EPIDEMIOLOGICAL AND AWARENESS STUDY OF TUBERCULOSIS IN
BATU PAHAT, JOHOR, MALAYSIA

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ABSTRACT

Tuberculosis (TB) remains one of the serious infectious diseases and has been characterized worldwide as an epidemic by World Health Organization (WHO). TB is still a public health problem in Malaysia. Baseline information on the disease situation is one of the prerequisites for the development of appropriate control measures. The cornerstone in proper management of TB patients is ensuring high awareness in communities about TB. Thus the current research is directed to investigate the epidemiology of TB, determined the level of public awareness of TB and some factors that are responsible for the emergence of TB. Retrospective method was used for collecting epidemiological data from the Batu Pahat chest clinic. All registered TB patients (total of 1213 patients) from 2008 to 2013 in Batu Pahat Chest Clinic were included in the study. On the other hand, the awareness study was carried out by the use of questionnaires. A two-stage cluster sampling method was used. 600 respondents were targeted which form the study sample. However, 498 questionnaires were returned. Descriptive data analysis was employed to describe the results in frequency and percentage distribution. It was discovered that there was an annually increase in TB incidence with pulmonary TB the most common infection in Batu Pahat. Almost all (92.7%) the TB cases were new. On the other hand, majority (87.0%) of respondents have heard about TB. Common symptoms identified by respondents were coughing for over 2 weeks (51.8%), hemoptysis (49.2%) and difficulty in breathing (50.2%). Smoking cigarette (74.3%), living with individual having chronic cough (71.5%) and HIV/AIDS (65.7%) were the common risk factors of TB identified by respondents. Most of the respondents (83.5%) were aware of the existence of TB drugs. However, the standard DOTs treatment duration of 6-9 months was identified by few (12.4%) respondents. This research provided information regarding TB status in Batu Pahat. The level of awareness among Batu Pahat general public about TB is fairly good. Meanwhile, more need to be done especially on diabetes as the risk factors of TB and treatment duration.
**ABSTRAK**

Tuberkulosis (TB) atau batuk kering merupakan satu daripada penyakit berjangkit yang paling serius sedunia dan nyatakan sebagai wabak oleh Pertubuhan Kesihatan Sedunia (WHO). TB kekal menjadi masalah penyakit umum di Malaysia. Maklumat asas tentang keadaan penyakit ini merupakan salah satu prasyarat untuk membangunkan langkah-langkah kawalan yang sesuai. Hal utama dalam pengurusan pesakit TB adalah bagi memastikan kesedaran yang tinggi wujud di kalangan komuniti tentang tibi. Oleh itu, penyelidikan ini telah di jalan untuk mengkaji epidemiologi TB, menentukan tahap kesedaran awam tentang TB dan beberapa faktor yang menjadi penyebab kemunculan TB. Kaedah retrospektif digunakan untuk mengumpul maklumat epidemiologi daripada Klinik Dada Batu Pahat. Kesemua pesakit TB berdaftar (berjumlah 1,213 pesakit) dari tahun 2008 hingga 2013 di Klinik Dada Batu Pahat terlibat dalam kajian ini. Selain itu, kajian tahap kesedaran dijalankan menggunakan kaedah soal selidik. A dua peringkat kaedah persampelan kelompok telah digunakan. Seramai 600 responden sasaran menjadi sampel untuk menjawab persoalan kajian. Bagaimanapun, hanya 498 soal selidik dikembalikan. Analisis data diskriptif digunakan untuk menggambarkan keputusan dalam bentuk kekerapan dan taburan peratus. Didapati peningkatan tahunan bagi insiden TB dengan tibi paru-paru merupakan jangkitan yang paling biasa di Batu Pahat. Hampir semua (92.7%) kes tibi adalah baru. Didapti, majoriti (86.9%) responden mengetahui akan TB. Tanda-tanda biasa yang dikenalpasti oleh responden adalah batuk melebihi dua minggu (51.8%), hemoptesis (49.2%) dan kesukaran bernafas (50.2%). Merokok (74.3%), tinggal bersama individu mempunyai batuk kronik (71.5%) dan HIV/AIDS (65.7%) merupakan faktor risiko utama tibi yang dikenalpasti oleh responden. Kebanyakan responden (83.5%) tahu akan kewujudan ubat TB. Walau bagaimanapun, piawai rawatan DOT dalam tempoh 6-9 bulan dikenalpasti oleh beberapa (12.4%) responden. Penyelidikan ini memberi maklumat berhubung status tibi di Batu Pahat. Tahap kesedaran masyarakat umum di Batu Pahat tentang tibi adalah memuaskan.
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CHAPTER 1

INTRODUCTION

1.1 Background of the research

Tuberculosis (TB) remains one of the most serious infectious diseases both in terms of disease burden and resistance to conventional antibiotic therapy and has been characterized worldwide as an epidemic by World Health Organization (WHO) (Aldwell et al., 2005; Dou et al., 2008; Nissapatorn et al., 2005). TB is endemic in all countries in the world and it kills more people today than any other bacterial disease (Hunter et al., 2006).

It is estimated that one third of the world population i.e. around 2 billion people are latently infected with TB. Around 10% of TB infected persons become sick with active disease, and this high level of latent infection is a suggestion of long-term co-existence of human host and bacterial pathogen (Besharat, 2009; Thomas et al., 2007; Hershkovitz et al., 2008). WHO declared TB in 1993 as a global public health emergency (Rennie, Pai, & Selvadurai, 2011; Abdallah & Ali, 2012), and it is the only disease that has been ever declared as global emergency by WHO (Palomino, 2009).

TB is one of the most important infectious causes of morbidity and mortality among adults (Nissapatorn et al., 2003; Liao et al., 2012). It causes more adult deaths in the world than any other communicable disease in developing countries where 95% of all TB cases occur (Itah & Udofia, 1997). Between 8 to 9 million people develop the disease (Atif et al., 2012; Piuri, Jacobs, & Hatfull, 2009), and approximately 2 million die from TB annually (Nissapatorn et al., 2003; Rennie et
With the emergence of drug resistance and the HIV/AIDS epidemic, TB is making a resurgence all over the world (Thomas et al., 2007). In 1995, it was estimated that 8.8 million cases of TB occurred worldwide, 5.5 million (95%) of them in developing countries of Asia, Africa 1.5 million, the Middle East 745,000 and Latin America 600,000. Almost 3 million deaths from TB occurred in 1995, 98% of them in developing countries (Jetan et al., 2010). It is miserably true that 75% of TB cases in developing countries engage adults in the most productive age group, 15-50 years (Itah & Udoﬁa, 1997). The worldwide burden of TB mainly lies in the 22 high prevalence countries and about 50% of prevalence occurs in 5 countries of South East Asia (Liao et al., 2012), namely; India, Indonesia, Bangladesh, Thailand and Myanmar (Tasnim, Rahman & Hoque, 2012).

Around early 1940s and 1950s, TB was the number one cause of death in Malaysia, TB patients were admitted to many sanatoria in various parts of the country and were always managed by surgical means. Chemotherapy of TB became available only in the late 1950s. Malaysian government launched its National TB Control Program (NTP) in 1961 when realized its seriousness (Jetan et al., 2010). Despite control and preventive measures taken, TB is still a public health problem in Malaysia (Rafiza, Rampal & Tahir, 2011). TB was the second most common notifiable communicable disease in Malaysia in 2001 (Jetan et al., 2010). Apart from being a deadly disease, TB is also an expensive disease which can give a great economic problem to the country. The TB drugs cost constituted the highest proportion of the cost to the public services (31.7%) while the cost to the patient constitutes 80% of the total treatments cost (Nor et al., 2011).

The re-emergence of this predicament can be attributed to the high influx of foreign workers from high TB burden neighbouring countries such as India and China into the community (Rafiza et al., 2011) and this become one of the reasons why TB could be called “a disease without borders” in Malaysia (Nissapatorn et al., 2003). The immigrant workers, particularly those from high TB burden neighbouring countries constitute about 10% of TB notified cases in Malaysia (Jetan et al., 2010). In Sabah, East Malaysia, immigrants contributed more than 24% of the newly detected TB cases (Nissapatorn et al., 2003).
1.2 Problems

Despite full implementation of Direct Observation Therapy short-course (DOTs) programme and accessibility to TB drugs, the number of TB patients in Batu Pahat chest clinic progressively increased every year.

Baseline information on the disease situation is one of the prerequisites for the development of appropriate control measures. Batu Pahat is an endemic area of TB and no previous study has documented the epidemiology of the disease.

The cornerstone in proper management of TB patients is ensuring high awareness in communities about health in general and pulmonary TB. To the best of our knowledge very few studies have been conducted on assessing public awareness of TB in Malaysia. Thus, the current research directed to investigate the epidemiology of TB, the level of public awareness of TB with regard to clinical symptoms, related risk factors, treatment and attitude have been determined and some factors that are responsible for the emergence of TB have also been discussed.

1.3 Research Questions

1. How is the epidemiology of TB in Batu Pahat, Johor?
2. What is the level of knowledge and awareness of TB infection in Batu Pahat district, Johor?
3. What are the main factors of the emergence of TB cases in Batu Pahat district, Johor?

1.4 Aim and Objective

TB incidence remains endemic in the country. Due the emergence of TB cases among population living in the border of neighbouring countries, Batu Pahat is seen as one of the areas at risk for TB incidence. Therefore, this study aims to investigate the pattern of TB incidence using reconnaissance and direct visit to health
institutions responsible for getting clearer picture focusing in Batu Pahat region. The main objectives of this project are;

1. To investigate the epidemiology of TB in Batu Pahat, Johor.
2. To determine the knowledge and level of awareness (of the symptom, risk factors, and Treatment) of TB infection in Batu Pahat district, Johor.
3. To identify the main factors of the emergence of TB cases that may exist in Batu Pahat district, Johor.

These studies consist of the following part; epidemiological study and awareness survey study. The epidemiological study was carried out at the chest clinic Batu Pahat by reviewing the patient’s medical records and extracting some information such as: socio-demographic profiles, TB incidence cases, type of TB, TB case category, clinical presentation, co-morbidity and breaking down of TB patients by district.

The awareness study was carried out by the used of questionnaires, where the questionnaires were administered to the Batu Pahat general public. It consists of the questions on; demographic profile, awareness, knowledge and attitude of the respondents about TB risk factors, TB clinical symptoms, TB treatment and the attitude when any of the symptoms is suspected. Factors that are responsible for emergence of TB were discussed based on the result of both epidemiological and awareness studies.

1.5 Scope of the study

The scope is restricted to matters arising from epidemiology and awareness of TB in Batu Pahat. Three sub-districts were selected in the case study area. These sub-districts were Sri Gading, Simpang Kanan and Peserai. Preliminary study showed that TB incidence is increasing annually. The motivating factor is that no study was carried out on TB in Batu Pahat. The study investigated the epidemiology of TB and determined the level of awareness of TB in Batu Pahat. The study used secondary data from Batu Pahat Chest Clinic for the investigation of epidemiology of TB whilst, for the level of awareness, questionnaires were utilized. The targeted respondents were general public.
1.6 Significance of the research

Particularly in developing countries, epidemiological surveys are expensive and faced with so many constraints. In this study, extracting epidemiological data from hospital based records is well utilized which is less expensive source. Epidemiological studies are more essential for local policy makers concerning TB control, as vulnerable groups are usually highlighted. This study is well applicable in this respect (Abdallah & Ali, 2012). Epidemiological study of TB in each area causes an increase in knowledge and create a room for the successful implementation of a national TB control programme (Moulana et al., 2005; Roy & Chauhan, 2003).

Likewise, public awareness of TB plays a significant role in disease control. Lack of awareness of TB along with delay in early detection and inadequate health service resources has been associated with low TB detection rates and the interruption of TB treatment (Koay, 2004; Lu et al., 2010). In contrast, enhanced public awareness of TB could prop up patient detection, early diagnosis and treatment completion. Because public awareness of TB has a significant impact on TB control, the Global Plan to Stop TB 2006–2015 and the Stop TB Strategy launched by the World Health Organization (WHO) positioned advocacy, communication and social mobilization (ACSM) as important components in TB control programmes (Lu et al., 2010).

Delayed presentation is considered as a basis for growing burden of TB in developing countries. Making diagnosis and treatment of TB universally available and accessible is one of the objectives of 'Stop TB' programme. People can only access these services if they are aware of the symptoms of disease, seek early care, and adhere to treatment. More so, early diagnosis and adherence to treatment may decrease emergence of drug resistant strains (Gilani & Khurram, 2009). Knowledge and awareness regarding various aspects of TB among masses is very important to address this problem (Das et al., 2012).

The international society has adopted early case detection and treatment of infectious cases as the main strategy to reduce pulmonary TB infection. To enhance case detection and promote treatment completion, it is important to advise suspected sufferers to seek medical help early. Increasing knowledge about TB could help in achieving this goal; raising TB awareness among the general public should therefore be a main concern for TB control programmes (Lu et al., 2010). Many international
studies have reported poor knowledge, attitudes and practices about TB (Mushtaq et al., 2011).
CHAPTER 2

LITERATURE REVIEW

This chapter emphasized on the related information on TB causative agent (*Mycobacterium tuberculosis*), epidemiological study of TB, awareness study of TB and Batu Pahat itself. The sub-headings below give a brief review of the literatures.

2.1 History of TB

TB is an ancient disease, it has plagued humankind throughout known history and human prehistory. It can be hypothesize that the genus *Mycobacterium* was originated more than 150 million years ago (Daniel, 2006). Progenitor of *M. tuberculosis* was present in East Africa as early as 3 million years ago, and might have already affected early hominids (Gutierrez *et al.*, 2005; Daniel, 2006; Ahmad, 2011). TB was present in Egypt during the reign of the pharaohs, evidence of spinal and rib lesions pathognomonic of TB have been identified in mummies from that period (Chernick, 2004).

The earliest evidence of TB in human and animals was provided by bone finds chiefly fragments of vertebrae – showing the gibbus typical of tuberculous Pott’s disease. The oldest examples of spinal TB, in form of fossil bones, date back to about 8000 BC (Herzog, 1998).

TB was well known in old Greece, then it was called phthisis, Hippocrates clearly recognized TB and also understood its clinical manifestation. “Phthisis makes its attacks mainly between the age of eighteen and thirty-five,” he wrote in his aphorisms, clearly recognizing the preference of young adults for active TB
English speaking people called it consumption, and later the “Captain of all the Men of Death,” and “The Great White Plague.” The enlarged cervical lymph nodes were called “Scrofula” or “The King’s Evil” (Dodor, 2009). Some few people, suspected the contagious nature of TB. Spain and Italy, for example, had policy to prevent its spread as early as 1699. Patients affected were strictly isolated, and when they died, their bedding and the doors to their rooms were burned and their rooms were re-plastered (Dodor, 2009).

In 1790, Benjamin Marten first suggested that TB is infectious in nature, who attributed the disease to “some certain species of animalcula.” French military surgeon Jean-Antoine Villemin demonstrated the infectious nature of TB in 1865 convincingly when he inoculated a rabbit with “a small amount of purulent liquid from a tuberculous cavity” removed at autopsy from an individual who died of TB, it was generally discredited at that time (Daniel, 2006; Dodor, 2009).

This history changed dramatically on March 24, 1882, when a German physician and microbiologist Hermann Heinrich Robert Koch made his reasonably famous presentation, Die Aetiologie der Tuberculose, to the Berlin Physiological Society after he was able to identify and isolate the causative organism *M. tuberculosis* (Daniel, 2006; Dodor, 2009; Cole *et al.*, 1998). As early as 1886, Antonin Marfan recommended the existence of acquired immunity to TB. Albert Calmette and Camille Gue´rin in 1908 borrowed Pasteur’s technique to create a vaccine against TB. After serendipitously knowing that growth in ox bile diminished the virulence of *M. bovis*, Calmette and Gue´rin carefully performed 230 serial passages of a single isolate of the organism, sufficient for it to lose its ability to cause progressive fatal TB in a variety of animals: guinea pigs, rabbits, cows, horses, monkeys, and chimpanzees. These bacteriologists called their vaccine Bacille Bile´ (from bile) Calmette et Gue´rin, which was shortened to Bacille Calmette Gue´rin, and then to its household name, BCG (Murray, 2004; Dodor, 2009).

Benjamin Weill-Halle and Raymond Turpin were the first people to use this vaccine in 1921, particularly in children at high risk of infection, and soon became popular throughout the rest of Europe (Herzog, 1998). Following the initial success, it is use all over the world. WHO in 1940s, started promoting mass vaccination with BCG in its campaign to control TB (Dodor, 2009). The medications that were used in the treatment of other diseases were also tried on TB. For example, cod liver oil,
prescribed for rheumatism was later given for TB in the late eighteenth century (Dodor, 2009). In the absence of effective drugs, other measures were tried, such as advising patients to move to warmer climates. A movement towards high altitude, where the air was believed to be helpful, began in 1859 with establishment of a sanatorium for TB patients by a German physician, Herman Brehmer (Dodor, 2009). Later, surgical resection (removal) of the affected parts of the lung became the predominant observe in most parts of the world (Dodor, 2009).

The discovery of para-amino salicylic acid (PAS) by Jorgen Lehmann in 1943 and of thiosemicarbazone by Gerhard Domagk during wartime Germany and culminating in 1945 yielded the first therapeutic agents with efficacy in the treatment of TB (Daniel, 2006; Murray, 2004). In 1943 Albert Schatz, Elizabeth Bugie, and Selman Waksman reported the isolation of streptomycin from soil fungus and showed it to be active against the tubercle bacilli in vitro, leading to its administration for the first time to a human patient on November 20, 1944, the first antibiotic and first bactericidal agent effective against *M. tuberculosis* (Daniel, 2006; Dodor, 2009; Murray, 2004). Within a few months it had been used with dramatic results to treat a young woman with TB (Daniel, 2006).

Isoniazid followed in 1952, the first oral mycobactericidal (Daniel, 2006; Dodor, 2009). For nearly 15 years, “triple therapy” remained the standard treatment for all forms of TB. Not only did sanatoriums closed, but also therapeutic mainstays such as pneumothorax and pneumoperitoneum became outdated, and surgical measures such as thoracoplasty and the surgeons who did them vanished. Finally, the availability of rifampin in the mid-1960s and the rejuvenation of pyrazinamide, an older agent that had been suspended owing to its toxicity, allowed the development of current “short-course” antiTB chemotherapy (Murray, 2004).

### 2.2 Classification of *M. tuberculosis*

According to Cole *et al.* (1998), the taxonomic classification for *M. tuberculosis* is as follows:

Kingdom: Bacteria
Phylum: Actinobacteria
Class: Actinobacteria
Order: Actinomycetales
Suborder: Corynebacterineae
Family: Mycobacteriaceae
Genus: Mycobacterium
Species: tuberculosis

*M. tuberculosis* comes from the genus *Mycobacterium*, which is composed of approximately 100 recognized and proposed species. The most familiar of the species are *M. tuberculosis* and *M. leprae* (leprosy). It belongs to a group of closely related bacterial species termed the *Mycobacterium tuberculosis* complex. It has the following members that include *M. africanum*, *M. bovis* (Dassie’s bacillus), *M. caprae*, *M. microti*, *M. mungi*, *M. orygis* and *M. pinnipedii*. This group may also include the *M. canettii* clade. (Cole et al., 1998; Hershkovitz et al., 2008; Talip et al., 2013).

Nowadays the common cause of human TB is *M. tuberculosis*. *M. bovis* has a wider host range and is the major cause of TB in other animal species. Although in the years before the widespread of milk pasteurization, the cattle- infecting species *M. bovis* was the common cause of human TB. It is estimated that in the pre-antibiotic era *M. bovis* was responsible for about 6% of TB deaths in humans (Hershkovitz et al., 2008; Nester et al., 2009).

The recognized members of the *M. tuberculosis* complex are all clonal in their spread. The main human infecting species are classified into seven oligotypes: type 1 include the East African-Indian (EAI) and some Manu (Indian) strains; type 2 is the Beijing group; type 3 consists of the Central Asian (CAS) strains; type 4 include Ghana and Haarlem (H/T), Latin America-Mediterranean (LAM) and X strains; types 5 and 6 correspond to *M. africanum* and are observed mostly and at very high frequency in West Africa. A seventh type was isolated from the Horn of Africa (Cole et al., 1998).

Other species of this complex belong to a number of oligotypes and do not usually infect humans. Type 2 and 3 are more related to each other closely than the other types. Types 5 and 6 are most closely aligned with the species normally not infectious to humans. Type 3 is divided into two clades: CAS-Kili (found in Tanzania) and CAS-Delhi (found in India and Saudi Arabia) (Cole et al., 1998).
2.3 Morphology of *M. tuberculosis*

*M. tuberculosis* is a slightly curved or straight, thin, non-motile rod-shaped bacilli that grows in sinuous masses or strands called cords; the rods are 2-4 micrometers in length and 0.2-0.5 um in width (Todar, 2008; Lapierre, 2011; Talaro & Chess, 2012). Unlike other pathogens, it produces no toxins, fimbriae, capsule or enzymes that contribute to infectiousness. Most strains contain complex waxes and a cord factor that contribute to virulence by preventing the bacteria from being destroyed by lysosomes of macrophages (Talaro & Chess, 2012; Willey, Sherwood & Woolverton, 2011).

The cell wall of this bacterium differs substantially from that of gram-positive and gram-negative bacteria in that it contains several unique lipid and glycolipid. Around 60% of the dry weights of the *M. tuberculosis* cell wall consist of lipids, a much higher percentage than that in most other bacteria. This lipid content imparts the characteristic of acid fastness and is responsible for its resistance to drying and disinfectants, and its pathogenicity (Nester *et al.*, 2009; Talaro & Chess, 2012).

The cell wall also has lipoarabinomannan, trehalose dimycolate, and phthiocerol dimycocerosate in addition to mycolic acid. These compounds are directly toxic to eukaryotic cells and generate a hydrophobic barrier around the bacterium that facilitates resistance and impermeability to antimicrobial agents. And also protects against the killing by acid and alkaline compounds, osmotic lysis and lysozymes (Willey *et al.*, 2011).

2.4 Cultural characteristics of *M. tuberculosis*

*M. tuberculosis* is an obligate aerobe and it grows very slow with a generation time of 15-20 hours, which is extremely slow compared to the growth of other bacteria, that have division times measured in minutes (*Escherichia coli* can divide roughly every 20 minutes) a physiological feature that may contribute to its virulence (Cole *et al.*, 1998; Cowan, 2009). If a Gram stain is performed on this bacterium, it stains very weakly Gram-positive or not at all (cells referred to as "ghosts"); hence Ziehl-Neelsen staining, or acid-fast staining, is used.
Two media are used to grow this bacterium; Middlebrook's medium which is an agar based medium and Lowenstein-Jensen medium which is an egg based medium. It produces colonies that are small and buff coloured when grown on either medium. Both the two media contain inhibitors to keep contaminants from out-growing the bacterium. It takes a period of 4-6 weeks to get visual colonies on either type of media (Cole et al., 1998; Todar, 2008; Lapierre, 2011).

2.5 Transmission of TB

TB can be transmitted in the following ways: inhalation (most common), ingestion, through breaks in skin (rare), intercourse (rare) and intra-partum (rare) (Lapierre, 2011). It is a communicable disease and patients with pulmonary TB are the most important source of infection. It is spread mostly through the airborne particles. When infectious people cough, sneeze, talk, laugh or spit, droplets nuclei containing *M. tuberculosis* are sprayed into the air. Infection is initiated by inhalation of droplet nuclei, which are particles of 1–5 µm in diameter containing *M. tuberculosis*, expectorated by patients with active pulmonary TB, typically when the patient coughs (Ahmad, 2011; Talip et al., 2013; Desalu et al., 2013).

People nearby may inhale the bacteria and become infected. The tubercle bacilli are extremely resistant to drying and can survive for 6-8 months in dried sputum. Ten (10) or fewer organisms inhaled are not enough to cause infection (Black, 2008; Desalu et al., 2013). The infectiousness of the person depends on several factors such as the infectiousness of the source case, the closeness of contact, the bacillary load inhaled, and the immune status of the potential host (Ahmad, 2011; Talaro & Chess, 2012; Talip et al., 2013). An individual can be infected by *M. tuberculosis* for several years without becoming sick or spreading the organism to other people. But if the immune system is weakened by immunosuppressive disease like HIV infection, diabetes mellitus, malignancy, chronic kidney disease, extremes of ages, and immunosuppressive agent, latent TB infection can develop into active TB disease. If such person with active disease is left untreated, he or she will infect on the average between 10 and 15 people every year (Desalu et al., 2013).

TB infection means that *M. tuberculosis* is in the body, but the immune system is keeping the bacteria under control. The immune system does this by
producing macrophages that surround the tubercle bacilli. The cells form a hard shell that keeps the bacilli contained and under control. People who have TB infection (latent) but not TB disease are NOT infectious, i.e. they cannot spread the infection to other people. These people usually have a normal chest x-ray. Therefore, TB infection is not a TB disease (Harries et al., 2006).

2.6 Risk Groups

The following are risk factors predisposing group to TB disease: being born in a high-risk country, travelling to countries with high prevalence, age, sex, malnutrition, working in places like (nursing homes, prisons, and some hospitals), smoking, intravenous drug use, alcoholism, corticosteroid drugs, HIV, homeless, poverty and ethnicity (Harries et al., 2006; Salek et al., 2008; Ahmad, 2011; Lapierre, 2011).

HIV infection is the number one predisposing factors for \textit{M. tuberculosis} infection. About 10% of all HIV-positive individuals harbour \textit{M. tuberculosis}. Only 3-4% of TB infected individuals will develop active disease upon initial infection, 5-10% within one year. This percentage is much higher if the individual is HIV-positive (Todor, 2008; Roy & Chauhan, 2003).

2.7 The TB Disease

TB disease has five stages, only about 10% percent of \textit{M. tuberculosis} infections progress to disease and even a smaller percent progress all the way to stage five. Usually the host will control the infection at some point. Disease progression depends on: Strain of MTB, Prior exposure, Vaccination, Infectious dose and Immune status of the host (Todar, 2008; Ahmad, 2011).
2.7.1 Stage 1

Droplet nuclei are inhaled. One droplet nuclei contains no more than 3 bacilli. Droplet nuclei are so small that they can remain air-borne for extended periods of time. The most effective (infective) droplet nuclei tend to have a diameter of 5 micrometers. Droplet nuclei are generated by during talking, coughing, and sneezing. Coughing generates about 3000 droplet nuclei. Talking for 5 minutes generates 3000 droplet nuclei but singing generates 3000 droplet nuclei in one minute. Sneezing generates the most droplet nuclei by far, which can spread to individuals up to 10 feet away (Todar, 2008).

2.7.2 Stage 2

This stage begins 7-21 days after the inhalation of the TB bacillus. The bacilli are picked up by special cells of the immune system, called macrophages, after they reach the alveoli in the lung. These macrophages usually reside within the tissue of the alveoli; their task is to swallow and inactivate any foreign object entering the alveolar space. The macrophages ingest the TB bacillus.

The actions that follow largely depend on the amount of TB bacilli and the potency of the macrophage. If the amount of TB bacilli is too high, or if the macrophage is not competent enough to resist the bacilli, \textit{M. tuberculosis} can multiply virtually unlimited within inactivated macrophages until the macrophages burst. New macrophages begin to extravasate from peripheral blood, which also phagocytose \textit{M. tuberculosis}, but also, they are inactivated and hence cannot destroy the bacteria (Todar, 2008; Nester \textit{et al}., 2009; Muller, 2011).

2.7.3 Stage 3

At this stage, the infiltration of lymphocytes begins. The lymphocytes, specifically T-cells, recognize, processed and presented \textit{M. tuberculosis} antigen in context of MHC molecules. This leads to T-cell activation and the release of cytokines including gamma interferon (IFN). The release of IFN causes in the activation of
macrophages. These activated macrophages are now able to destroy *M. tuberculosis* (Todar, 2008). Individual becomes tuberculin skin test positive at this very stage.

This tuberculin reaction is the result of a vigorous cell mediated immune (CMI) response developed by the host, which must be mounted to control *M. tuberculosis* infection. Even though, a CMI response is necessary to control *M. tuberculosis* infection, it is also responsible for a lot of pathology associated with TB. Activated macrophages may release reactive intermediates and lytic enzymes, including Interleukin 1 (IL-1), tumor necrosis factor (TNF), and gamma IFN that facilitate the development of immune pathology (Todar, 2008).

Tubercle formation also begins at this stage. The tubercle is characterized by "caseation necrosis" in its centre, meaning it takes on a semi-solid or "cheesy" consistency. Within these tubercles, *M. tuberculosis* cannot multiply because of the low pH and anoxic situation. However, *M. tuberculosis* can persist within these tubercles for extended periods (Todar, 2008).

### 2.7.4 Stage 4

Although, a lot of activated macrophages can be found surrounding the tubercles, but many other macrophages present remain inactivated or poorly activated. *M. tuberculosis* uses these macrophages to replicate, and hence, enabling the tubercles to grow (Todar, 2008). The growing tubercle may invade a bronchus. When this happens, *M. tuberculosis* infection can spread to other parts of the lung. Similarly, the tubercle may enter an artery or other blood supply line. The hematogenous spread of *M. tuberculosis* may result in extrapulmonary TB otherwise known as milliary TB. It is named "milliary" because the metastasizing tubercles are about the same size as a millet seed, a grain commonly grown in Africa (Todar, 2008).

### 2.7.5 Stage 5

The caseous centers of the tubercles liquefy for unfamiliar reasons, and become conducive to *M. tuberculosis* to multiply rapidly. The large bacilli load causes the walls of nearby bronchi to become necrotic and rupture. The consequences of this, leads to cavity formation. Hence, the *M. tuberculosis* spill into other airways and
rapidly spread to other parts of the lung (Todar, 2008). As stated earlier, only a very small percent of *M. tuberculosis* infections result in disease and even a smaller percentage of *M. tuberculosis* infections progress to an advanced stage.

Generally, the host will begin to control the infection at some point. When the primary lesion heals, it becomes calcifies and fibrous. When this happens, the lesion is referred to as the Ghon complex. (Todar, 2008; Muller, 2011). Normally, the Ghon complex is readily visible upon chest X-ray. Small metastatic foci containing low numbers of *M. tuberculosis* may also calcify. Though, in many cases these foci will contain viable bacilli. These foci are referred to Simon foci, which are also visible upon chest X-ray and are often the site of disease reactivation (Todar, 2008; Muller, 2011).

### 2.8 Clinical presentation or symptoms of TB

Symptoms of TB depend on where the TB bacteria are growing in the body. In the case of pulmonary TB, it may cause symptoms, including chronic cough, pain in the chest, dyspnoea, haemoptysis, weakness or fatigue, severe weight loss, low-grade fever, loss appetite and drenching night sweat (Itah & Udoafia, 1997; Zaman, 2010; Desalu *et al.*, 2013; Talip *et al.*, 2013). While Extrapulmonary TB can have many manifestations, such as cervical lymphadenitis, pericarditis, synovitis, pleuritis, hepatitis, peritonitis, meningitis, osteomyelitis, pyelonephritis, ovary infection and less commonly the skin (Lapierre, 2011; Talip *et al.*, 2013).

### 2.9 Investigation of TB

In Malaysia, TB is diagnosed using clinical, radiological and or bacteriological evidence. Three sputum samples are collected for direct smears for acid-fast bacilli and for culture (Boyle *et al.*, 2002).

Table 2.1 below summarizes some of the investigative methods used in the diagnosis of tuberculosis and identifies the advantages and disadvantages of each, emphasizing methods that are relevant to developing countries.
Table 2.2 Investigative methods used in the diagnosis of TB

<table>
<thead>
<tr>
<th>Type(s) of test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum smear microscopy</td>
<td>Smear microscopy is the only means by which the diagnosis of PTB can be confirmed in most developing countries. It is cheap and affordable and can be performed with minimal skill.</td>
<td>May be problematic depending on the competence of the laboratory staff. Cannot be used in children since they cannot produce sputum. It is not sensitive and may pick other Mycobacteria species.</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>When sputum smear is negative, culture may be positive. It is commonly used in monitoring drug sensitivity patterns in recurrent TB, and community prevalence of drug-resistant TB.</td>
<td>It needs skilled laboratory facilities, which may not be available in most developing countries. It is very slow and takes 4-8 weeks to get results. It is very expensive and may not be affordable to most developing countries.</td>
</tr>
<tr>
<td>Radiological test</td>
<td>It identifies sputum negative cases missed by sputum microscopy. Very useful in the diagnosis of TB in children since they cannot produce sputum.</td>
<td>It is unreliable; abnormalities identified on a chest radiograph may be due to TB or a variety of other conditions. Individuals previously treated for TB may show signs of the disease on radiographic examination.</td>
</tr>
<tr>
<td>Tuberculin test</td>
<td>Very useful in measuring the prevalence of latent TB in the community, especially if not vaccinated with BCG. Very valuable in making diagnosis in a young child at an age when fewer children in the community will normally have a positive test.</td>
<td>A positive test may not be caused by TB and a negative test does not always rule it out, especially in HIV positive. It is not routinely available in many peripheral health institutions; it is expensive, has a very short expiry date, must be kept protected from light and heat and requires some technical skills in its administration and reading.</td>
</tr>
<tr>
<td>Others- biopsies of lymph nodes, laryngeal swabs, etc</td>
<td>They are very fast and specific. Immunological tests, for example, are very useful in patients who cannot produce sputum. They are very useful in research work on TB.</td>
<td>Most of the tests are expensive and cannot be afforded by most developing countries. Technical skills are needed in their performance. Expensive equipments are needed for most of these tests.</td>
</tr>
<tr>
<td>Line probe Assay</td>
<td>Short TAT, Detects Rif and INH Resistance, High sensitivity for MDR-TB.</td>
<td>Reduced sensitivity in smear negative.</td>
</tr>
</tbody>
</table>

Adapted from Dodor (2009).

2.10 Definition of epidemiology

The term epidemiology is derived from the word ‘epidemic’, which appears to have been derived from epidemeion, a word used by Hippocrates when describing a disease that was ‘visiting the people’ (Woodward, 2005). Epidemiology can be defined as the study of the distribution and determinants of disease in human populations. In other words, it provides the answers to questions on how much disease there is, who gets it and what specific factors put individuals at risk. Modern
use of the term retains the restriction to human populations but has broadened the scope to include any type of disease, including those that are far from transient (Silman & Macfalane, 2002).

The distribution of disease studied is often a geographical one, but by distribution by age, sex, social class, marital status, racial group and occupation, etc. are also often of interest. Sometimes the same geographical population is compared at different time to investigate trends in the disease (Silman & Macfalane, 2002). The determinants of disease are the factors that precipitate disease. Study of the determinant of disease is essentially a descriptive exercise; study of determinants considers the etiology of disease (Silman & Macfalane, 2002).

2.11 Global TB Epidemiology

An epidemiological trend of a disease in the society gives an insight into its behavioral pattern over a period of time and enables us not to only assess the impact of intervention programmes but also to predict the likely scenario in future. The behavior of the disease in pre-chemotherapy era was assessed using TB mortality, rates as an epidemiological index (Chadha, 1997).

The specific mortality data of disease show that TB in England peaked around 1740 with about 900 TB deaths per 100,000 populations annually. The majority of the capitals of western European countries attained their mortality peaks in first half of 19th century while those of east Europe, a few decades later (Chadha, 1997). In Czechoslovakia, Norway, Netherlands and other developed countries including USA, TB mortality declined considerably from 200-400/100,000 population annually at the turn of the century during the next 40 years. Mortality records in Canada showed 3% per annum decline in TB mortality before the introduction of specific treatment (Chadha, 1997). The incidence cases fell by 58% from 1921 to 1940 in Denmark. In Netherlands, 5.4% annual decline in annual risk of infection (ARI) was observed in the pre-chemotherapy period. It was similarly observed that, there was annual decline in the risk of infection in Vienna and 4.7% in Prague (Chadha, 1997).

Incidence of TB in Russian has risen over the past 15 years, from 34.2 per 100,000 populations in 1991 to 115/100000 in 2004. Despite intensive national and regional
efforts to improve TB services, the mortality continues to rise, with estimates of 21 deaths per 100,000 populations in 2004. Now TB is the leading infectious cause of death in Russia (Mathew et al., 2006). TB remains an important health burden in Serbia. There has been no reduction in the incidence from 1994 to 2004; the incidence in 1994 was 34 per 100,000 and in 2004 it was 35 per 100,000 populations (Vukovic & Nagorni-obradovic, 2011).

From 1920 to 1950, TB mortality accounting for 35% of all deaths remained constant at 65 per 100,000 populations in Alaska. Tuberculin surveys carried out from 1938 to 1948 in Algeria and Tunisia showed negligible decline in risk of infection (Chadha, 1997). There was drastic increase in TB incidence rate in 2007 in Libya from 17 cases (all forms) per 100,000 populations to 40 cases (all forms) per 100,000 population in 2008 (Solliman, 2012). In Morocco, TB prevalence is also highly, it affected more than 26,000 people in 2009, with the incidence of around 82 new cases per 100,000 and in 2008 it was 81 per 100,000 populations (Tachfouti, Slama & Berraho, 2012). TB is a serious public health challenge in Nigeria with an estimated prevalence of nearly 900,000 cases and with the second highest TB disease burden in Africa and ranks fifth among the 22 high TB burden countries in the world. In Nigeria, there were 90,447 TB cases notified in 2010 with 41,416 (58%) cases as new smear positives (Desalu et al., 2013). Even in the wealthiest African country, the Republic of South Africa, TB incidence is very high with 948 per 100000 in 2007 (Stuckler et al., 2011).

In 2005, the TB prevalence was reported as 6.8 per 100 000 in Iran, but according to a WHO report, 12 Iranians per 100 000 suffered from TB (Besharat, 2009; Dooley et al., 2011). Globally, Pakistan ranks eighth for the high TB incidence. In Pakistan, the prevalence of TB is 297 cases per 100,000 population and nearly 0.3 million new cases arise annually (Mushtaq et al., 2011). Whereas Bangladesh rank sixth among the high TB burden countries with the incident rate of 225 per 100,000 population per year, with 353,000 new cases, 70,000 deaths in 2007 (Zaman, 2010; Tasnim et al., 2012).

India alone accounts for one-third global burden of TB and every year more than 1.8 million new cases emerge in the country, Approximately 400,000 people die from TB every and year in India, more than 1,000 every day and 100 million work-days are lost (Yadav, Mathur, & Dixit, 2006). China ranked the second largest TB
burden country in the world, just behind India 1,000,000 TB cases (Chen et al., 2013). In 2009, Japan had intermediate TB incidence of 19.0/100,000 per population (Tamaru et al., 2012). Taiwan is a middle-burden country with an annual TB incidence of around 70 per 100,000 population from 1997 through 2005 (Ng et al., 2012).

As much as 45 per cent of the populations are infected with TB in Nepal and each year an estimated 44,000 of these people infected with TB develop active disease. Over 8,000 of these people die each year (Thomas et al., 2007).

2.12 Epidemiology of TB in Malaysia

The disease is an ancient, and the cure is half-century-old. And yet, this year will see more Malaysians die of TB than any other infectious disease. As in other developed and industrialized countries, TB problem declined significantly between 1970 and 1990 in Malaysia. Though, from early 1995 till 2002 the incidence of TB slowly increased with an incidence rate of 59.8 in 1994, 58 in 1995 slowly rising to 65.6 in year 1999 and 65.9 in the year 2000 (Aziah, 2004).

In the year 2000, 2001 and 2002 the number of TB cases in Malaysia are 15,643, 14,820 and 14,389 respectively with the mean mortality rate of 6.2/100,000 population. In the year 2002 alone, Malaysia had 1035 deaths directly due to TB (Aziah, 2004). The new cases of TB were reported to be 15,429 for the year 2004 in Malaysia. The total number of deaths due to TB reported was 1,245 (Nor et al., 2011). The incidence rate of TB in Malaysia has been stagnant at around 58.7 to 65.6 per 100,000 populations in the last ten years. However, the absolute number of new cases has been increasing from the figures of about 15,000 new cases in 2002 up to 16,665 in 2006 (Rafiza et al., 2011). The notification rate among smear-positive patients was 36 per 100,000 in 2007 in Malaysia (Rundi, 2010). In the year 2010, a total of 18,517 individuals have been infected, which is an increase of 6% from the previous year (17,341 cases in year 2009). The highest cases registered in that year was in Sabah, totaling 3278 cases, followed by Selangor (2829 cases), Johor (2058 cases), Sarawak (1991 cases) and Kuala Lumpur / Putrajaya (1455 cases) (Mokhtar et al., 2012).
2.13 Retrospective study

Retrospective study uses data that have been recorded for reasons other than research. In health care these are usually called “chart reviews” because the data source is the medical record (Gearing et al., 2006). This includes nursing and physician notes, ambulatory and emergency room reports, consultations, admission and discharge documentation, laboratory and diagnostic testing reports, and other clinical or administrative data (Hess, 2004).

Most times investigators view retrospective data as “quick and dirty” because the data are quickly extracted from existing records to answer a question. Although, a well done retrospective study may not be quick and is certainly not “dirty” (Hess, 2004). The systematic investigation of historical records has guided various clinical researches for over eight decades. The scientific employment of existing health records is common in epidemiological investigations and in clinical research. Investigations using this method have been reported to cover 25% of all scientific articles in emergency medical journals (Gearing et al., 2006).

2.13.1 Advantages of conducting retrospective study

The following are the advantages of conducting chart reviews:

1. It is relatively inexpensive;
2. ability to research the rich readily accessible existing data;
3. easier access to conditions where there is a long latency between exposure and disease;
4. allowing the study of rare occurrences;
5. And most importantly, the generation of hypotheses that then would be tested prospectively (Gearing et al., 2006).

2.13.2 Disadvantages of conducting retrospective study

The drawbacks of retrospective study are: unfinished documentation, as well as missing charts, information that is unrecoverable or unrecorded, difficulty in interpreting information found in the documents (e.g. jargon, acronyms, and
photocopies), problematic verification of information and difficulty in establishing cause and effect, inconsistency in the quality of information recorded by medical professionals have discouraged researchers from adopting this methodology (Gearing et al., 2006).

2.14 Socio-demography

Socio-demography have great influence in TB infection, these includes: gender, age groups, race, family income, level of education and smoking.

2.14.1 Gender

Men were affected with TB more than women, hence, TB is more common in males than in females with a wide variation between countries (Gupta, Gupta, & Jamwal, 1993; Abdallah & Ali, 2012). In most countries, the case notifications are higher in males than in females. There were 1.4 million smear-positive TB cases in men and 775,000 in women in 2004 (Zaman, 2010).

According to study by Abdallah & Ali (2012) in Eastern Sudan, majority of TB patients were males. An epidemiological study by Kadri et al. (2003) in India found that 54.09% of TB cases were in males while 45.91% were in females. Besharat et al. (2009) found a prevalence of about 39.2 and 37.1 per 100,000 in males and females, respectively in Northeast of Iran. Jetan et al. (2010) found in their study in Malaysia that more cases were reported among males (n=85; 65%) than females (n= 46; 35%). Study in Kota Bharu, Kelantan Malaysia showed TB cases in 316 males and 156 females (Nor et al., 2011).

Similar to above study, in Brazil, Cavalini (2010) found in the frequency distribution by gender, males to be 63.1% while females 36.9%. Sex wise distribution of the population surveyed in India by Gupta et al. (1993) showed 2691 males and 2309 females and the total percentage of male TB cases was 64% and only 36% cases were found among the females surveyed. Similarly, Shetty et al. (2006) showed that the sex distribution was 58% men and 42% women in South India. Also in South India, Majra (2007) found that majority 190 (76%) of patients with TB and other co-morbid conditions were males and few 60 (24%) were females.
Contrary to above findings, Salek et al. (2008) in Tehran, Iran found out that out of 3,417 registered TB patients between 1999-2003 at Center for Communicable Disease Control of Golestan province, 2,773 (81%) were available and out of which only 47% were male while the remaining 53% were female.

2.14.2 Age group

Age groups undoubtedly contributes to the incidence of TB (Nissapatorn et al., 2003). Generally, greater than 90% of all TB cases are found in adults aged 25-64 and older, with the largest fraction among > 64 year olds (Liao et al., 2012).

According to Nor et al. (2011) 75% of TB cases in developing countries are among the economically productive age group. Study in Malaysia in the year 2000 showed that incidence of TB was highest among the 20-54 years age group. According to Jetan et al. (2010) in their study in Malaysia, age group mostly affected was 21-40 years old (n=49; 37%), followed by the 41-60 year old age group (n=42; 32%). The age group with the fewest cases was found to be age 0-20 years old (n=4; 3%). The 21-60 year old age group constituted the majority of cases (n=91; 69.5%).

Study in Nigeria by Itah & Udofia (1997) revealed that the highest number of samples were obtained from patients of ages between 16-35 years old, with an incidence of 731 (55.2%) of the total (1,324) samples. Followed by adults 36 years old and above with incidences of 29%, and finally by children 1-15 years old 15–8%.

Shetty et al. (2006) in South India found the age of the TB patients to be ranged from 15 to 83 years; 27%, 24.9%, 12.7% and 33.3% of subjects were in the 15–24, 25–34, 35–44 and >45 year age groups respectively. According to Majra (2007), Majority of the patients 177 (70.8%) were age group of 21-50 years, 57 (22.8%) were more than 50 years and 16 (6.4%) were <20 years of age. Cavalini (2010) said the proportion of patients in the 30-59 age group bracket was over 56% for all hospital sectors and for all clinical forms of TB (Cavalini, 2010a). In Indian study, Kadri et al. (2003) found that 47.06% of TB patients belonged to 0-19 age group, 49.21% belonged to 20-59 age group while 3.73% were ≥ 60 years of age.
2.14.3 Race

In a similar study carried out in University of Malaya medical center Kuala Lumpur, Malaysia by Jetan et al. (2010), found out that most cases occurred among Malays (56 cases; 43%), followed by the Chinese (29 cases; 22%), Indians (22 cases; 17%) and others (18%). Most cases (n=109; 83%) occurred among Malaysians. Twenty-two cases (17%) were recorded among Indonesians and Myanmar people. According to Nor et al. (2011), in their study in Kota Bharu, Kelantan, the majority of patients were Malays (95.1%), Malaysian citizen (98.7%).

Contrary to above studies, a study in Chest clinic Penang by Elamin et al. (2004), found 55.5% of TB patients to be Chinese and 33.8% Malay after analysis was carried out on 207 patients.

2.14.4 Family income

The relationship between poverty and TB is well-documented, and the highest rates of TB were found in the poorest section of the community. TB occurs more frequently among low-income populace living in overcrowded. It is usually considered a disease of poor, associated with poor-resource countries (Gupta et al., 1993; Shetty et al., 2006; Zaman, 2010; Abdallah & Ali, 2012). And majority of infected individuals are malnourished, have underlying diseases or are from the lower socioeconomic classes (Besharat, 2009).

Nor et al. (2011) defined family income as the total household income earned by the patients. And it was found that among the patients, 71% had lower family income (<RM 1000). According to Majra (2007), out of 250 TB patients studied, about have of them belonged to low socio-economic group. Elamin et al. (2004) revealed in their study that majority of the patients 109 (52.2%) had no monthly income, and among the working patients, majority of them had a low monthly income <RM500 (4.4%), RM500-999 65(31.4%), RM1000-1499 17(8.2%), RM1500-1999 3(1.4%), >RM2000 4(1.9%).
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