daya Kurang Tahan Penyakit (AIDS), diabetes mellitus (DM) dan penyakit hepatitis. Melihat secara global populasi pesakit di penjara adalah berisiko tinggi mendapat penyakit ini berbanding populasi umum. Walaubagaimana pun tidak terdapat data yang mencukupi berkenaan jenis-jenis TB beserta dengan komorbiditinya di Malaysia. Tujuan kajian ini adalah untuk mengumpul data yang komprehensif berkenaan epidimiologi dan outcome dari rawatan TB sendiri dengan komorbiditi di hospital dan penjara di empat negeri di Malaysia. i.e Pulau Pinang, Sabah, Sarawak dan Selangor. Kajian retrospektif telah dijalankan dengan mengumpul data dari 9337 pesakit, dari rekod pesakit yang terdapat di hospital dan penjara dan juga satu kajian prospektif secara sesi soal-jawab, dari Januari 2006 sehingga Disember 2008. Daripada 9337 pesakit terpilih, 405 adalah dari penjara dan selebihnya adalah dari populasi umum. Data yang diperoleh telah dianalisa menggunakan perisian "Statistical Package for the Social Sciences" (SPSS). Jumlah tertinggi pesakit adalah dari negeri Sabah. Dari jumlah keseluruhan pesakit, majoriti pesakit (7781) menghidapi TB pulmonary (PTB). Daripada 1222 kes jangkitan *extrapulmonary tuberculosis* (EPTB), kebanyakannya adalah kes-kes lymphadenitis TB [325 (26.6%)]. Terdapat 8159 (87.4%) pesakit kes baru didaftar dan 675 (7.2%) adalah kes relaps (berulang).

Terdapat 6650 (71.2%) pesakt mempunyai sputum smear positif. Apabila faktor sosio-demografik dikaitkan dengan prevelans dari ketiga-tiga jenis TB di dapati kejadian adalah lebih tinggi di kalangan lelaki, tidak berkahwin, bangsa Melayu dan berumur diantara 31 – 50 tahun. Lebih daripada itu, kejadian PTB, EPTB beserta komorbiditi lebih tingi secara signifikan terjadi di populasi bandar. Meminum alkohol telah dikenalpasti sebagai faktor risiko untuk kombinasi PTB dengan EPTB. Prevalens TB-Hepatitis dan TB-HIV adalah lebih tinggi kepada lelaki belum berkahwin, tidak bekerja dan perokok dari kalangan bangsa Melayu, sementara TB-DM lebih tinggi di dalam bangsa Cina. Golongan yang berumur 56-65 tahun adalah lebih terdedah kepada TB-DM, manakala TB-HIV dan TB-hepatitis adalah lebih kepada golongan umur yang aktif secara seksual. Pesakit dengan DM mempunyai insiden lebih tinggi mendapat PTB (87.5%) dan pesakit dengan HIV/AIDS mempunyai insiden lebih tinggi mendapat EPTB (26.1%) dan PTB bersama EPTB (6.1%). Kadar insiden TB di penjara adalah 440/100,000 populasi. Penjara Selangor mencatat insiden yang tertinggi (755/100,000). Kebanyakan pesakit (78.9%) mengatakan batuk adalah simptom yang dihadapi. Ujian sensitiviti kultur adalah lebih pasti untuk diagnosis yang mana 70.6% pesakit memberi respond positif. Daripada 9337 pesakit, 7241 (77.6%) pesakit telah berjaya dirawat. Kejayaan rawatan adalah lebih tinggi dikalangan pesakit PTB (79.5%). Apabila TB-DM, TB-HIV/AIDS DAN TB-Hepatitis di nilai, 73.3%, 68.6% dan75.4% pesakit berjaya dirawat masing masing. Kadar mortaliti adalah lebih tinggi (23.8%) di kalangan kumpulan pesakit TB-DM-HIV. Faktor risiko yang dikenalpasti menyumbang kepada kadar mortaliti yang tinggi dalam kumpulan pesakit ini adalah usia yang meningkat, meminum alkohol dan bangsa Cina.

EPIDEMIOLOGICAL / CLINICAL EVALUATION OF TUBERCULOSIS ALONG WITH ITS CO-MORBID STATUS IN GENERAL POPULATION AND IN PRISONS IN MALAYSIA

ABSTRACT

The threat of tuberculosis (TB) seemed to have become increasingly looming with the fatal combination of co-morbid conditions like human immunodeficiency virus (HIV)-acquired immune deficiency syndrome (AIDS), diabetes mellitus (DM) and hepatitis. Globally, prison population is at a higher risk to acquire these diseases as compared to general population. However, there is no substantial data concerning the different types of TB and its co-morbidities in Malaysia. The aim of the present study was to obtain a comprehensive data pertaining to the epidemiology and clinical evaluation of TB alone and with co-morbidities in the hospitals and prisons of the four states of Malaysia i.e. Penang, Sabah, Sarawak and Selangor. A retrospective study was performed by collecting data of 9337 patients, from the patient records available at the hospitals and prisons and a prospective study was also conducted through direct question-answer session from January 2006 to December 2008. Out of the total selected 9337 patients, 405 were from the prisons and the remaining were from the general population. Data obtained was analyzed with Statistical Package for the Social Sciences (SPSS) software. The highest number of patients was from Sabah state. Among the total selected patients, majority of them (7781) had pulmonary tuberculosis (PTB). Out of the total number of 1222 patients with confirmed extra-pulmonary tuberculosis (EPTB), majority were suffering from lymphadenitis *TB* [325 (26.6%)]. Among the total number of cases, 8159 (87.4%) were newly registered and 675 (7.2%) were relapsed cases. Of the total number of patients 6650 (71.2%) were

found to be sputum smear positive. When socio-demographic factors were related to the prevalence of the three types of TB the occurrence was higher among the male population, unmarried, Malay race and the age group 31 - 50 yr. Furthermore, the occurrence of PTB, EPTB along with co-morbidity were significantly higher in urban population. Alcohol consumption was identified as a risk factor for PTB with EPTB combination. The prevalence of TB-Hepatitis and TB-HIV was higher in unmarried and unemployed male smokers of Malay race, whereas tuberculosis-Diabetes Mellitus (TB-DM) was predominantly seen in Chinese race. The older age group (56-65 yr) was highly affected with TB-DM, whereas TB-HIV and TB-Hepatitis was more in the sexually active age group. Patients with DM had a higher incidence of PTB (87.5%) and patients with HIV/AIDS had a higher incidence of EPTB (26.1%) and PTB with EPTB (6.1%). The incidence rate of TB in the prison was 440/100,000 populations. The higher incidence rate (755/100,000 population) was seen in Selangor prisons. Majority of the patients (78.9%) in the study complained of cough as the symptom experienced. Culture sensitivity test was the most reliable laboratory test for diagnosis, as 70.6% of the patients responded positively. Of the 9337 patients in the present study, 7241 (77.6%) patients were successfully treated. The Odd Ratio (OR) of patients treated successfully in the hospital compared to those in the prison was 6.696. The treatment success rate was highest in PTB group patients (79.5%). When TB-DM, TB- HIV/AIDS and TB-Hepatitis cases were assessed, 73.3%, 68.6% and 75.4% of patients were successfully treated respectively. The mortality rate was higher (23.8%) in the TB-DM-HIV group of patients. The risk factors identified for higher mortality rate in this group of patients were increased age, alcohol consumption and Chinese race.

CHAPTER 1
INTRODUCTION

1.1 General Introduction and Historical Background of TB

Tuberculosis (TB) is one of the most dreadful diseases, accounting for the life of number of humans. This outrageous disease is caused by *Mycobacterium tuberculosis* (MTB). Even though evidence exist that this disease was prevalent in the pre-historical era, revolutionary changes took place only in 1888 when Robert Koch discovered *Mycobacterium tuberculosis* (Daniel, 2006).

The genus *Mycobacterium* originated more than 150 million years ago (Hayman, 1984). In East Africa early progenitor of *Mycobacterium tuberculosis* was present as early as 3 million years ago, and literature suggests that it may have infected early hominids prevalent at that time (Gutierrez *et al.* 2005). Previous studies suggested that all members of *Mycobacterium tuberculosis* complex are the clonal progeny of a single successful ancestor, resulting from an evolutionary tail back that occurred 15,000 to 20,000 years ago (Sreevatsan *et al.*, 1997).

All kinds of currently present *Mycobacterium tuberculosis* (MTB) pathogen are found in East Africa. However, the spreading causes vary around the globe (Gagneux, 2006). *Mycobacterium tuberculosis* was detected in the DNA obtained from the tissues of Egyptian mummies roughly around 5400 years old. These findings further emphasize that TB was prevalent way back in the history. There are evidences describing the prevalence of tuberculosis in India and China 3300 and 2300 years ago respectively (Daniel, 2006). Archaeologist proved on the basis of archaeological evidence that tuberculosis was prevalent in America during the pre Columbian period (Arriaza *et al.*, 1995). Due to historical background and wide-spreading nature of tuberculosis, it was known by many

different names throughout the history like, King's Evil, Scrofula, Phthisis, White Plague etc. (Daniel, 1997; Daniel, 2006).

Laennec, with the invention of the stethoscope, elucidated the pathogenesis of tuberculosis and unified the concept of the disease, whether pulmonary or extrapulmonary (Daniel, 2004). Hermann Heinrich Robert Koch (1882) changed the history of tuberculosis significantly (Daniel, 2005). The bacillus causing TB known as "*Mycobacterium tuberculosis*" was described first by him. Due to his legendry contributions to bacteriology, for illumination of the etiology of TB he was awarded the Noble Prize in Medicine or Physiology in 1905. In 1890s Robert Koch prepared tuberculin which was used for pre-symptomatic TB test later-on.

In 1920's Assman introduced the theory of "Re-infection" (once treatment was completed the person gets infected again) which is still acceptable among doctors. Due to wide spreading nature of TB separate hospitals & clinics were used for treatment to save the life of coming generations. Such isolated treatment prevented the widespread of TB. There was a dramatic decrease in the mortality rates in the early and mid 19th century (Wilson, 1990).

1.1.1 History of Tuberculosis Therapy

Once it was assured that TB was an infectious disease, effective TB treatment methods were developed and in last 200 years, many new drugs have comming to existence. In the 18th century pulmonary collapse therapy was introduced by Italian physician Carlo Forlanini which was well accepted, especially for cavity closure, which modified into two other modes of treatment namely artificial and bilateral pneumothorax (Daniel, 1997).

Vaccine Development:

With smallpox vaccine invention, researchers hoped to use a less virulent strain of *M. tuberculosis* called *M. bovis*, which is the bovine strain of tuberculosis to prepare the vaccine. From 1908 to 1919, Albert Calmette and Camille Guérin in France serially passed *M. bovis* 230 times to result in a strain called Bacilli Calmette-Guérin, which was named as BCG vaccine. This vaccine was, for the first time, used in humans in 1921 and is still in use. However, *M. bovis* was equally contagious in humans because of cattle to human transmission.

Sanatoriums:

For TB management many sanatoriums were opened in the 20th century for the treatment and isolation of tuberculosis patients. Initially, they were only open to the privileged class but later on they were open for the privileged and under privileged patients. With the discovery of streptomycin and isoniazid in the 1940s, many of the sanatoriums were closed.

1.1.2 Chemotherapeutic History of Tuberculosis

Mortality rates due to TB began to decline in the early and mid 19th century (Wilson, 1990). The explanation for this decline remains unknown. Improvement in the socio-economic conditions, healthier food and introduction of chemotherapy might have contributed to the decline.

Even though chemotherapy against infectious diseases, using sulfonamide and penicillin, had been underway for several years, these molecules were ineffective against *Mycobacterium tuberculosis*. During World War II Para amino salicylic (PAS) and Thiosemicarbazone were discovered and in due course these were the first therapeutic

agents which showed efficacy in the treatment of tuberculosis (Ryan, 1992). Later in 1944 another success story came into the limelight, when Selman A. Waksman, Albert Schatz, and Elizabeth Bugie reported that purified streptomycin isolated and purified from *Streptomyces griseus*, the first antibiotic and first bactericidal agent was effective against MTB (Schatz, 1944; Ryan, 1992). A rapid succession of anti-TB drugs were developed in the following years. These were important because with streptomycin monotherapy, resistant mutants began to appear with a few months, menacing the success of antibiotic therapy. However, in the later years it was demonstrated that this problem could be overcome with a combination of two or three drugs.

1.2 Epidemiology

1.2.1 Epidemiology of Tuberculosis

It is believed that one among three is either infected with *Mycobacterium tuberculosis* or is at risk of developing the disease. According to WHO (2004a) global statistics on epidemiology of tuberculosis South East Asian region predominates and constitutes about 1.6 million cases followed by Africa and Western Pacific region, contributing to about 1.1 million cases. While, America and Europe accounted for 250,000 cases each in the same year. The global estimate for epidemiology of tuberculosis for the year 2004 was 8.9 million new cases and 1.7 million deaths (WHO, 2006). It was reported that the global incidence rate of tuberculosis was growing approximately 1.1% per year, and the number of new cases at 2.4% per year, while the number of deaths surpass the number of those caused by heart disease, cancer or any other infectious disease (WHO, 2004a). Most cases of tuberculosis (5-6 million) were diagnosed in the people aged between 15-49 years. It was observed that occurrence of TB was higher in male as compared to female. Furthermore, more than 90% of all tuberculosis cases and deaths occurred in the developing countries (Bloom, 1992).

In the early 1940s and 1950s, Tuberculosis was leading disease in the list of causes for death in Malaysia and it has been reported that tuberculosis was among the top five communicable diseases (Iyawoo, 2004). TB chemotherapy was available only in the late 1950s, when TB was the major cause of morbidity and mortality (MOH Malaysia, 2002). National TB control programme was introduced in 1961, and it played an important role in controlling TB across Malaysia. However in the last decade there has been a steady rise in the number of TB notifications in Malaysia. The incidence of TB in 1997 was 63.6 per 100,000 populations as compared to 61.0 per 100,000 populations in 1996 (MOH Malaysia, 1998). In the year 2000, total notified cases of TB were 15,057 and the incidence rate per 100,000 populations was 64.7%.

In Malaysia, highest disease burden was reported in Sabah followed by Wilayah Persekutuan, Sarawak and Pulau Pinang respectively (MOH Malaysia, 2000). Sabah accounted for about 29% or one third of the total new cases detected at national level and the annual notification rate were also the highest compared to other states in Malaysia (Jenarun *et al.*, 2003; Jiloris *et al.*, 2004). About 10% of TB cases notified in Malaysia were discovered among the immigrant population (Iyawoo, 2004). Treatment success rate in term of completion of treatment was about 82%. On the other hand, the mortality rate steadily declined in the year 2000 from 14 deaths to 7 deaths per 100,000 populations (Jiloris *et al.*, 2004). WHO classified Malaysia as an 'intermediate' TB burden country in 2004a. In the last 20 years, the incidence rate has been stagnating although there was a slight upward trend between 2004 and 2006; from 60.3 to 62.6 per 100,000 (MOH Malaysia, 2006).

Malaysia for the first time implemented DOTS therapy in 1999, while WHO gives other measures in addition to DOTS such as organizing services close to the patient's home, considering patient's needs, and providing incentives in the form of free medications and monetary reimbursement. In Malaysia, medications are fully funded by the government. Charity organizations provide travel allowances and pocket money to the underprivileged patients.

1.2.2 Epidemiology of Tuberculosis with HIV/AIDS

AIDS (Acquired Immune Deficiency Syndrome) was thought to be a gay related immune deficiency syndrome. But later on, it was evident that sexual activity, contaminated needles, and blood products accounted for AIDS (Ford, 1992).

Tuberculosis desolate HIV/AIDS patients and affects their progress badly. Nearly 9.27 million people contracted TB in 2007; an increase of about 30,000 over the previous year (2006) was in line with the population growth. The above stated figures i.e. 9.27 million also includes approximately 1.4 million people with HIV/AIDS as compared to estimated 0.6 million in 2006. In the year 2007 out of 1.75 million deaths, 0.456 million tuberculosis deaths were thought to be caused by HIV/AIDS. It means about one in four TB deaths are caused by TB with HIV/AIDS (WHO, 2009). HIV has killed over 20 million people worldwide. Sub Saharan Africa accounts for 10% of the total world population but almost 2/3 of the population has been reported to be suffering with HIV (UNAIDS, 2004).

In Malaysia the first case of HIV/AIDS was identified in 1986, and in the year 1999 HIV had an incidence rate of 20.80 per 100,000 populations, which increased to 30.3 per 100,000 populations in the year 2002 and in the year 2003 the incidence rate was controlled to 26.9 per 100,000 populations (MOH, 2004). Over two-thirds of HIV/AIDS

cases are prevalent among intravenous drug users (IVDUs) and there has been exponential rise in the number of drug users reported globally (Friedland and Klein, 1987). In Malaysia the prevalence of HIV among IVDUs remains disturbingly high; nearly 76% of all the HIV/AIDS cases reported between 1986 and 2000 were among IVDUs [Ministry of Health, (MOH) 2004]. In the early 1990s, incidence rate of TB began to increase in USA and Western European countries (Raviglione *et al.*, 1993). Factors that were related to the increased rates include the human immunodeficiency virus (HIV) pandemic, homelessness and poverty, widening gap between rich and poor, increase in the number of refugees and the reduction of governmental support in prevention and treatment programmes (Brudney and Dobkin, 1991; Valadas and Antunes, 2005).

For many years, the efforts to tackle TB and HIV/AIDS have been largely separate, despite the overlapping epidemiology. However, it is now increasingly acknowledged that only through combined and co-ordinated efforts for both TB and HIV/AIDS can halt, this dual epidemic. According to WHO report (2009) out of 1.8 million people who died from TB in 2008 worldwide, 0.5 million were infected with HIV, signifying the relation between the two deadly dangerous diseases. The HIV/AIDS epidemic is reviving an old problem in well resourced countries and worsening the existing problem of TB in less resourceful countries (Dye *et al.*, 1999; Hausler *et al.*, 2006).

1.2.3 Epidemiology of Tuberculosis with Diabetes Mellitus

According to the International Diabetes Federation (IDF), there are currently 151 million people in the age group 20 to 79 years with clinically diagnosed diabetics in 134 countries. This accounts for an overall global prevalence of 4.6%. Most of these people have type II diabetes. Data confirmed that oral hypoglycemic agents are widely used to

control blood glucose levels, while significant number even uses insulin. Below the age of 20 the predominant type of diabetes found is type I, which requires treatment with insulin after diagnosis. About 4.9 million people worldwide have type I diabetes under the age of 20 according to IDF estimates (UKPDS, 1998). World Health Organization in 1998 has projected the prevalence of diabetes among adults worldwide will be more than double the existing, from 135 million to 300 million by the year 2025 (King *et al.*, 1998).

TB has already been declared a "global emergency" by the WHO in 1992 and was recognized as a single biggest killer. Diabetes mellitus was also recognised as an independent risk factor for developing lower respiratory tract infections (Winterbauer *et al.*, 1969). The frequency of occurrence of TB increases in diabetics resulting in a significantly higher mortality rate (Root, 1934; Jabbar *et al.*, 2006). The incidence of diabetes as such appears to be higher among tuberculosis patients (Jeon and Murray, 2008) as compared to the general population. Now, with diabetes assuming epidemic proportions with TB, it is vital to take measures for the prevention and control of this deadly combination.

Similar to the world findings, there was a significant increase in the diabetes mellitus cases in the Malaysian population. The number has increased from 1.4 million in 1998 to 1.8 million in 2002 (Nissapatorn *et al.*, 2005a).

1.2.4 Epidemiology of Multi Drug Resistant Tuberculosis (MDR-TB)

Multi-drug resistant tuberculosis (MDR-TB) is defined as a tuberculosis that is resistant to at least isoniazid and rifampicin. The MDR-TB commonly develops in the course of TB treatment (Iseman, 1999). The inadequate use of resources, particularly the available treatment strategies has lead to a worrying level of MDR-TB in many regions of

the world. According to 2008b, WHO report 489131 cases of MDR-TB emerged in 2006 and that the global proportion of MDR-TB among all the TB cases was 4.8%. India, China and Russian federation were estimated to have the highest number of MDR-TB cases. A total of 27 countries approximate for about 86% of the world MDR-TB cases were showing around the globe (WHO, 2008b; Wright *et al.*, 2009). As with TB, 99% MDR-TB cases are from resource poor countries. However due to global immigration, of people from resource poor countries to develop countries there will be an increase in the MDR-TB cases in the developed world in the near future (Ormerod, 2005). There were an estimated 500,000 cases of multidrug-resistant (MDR) tuberculosis in 2007 (including 289,000 new cases); of these, 131,000 were in India, 112,000 in China, 43,000 in Russia, 16,000 in South Africa, and 15,000 in Bangladesh; 55 countries had reported cases of extensively drug-resistant (XDR) tuberculosis by the end of 2008. These last figures are reason for considerable concern and highlight a potential threat to our ability to treat tuberculosis (Donald, 2009).

The various risk factors identified for MDR-TB can be broadly divided into two categories, those factors that facilitate the selection of resistance in the community and the special conditions which make the people vulnerable to this resistance (Caminero, 2010). The risk factors under the first category include but are not limited to inadequate supply or poor quality of TB drugs, inadequate adherence to the treatment, social barrier, lack of money, poor infection control in health centers and hospitals, high prevalence of highly virulent MDR strains of MTB, HIV infection, non standardized treatment and non-implementation of DOTS and DOTS expansion strategies (WHO, 2008b; Borrell and Gagneux, 2009; Migliori *et al.*, 2009). The risk factors for the latter category include but are not limited to failure of the WHO category II TB drug regimen, chronic patients, contacts of MDR-TB cases, failure of WHO category I TB drug treatment regimen,

relapse and return cases, exposure at institutions reporting with high MDR-TB prevalence, residence in areas with high MDR-TB burden and usage of poor quality TB drugs (WHO, 2008b).

1.3 Tuberculosis among Prison inmates

Different studies published as well as the WHO data shows that TB is a major problem among prison population. Prisoners are at a high risk for acquisition of MTB infection and development of TB infection compared to the general population due to overcrowding, closed living conditions, insufficient ventilation, generally low socioeconomic status, poor nutrition and poor health of prison inmates, delay test findings and inadequate therapeutic intervention (Coninx, 1995; Aerts, 2000). There is increasing recognition that the high risk of TB infection in prisons poses a problem not only for those who are in prison but also for the society at large (Coninx, 2000).

TB incidence can also be related to the length of incarceration (Bellin *et al.*, 1993). Transmission patterns are generally difficult to establish, and the rate of unrecognized transmission may be quite high (Jones *et al.*, 1999; Mac Intyre *et al.*, 1999). Above all, strains isolated in these settings are often Multidrug resistant (MDR) (Valway *et al.*, 1994; Coninx *et al.*, 1998). Moreover, a high rate of MDR-TB (up to 33%) has been observed in several prisons both in developed and developing countries (Valway *et al.*, 1994; Toungoussova *et al.*, 2003). The mortality rate among TB cases reached around 24% in some prisons and in some TB accounts for 50% of the overall prison deaths, worldwide, 10-100 time higher rates have been reported for TB in prisons than in local civilian population (WHO, 2000).

In the Selangor state, TB / HIV co-infection cases raised from 52 in 1998 to 137 in 2002. Most of these cases were reported from the prisons and drug rehabilitation centers (DRC). The rate of positive TB / HIV co-infection was found to be 12–15 % in prison / DRC in the period 2000 to 2002 (Venugopalan, 2004).

1.4 PATHOPHYSIOLOGY OF TUBERCULOSIS

1.4.1 Causative Organism

Tuberculosis is caused by the rod shape, non-spore forming, aerobic, non-motile *Mycobacterium tuberculosis* (Kathleen and Arther, 2002). Mycobacteria are around 0.5 x 0.2 μm in size, classified as acid fast bacilli with a distinctive cell wall structure. The cell wall contains a substantial amount of mycolic acid a fatty acid, covalently attached to the polysaccharide arabinogalactan by peptidoglycan linkages to provide an unusual lipid barrier. This unusual barrier is the one responsible for resistance to antibiotic and the post defence mechanisms. This organism is an obligatory aerobe that grows most successfully in human tissues having the highest partial pressure of oxygen, such as the lung, renal parenchyma and growing ends of bones (Peloquin and Berning, 1994). The other important characteristic of bacteria includes slow growth. The presence of lipoarabinomannan, a carbohydrate structural antigen on the outside of the organism, which is immunogenic, allows the organism to survive after engulfment by the macrophages in human (Knechel, 2009).

1.4.2 Pathogenesis

Mycobacterium tuberculosis is spread by airborne droplets transmitted by coughing, sneezing, talking or singing of a person with TB. Once the droplet is inhaled it settles through the air passage. The majority of the bacilli are entrapped by the mucus secretion present in the upper respiratory system (Frieden *et al.,* 2003). The bacilli

entrapped are driven out along with the mucus by the cilia present on the surface of the mucus producing goblet cells. This is the primary defensive mechanism that prevents occurrence of TB in most persons (Jensen *et al.,* 2005). In few persons when the bacilli bypass the ciliary diverge, they reach the alveoli and are engulfed by alveolus macrophages. The subsequent phagocytosis by macrophages initiates a series of events that may result in either complete bacilli destruction or progression into latent TB or progressive to active TB (Frieden *et al.,* 2003). The series of events are determined by the quality of host defence and the invading *mycobacterium* (Goyot-Revol *et al.,* 2006).

After being ingested by the macrophages the bacillus multiplies slowly (Frieden *et al.,* 2003). At the same time proteolytic enzymes and cytokines are produced by the macrophage to destroy the bacilli (Nicod, 2007). The cytokines so produced drags the T-Lymphocytes to the site. At this stage the macrophage surface bound bacilli antigen is presented to the T cell (Nicod, 2007). This process continue for a period of 2 to 12 weeks until a sufficient number of micro organisms grow to fully bring forth the T cells mediated immune response (Frieden *et al.,* 2003).

In patients with intact cell mediated immunity, the next stage is formation of a nodular type lesion known as granulomas surrounding the bacilli (Rosenkrands *et al.,* 2002). These lesions are formed as a result of accumulation of activated T lymphocytes and macrophages. The lesion environment limits the growth and multiplication and spread of the bacilli. The macrophages are destroyed in this environment and a solid necrosis is formed at the centre of the lesion. However, the bacilli adapt to the conditions and survive by changing their protein regulation (Li *et al.,* 2002; Dheda *et al.,* 2005).

After 2 to 3 weeks, the necrosis is called as caseous necrosis and is characterised with low oxygen levels, low pH and limited nutrition. These conditions restrict the growth further and the disease goes into the latent phase. In a person with ample immunity the necrosis undergoes fibrosis and calcification. This brings about successfully controlling the infection (Dheda *et al.*, 2005). In persons with weak immune system it progress to primary progressive tuberculosis (Li *et al.*, 2002). In these persons the granuloma formation is initiated but it is inefficient in containing the bacilli. The necrotic tissue undergoes liquefaction and then the fibrous cell wall loses its integrity and drains the semi liquid necrotic material into bronchus and blood vessels further spreading the bacilli (Dheda *et al.*, 2005).

1.4.3 Drug Resistance *Mycobacterium tuberculosis*

Drug resistance TB is not a new phenomenon. It came into picture when *M. tuberculosis* strains that were resistant to streptomycin emerged immediately after discovery and introduction of streptomycin for the treatment of TB in 1944. Genetic resistance to an anti- TB drug is due to chromosomal mutations at a lower frequency. Even though the frequency of chromosomal mutations is low drug resistance is reaching alarming proportions at a greater speed due to the amplification of the mutations through human error (Zhang and Yew, 2009). The human errors include monotherapy due to irregular drug supply, inappropriate doctor prescription and in most cases it is poor patient adherence to the treatment. The subsequent transmission of this genetically modified strain to other individuals greatly intensified the problem. The drug resistance is currently classified by categorizing drug resistance in new cases and previously treated cases of TB in which the treatment lasts for at least one month (WHO, 2008b).

1.5 TRANSMISSION OF DISEASES

1.5.1 Tuberculosis

Tubercle bacilli are transmitted through the air by aerosolized droplet nuclei that are produced when a person with pulmonary or laryngeal TB coughs, sneezes, speaks or sings. This droplet nuclei, which contain one of three *M. tuberculosis* organisms, are small enough (1 to 5 μm) to remain suspended in the air for long periods of time and to reach the alveoli within the lungs when inhaled. Tubercle bacilli are not transmitted through inanimate objects (Knechel, 2009).

The factors that influence the likelihood of transmission of *M.tuberculosis*, include the number of organisms expelled into the air, the concentration of organisms in the air, duration of the exposure, and the immune system of the exposed individual. Family household contacts especially children, hospital, nursing homes, prisons such people are significantly on high risk to become infected. Individuals with HIV/AIDS or transplant patients are thought to be more likely to become infected with *M.tuberculosis* after exposure then normal immune function (American Thoracic Society, 2000).

Several techniques are effective in limiting airborne transmission of *M. tuberculosis* such as adequate room ventilation, where 6 or more air exchange per hour is desirable (American Thoracic Society, 2000), ultra violet radiation, coughing patient used masks and treating patient with effective anti-tuberculosis therapy.

1.5.2 Human Immunodeficiency Virus (HIV)

Skin of healthy individual does not allow HIV to get into the body. In fact HIV can enter into the body through an open cut or sore, or through contact with the mucous membranes. Transmission risk is very high when HIV comes in contact with the more

porous mucous membranes in the genitals, the anus, and the rectum, which are inefficient barriers to HIV. Transmission is also possible through oral sex because body fluids can enter the bloodstream through cuts in the mouth, but chances are low due to low concentration of body secretions. There are several modes of transmission that have been identified:

1. Unprotected vaginal, anal and oral sex.
2. Direct blood contact, which may occur through needle sharing, transfusions, accidents in health care settings, or certain blood products.
3. Mother to baby; before or during birth or through breast milk.
4. Sharing syringes (Needles) to inject illegal drugs or medicine can pass blood directly from one person's blood stream to another's. It is a very efficient way to transmit HIV and other blood borne viruses such as Hepatitis B (HBV) and Hepatitis C (HCV).
5. HIV/ AIDS prevention depends on the interception of transmission and can be prevented by avoiding needle sharing, sex with exposed person. The main means of prevention includes coverage of condoms during sexual intercourse (Baron *et al.*, 1994).

1.6 CLINICAL MANIFESTATION OF TUBERCULOSIS AND ITS CO-MORBID CONDITIONS:

1.6.1 Tuberculosis

1.6.1(a) Pulmonary Tuberculosis

Based on the immune system of the patient, tuberculosis might develop differently in each patient. The various stages include latency, primary TB, primary progressive TB and extra pulmonary TB (EPTB). The clinical manifestations of the first three stages are given in Appendix 1(Knechel, 2009). Approximately 10% of individuals who acquire TB infection and do not receive therapy for the latent infection will develop active TB. The

risk of developing active disease is highest in the first 2 years of infection (American Thoracic Society, 2000). Physical or emotional stress can destroy balance between the immune system and the infection, leading to active disease. The ability of the host to respond to the organism may also be reduced by certain diseases such as diabetes mellitus, silicosis, diseases associated with immunosuppressant (HIV/AIDS, person on corticosteroids and immunosuppressive agent treatment). The likelihood of developing active TB disease is greater in persons with these diseases (Barnes *et al., 1991*; American Thoracic Society, 2000). HIV infected persons, especially with low T cell counts, develop active TB disease rapidly after becoming infected with *M. Tuberculosis* up to 50% of these individuals may develop active disease in the first two years after infection (Daley *et al.,* 1992). Other factors also contribute to the development of active disease like gastrectomy, intestinal bypass surgery, intravenous drug user (IVDU). Children's less than 2 years of age may also be at an increased risk of developing active TB (American Thoracic Society, 1990; American Thoracic Society, 2000).

1.6.1(b) Extra Pulmonary Tuberculosis

Tuberculosis of organs other than the lungs is called extra pulmonary tuberculosis. EPTB includes the pleura (TB pleurisy), peripheral lymph nodes, abdomen, genito-urinary tract, skin, joints and bones, and the brain (MOH, Malaysia 2002). The most serious cases are when TB is found in the central nervous system where the infection can lead to tuberculomas or meningitis. If left untreated, meningitis may be fatal. People with frequent headache and changes in mental status after possible exposure to the organism should go for diagnosis. Another lethal form is infection of the blood stream with *Mycobacterium tuberculosis* causing military TB. Lymphatic TB is the most common EPTB.

The incidence of EPTB decreases with age. However the incidence increases in geriatric population. In the past AIDS era in USA, 1008 patients with extra pulmonary tuberculosis were older than 65 years. Two thirds of 4 million infected people with both HIV and TB were diagnosed to have extra pulmonary tuberculosis.

Different types of EPTB have been reported which shows different types of clinical sign and symptoms like, Miliary TB were constitutional symptoms (fevers, chills, sweats) and diagnosed by chest X-ray, symptoms of gastrointestinal TB at presentation included (weight loss, fever and abdominal distention), and common symptoms of spinal TB included fever, progressive lower extremity weakness or paraplegia, and back pain, while diagnosed by radiographic evidence (X-ray, CT, or MRI) etc (Fader *et al.*, 2010).

1.6.2 HIV

Early sign and symptoms of HIV infection are variable. Generally the sign and symptoms range from mild non-specific fatigue and malaise to fever, night sweats and weight loss (Miedzinski, 1992). The Centers for disease control has classified HIV infection into various groups as discussed below: (CDC, 1986)

Group I: Acute HIV infection:

Patients who within one month of exposure develop the first clinical evidence of HIV infection, which may appear as an acute retroviral syndrome fall under this group. This is a mononucleosis-like syndrome with symptoms including fever, rash, diarrhea, lymphadenopathy, myalgia, arthralgia, and fatigue. Development of antibodies usually follows.

Group II: Asymptomatic HIV infection:

A group in which, most persons develop antibodies to the HIV within 6 to 12 weeks after exposure. Although individuals may remain asymptomatic for months or years, they can transmit the virus.

Group III: Persistent generalized lymphadenopathy:

A group in which, most patients develops persistent generalized lymphadenopathy that lasts longer than 3 months.

Group IV: HIV-associated diseases

A group, who is clinically variable and has signs and symptoms of HIV infection other than or in addition to lymphadenopathy, based on clinical findings, patients in Group IV may be assigned to one or more of the following subgroups: (A) constitutional disease, also known as wasting syndrome. This subgroup is characterized by fever that lasts more than one month, involuntary weight loss of greater than 10% for baseline, or diarrhea persisting for more than one month, (B) neurological disease, (C) secondary infectious disease, (D) secondary cancers, and (E) other conditions resulting from HIV infections.

1.6.3 Diabetes Mellitus

It's not unusual to have diabetes mellitus (DM) and yet have no symptoms. Type 2 diabetes, in particular, develops slowly. Many people have type 2 diabetes for as long as eight years before its being diagnosed. When symptoms do develop, they often vary. But two symptoms that occur in most of the people with the disease are increased thirst and increase in the frequency of urination (CDC, 2004). Other signs and symptoms of DM

include extreme hunger, increased fatigue, irritability, unusual weight loss, blurred vision, slow-healing sores or frequent infections and neuropathy (Clark *et al.*, 2007).

1.6.4 TB/HIV Co-Infection

In an individual infected with both *M. tuberculosis* and HIV, TB could develop at any stage in the course of the HIV infection. The clinical presentation of tuberculosis in HIV infected patients varies depending on the severity of immunosuppression. Clinical presentation of tuberculosis in persons with early HIV infection has been found to be similar to that observed in persons with strong immune system and HIV-negative patients (Zumla *et al.*, 2000).

In HIV-positive patients the pathologic and clinical features of TB varies with the patient's CD4 lymphocyte count. Expression of TB is dependent on the stage of HIV infection as measured by CD4 counts. Patients with HIV and relatively good CD4 cell counts (> 250 cells/cubic mm) have TB similar to HIV negative persons while those with lower CD4 cell counts have atypical presentation. When the CD4 counts are greater than 200cells/mm^3, the patient's most often or not suffer with pulmonary TB. The manifestation of pulmonary TB includes infiltrates and cavitations in the apical posterior segments of the upper lobe and the superior segment of the lower lobe of the lungs as read radiologically and pleura effusions are common (Perlman *et al.*, 1997). As the level of immunosuppression increases and CD4 cell count decreases the presentation of the disease becomes atypical with interstitial non-cavitary lesions because of poor granuloma formation and these involve more of the lower lung fields as read radiologically. As the CD4 counts further fall extra pulmonary TB is more likely to occur with positive blood cultures for *M. tuberculosis* (Perlman *et al.*, 1997; Saltini, 1999). Furthermore, when CD4

cell count is greater than 200 and less than 500, reactivation of tuberculosis can occur in HIV infected individuals (Bhatia, 2001; Chan *et al.*, 2010).

In HIV negative patients, pulmonary tuberculosis is the most common form of tuberculosis observed and it accounts for about 80% of the total TB cases. In contrast in HIV positive patients, only 20% of the population is with pulmonary TB, while 53-62% of cases are with extra pulmonary TB (FitzGerald and Houston, 1999). The most common extra pulmonary site is the lymph node. However, neurological, pleural, pericardial, abdominal and virtually every-body site can be involved in HIV positive patients (Chan *et al.*, 2010).

HIV infected patients with dormant, previously contained loci of infection, eventually develop reactivation TB because of the gradual loss of cell-mediated immunity. Reactivation TB occurs early in the course of immune depression in HIV infected individuals. These cases are pathologically characterized by the formation of "hard" nodules with epitheloid cell granulomas, little caseous necrosis and few bacilli. Cavitation may also occur as an expression of typical reactivation of disease. In more advance stages of the HIV infection, the pathology is characterized by military acinar nodules composed of aggregates of macrophages with scanty lymphocyte reaction, little granuloma formation, marked necrosis and numerous extracellular bacilli (Saltini, 1999).

The presence of HIV co-infection may alter the radiologic findings in pulmonary TB (Long *et al.*, 1991). From the radiological findings it can be observed that in these patients the involvement of lower lobe of the lung is prominent, pleural effusion is more common; cavities are less common and intrathoracic adenopathies is evident (Long *et al.*, 1991).

1.7 DIAGNOSIS

1.7.1 HIV/AIDS

The diagnosis of HIV infection is generally achieved through antibody detection with serologic tests. The test which is used in general is ELISA (enzyme-linked immunosorbent assay) (Kassu, 2007). In Malaysia, ELISA and the particle agglutination (PA) are used as diagnostic tests for HIV/AIDS. The initial screening is done using the ELISA test at the screening centers, incase ELISA test is positive then it is further verified and confirmed by using PA test. Clinical specimens from individuals in high-risk groups (IVDUs and sexually wanton) are confirmed locally using ELISA test.

An individual is declared as "Diagnosed Case of AIDS", following clinical definitions outlined below according to WHO, 2001;

- A positive test for HIV antibodies by the ELISA and or Particle Agglutination test(s), or a positive supplementary test.
- A CD4 T cell lymphocyte count of less than 200μL.
- The presence of an AIDS indicator disease like *Pneumocystis carinii* pneumonia, Karposi's sarcoma, tuberculosis (pulmonary or extrapulmonary), toxoplasmosis of the brain and other serious opportunistic infections (Kumarasamy *et al.*, 2003).

1.7.2 Diabetes Mellitus

On the basis of clinical sign and symptoms following laboratory test are performed for diagnosis purposes:

- A random blood glucose $\geq$ 200mg / dL
- A fasting blood glucose (FBG) $\geq$ 126 mg / dL

Many factors can impair blood glucose level; these all factors must be excluded before a diagnosis of diabetes is made. Some acute illness (myocardial infarction),

pregnancy, stress, drug and other chemical may falsely elevate the plasma glucose concentrations (American Diabetes Association (ADA), 2003).

1.7.3 Tuberculosis

1.7.3 (a) Tuberculin Skin Test (TST)

Tuberculin Skin Test (TST) is the widely used laboratory test to identify patients actively infected with tuberculosis and for those with latent TB as well. There are different types of tuberculin skin test reported but the most commonly used one is Mantoux test. In this test procedure graded doses of tuberculin are injected intradermally on the forearm using a tuberculin syringe. Tuberculin is a Purified Protein Derivative (PPD), which is a collection of mixed proteins and other materials filtered from killed *M. tuberculosis* cultures. The test works on basic principle, that if the body has been exposed to infection with TB it will recognise the proteins and mount an immune response to it. This response would be expressed in the form of a lump, swelling or blister at the site of injection, revealing that the person is infected. Unfortunately, the skin test has a poor sensitivity and specificity (Deek *et al.,* 2003). The sensitivity of the test is low if the person being tested has had the BCG vaccination earlier in life or if they have a deprived immune system (immunocompromised) due to other illness or medical treatment and even some time shows false positive results (Ferrara *et al.,* 2005). On the forearm 0.1 ml of the 5 TU of PPD is injected intradermally. On examination after 48-72 hours a positive reaction is indicated by erythema and indurations of > 10 mm size (MOH Malaysia, 2002).

1.7.3 (b) Sputum Smear Microscopy (SSM)

Sputum smear microscopy (SSM) has been the first diagnostic test that has been used to screen for active PTB. SSM is based on the principle of Ziehl Neelson diagnostic

technique of direct smear microscopy of sputum (Koch and Cote, 1965). The unique properties of bacterial cell wall of *Mycobacterium tuberculosis* allow it to retain the primary stain of carbol fuchsin and methylene even after exposure to strong acid solutions, they are called acid-fast bacilli. In the Ziehl Neelson staining procedure, using carbol fuchsin and methylene blue, the acid-fast organisms appear pink or red under the microscope (Aggarwal, 2006).

Despite being widely used, microscopy has limitations as it is not specific for the detection of acid-fast bacilli (AFB) in sputum and can only detect AFB in 60-70% of culture positive specimens (Steingart *et al.,* 2006; Perkins and Cunningham, 2007). In contrast to old practices for detection of PTB, some new studies concluded that the examination of two sputum sample should be used to confirm TB (Leonard *et al.,* 2005).

1.7.3 (c) Culture

Cell culture techniques are the widely used methods to identify *M. tuberculosis,* pulmonary or extra-pulmonary. By assessing the effect of antibiotics on the cultured bacteria, this technique can also provide data on likely effectiveness of certain antibiotics. However, it is not always possible to obtain bacteria in the sample, especially in non-pulmonary TB and the test is therefore not always reliable. A drawback of this method is the time awaited to get the results, which can be anything in between six to eight weeks (Singh, 2006). However, rapid and more sensitive diagnostic methods are also available like Bactec, Polymerase chain reaction (PCR) but these are relatively expensive and are not available in all the diagnostic centres (Saiki, 1985).

1.7.3 (d) Chest X-ray

Chest x-ray is an important diagnostic tool for the physician, to check for lung abnormalities in people who have symptoms of TB disease. However the chest X-ray cannot confirm active TB, especially if the infection is not in the lungs or may be smear negative (Davis, 2010). The chest X-ray also has a poor ability to detect infection in the early stages of disease. The damage to the lungs may not yet have become sufficiently marked to be detectable by chest X-ray and thus people who have active TB can be missed including elderly and or HIV/AIDS patients (Knechel, 2009). Furthermore, scarring in the lungs remains after a previous TB disease even if the patient is completely cured and therefore it is difficult to distinguish past cured TB from current active disease.

1.7.4 Extra Pulmonary Tuberculosis

Diagnosis of EPTB is often difficult. A negative smear of acid-fast bacilli and failure to culture the bacilli contributed to ineffective EPTB diagnosis (Marjoriep, 2005). The recognition and understanding of the radiographic findings in the EPTB case may reduce the difficulty faced EPTB diagnosis (Engin *et al.*, 2002). The diagnosis of EPTB is often difficult as compared to pulmonary TB due to the low sensitivity of the usual diagnosis methods for the disease (AFB smear, Mantoux, culture and chest radiography tests). The sensitivity of the most commonly used methods range from 25% - 39% (Marco *et al,*. 1998).

1.7.4 (a) Tuberculosis Lymphadenitis

Tuberculosis lymphadenitis is the most common type of extra pulmonary tuberculosis. Lymphatic TB was known as scrofula and later-on was known as the king's evil (Grzybowski and Allen, 1995). It can be diagnosed by fine needle aspiration (FNA) of glands (lymph nodes glands). This type of specimen is submitted for AFB test and