KNOWLEDGE, ATTITUDE AND PREVENTIVE PRACTICES ON CENTRAL NERVOUS SYSTEM TUBERCULOSIS AMONG HEALTHCARE WORKERS

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by

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TB	Tuberculosis
CDC	Centers for Disease Control and Prevention
HIV	Human immunodeficiency virus
AIDS	Acquired immune deficiency syndrome
WHO	World Health Organization
MDG	Millennium development goal
MTB	*Mycobacterium Tuberculosis*
CNS	Central nervous system
NTBCP	National tuberculosis control programme
MDR-TB	Multidrug-resistance tuberculosis
MOH	Ministry of Health Malaysia
PTB	Pulmonary tuberculosis
EPTB	Extra-pulmonary tuberculosis
HCWs	Healthcare workers
KAP	Knowledge, attitude and practice
USM	Universiti Sains Malaysia
HKL	Hospital Kuala Lumpur
CSF	Cerebrospinal fluid
TBM	Tuberculous meningitis
CT	Computerized tomography
MRI	Magnetic resonance imaging
ICP	Intracranial pressure
BCG	Bacillus Calmette-Guerin

INH	Isoniazid
RIF	Rifampicin
PZA	Pyrazinamide
EMB	Ethambutol
IQR	Inter-quartile range
LTBI	Latent tuberculosis infection
TST	Tuberculin skin test
DOT / DOTS	Directly observed treatment, short-course
SPSS	Statistical Package for the Social Science
SD	Standard deviation
SLogR	Simple logistic regression
OR	Odd ratios
CI	Confidence intervals
MLogR	Multiple logistic regressions
LR	Likelihood-ratio statistic
ROC	Receiver Operating Characteristics
JEPeM	The Human Research Ethics Committee of USM
NMRR	National Medical Research Register
ICU	Intensive care unit
EVD	External ventricular drainage
C&S	Culture & Sensitivity
PPE	Personal protective equipment

PENGETAHUAN, SIKAP DAN AMALAN PENCEGAHAN TERHADAP TUBERKULOSIS SISTEM SARAF PUSAT DI KALANGAN PEKERJA PENJAGAAN KESIHATAN

ABSTRAK

Sejenis bakteria dipanggil "*Mycobacterium tuberculosis*" yang menyerang sistem saraf pusat telah menyebabkan kemunculan penyakit tuberkulosis (TB) sistem saraf pusat yang dilaporkan meliputi kira-kira 15% daripada keseluruhan kes TB ekstrapulmonari. Dalam fasa pertama, kajian ini bertujuan menentukan tahap pengetahuan, sikap dan amalan terhadap TB sistem saraf pusat dalam kalangan pekerja penjagaan kesihatan dan juga faktor yang mempengaruhinya serta menentukan kaitan di antara pengetahuan, sikap dan amalan serta persepsi diri mereka terhadap penyakit tersebut. Kajian ini secara berturutan juga meneroka tema yang mempengaruhi pengetahuan, sikap dan amalan terhadap pencegahan TB sistem saraf pusat dalam kalangan pekerja tersebut di dalam fasa kedua. Pendekatan kaedah kajian dua fasa secara mod campuran telah digunapakai dalam kajian keratan rentas ini yang berpandukan paradigma positivisma. Sejumlah 134 pekerja penjagaan kesihatan dari wad perubatan, wad neurologi dan unit forensik Hospital USM dan HKL melibatkan diri dalam fasa pertama kajian yang dinilai menggunakan borang kaji selidik pengetahuan, sikap dan amalan yang baru digubal. Dalam fasa kedua seramai 21 pekerja penjagaan kesihatan mengambil bahagian dalam empat diskusi fokus berkumpulan yang menggunakan panduan temuduga separa berstruktur. Data terkumpul dari fasa pertama telah dianalisa dengan menggunakan regresi logistik manakala untuk fasa kedua, penjanaan tema telah digunapakai melalui analisis

tematik. Dalam fasa pertama, profil pekerja penjagaan kesihatan menunjukkan purata (SD) umur mereka adalah 33.0(9.2) tahun yang telah bekerja kira-kira 7.0(9.0) tahun secara median (IQR). Daripada 134 pekerja penjagaan kesihatan, 56.7% mempunyai pengetahuan yang baik terhadap TB sistem saraf pusat manakala majoriti daripada mereka, 53.7% bersikap negatif dan didapati tiada perbezaan pada tahap amalan mereka. Umur dan tempoh pekerjaan pekerja penjagaan kesihatan kedua-duanya menunjukkan kaitan sebanyak 5% kebarangkalian mereka berpengetahuan rendah manakala secara berturutan sekurang-kurangnya 4% dan 5% kebarangkalian mereka bersikap negatif terhadap TB sistem saraf pusat. Dalam pada itu, umur pekerja penjagaan kesihatan dan wad neurologi menunjukkan kaitan sebanyak 4% kebarangkalian dan sekurang-kurangnya 96% kebarangkalian mereka mempunyai amalan kurang baik. Faktor yang berkait dengan persepsi diri pekerja penjagaan kesihatan terhadap tahap pengetahuan mereka adalah sikap negatif mereka dan tempoh dalam perkhidmatan yang merekodkan secara berturutan sekurang-kurangnya 65% dan sebanyak 6% kecenderungan mereka berpersepsi mempunyai tahap pengetahuan yang mencukupi tentang TB sistem saraf pusat. Dalam fasa kedua, faktor penyebaran TB sistem saraf pusat dan kesediaan pekerja penjagaan kesihatan mempengaruhi pengetahuan, sikap dan amalan mereka terhadap pencegahan penyakit tersebut. Walaupun kejadian kemasukkan pesakit disebabkan TB sistem saraf pusat jarang berlaku, namun pekerja penjagaan kesihatan tanpa dijangka menunjukkan tahap pengetahuan yang baik terhadap penyakit tersebut meskipun kebanyakkan daripada mereka bersikap negatif yang digambarkan melalui cara mereka berfikir dan bertindak balas semasa mengendalikan pesakit TB sistem saraf pusat.

KNOWLEDGE, ATTITUDE AND PREVENTIVE PRACTICES ON CENTRAL NERVOUS SYSTEM TUBERCULOSIS AMONG HEALTHCARE WORKERS

ABSTRACT

A bacterium called *Mycobacterium tuberculosis* which affected the CNS has caused the emergence of CNS tuberculosis which covered approximately 15% of the total cases of extra-pulmonary TB cases. The first phase of this study was intended to determine the level of KAP on CNS tuberculosis among healthcare workers as well as its associated factors and to determine the association between KAP and self-sufficient perception among the HCWs towards the disease. This study sequentially also explored the themes that influence KAP on CNS tuberculosis prevention among the HCWs in the second phase. A two-phase mixed methods study approach was used in this cross-sectional study underpinned by positivism paradigm. A total of 134 HCWs from medical wards, neurology wards and forensic units of Hospital USM and HKL participated in phase one which were evaluated by using a newly developed self-administered questionnaire of KAP. In phase two, a number of 21 HCWs participated in four focus group discussions by using a semi-structured interview guide. Data collected from first phase was analysed by using logistic regression while in phase two, generation of themes was applied through thematic analysis. In phase one, the profile of HCWs showed that their mean (SD) age was 33.0(9.2) year-old who have worked about 7.0(9.0) years in median (IQR). Out of 134 HCWs, 56.7% had good knowledge on CNS tuberculosis while majority of them, 53.7% had negative attitude and there was no difference in their level of

practice. The healthcare workers' age and duration of employment were associated by both 5% times the likelihood on getting poor knowledge while respectively by 4% and 5% times the likelihood to have negative attitude towards CNS tuberculosis. In the meantime, age of HCWs and their workplace of neurology ward were associated respectively by 4% more likely and 96% less likely to have poor practice. The associated factors of self-sufficient knowledge perception of HCWs were their negative attitude and duration of employment respectively by 65% less likely and 6% more likely to perceive themselves as having sufficient level of knowledge on CNS tuberculosis. In the second phase, the factors of transmission of CNS tuberculosis and the willingness of HCWs affected their KAP towards the disease prevention. Despite the rare occurrence of admitted patients with CNS tuberculosis, the HCWs unexpectedly gain good knowledge on the disease although majority of them presented with negative attitude which depicted by their way of thinking and reacting while handling the CNS tuberculosis patients.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

In general, tuberculosis (TB) is one of the most common infectious disease and one of the largest cause of deaths worldwide which to date has infecting one third of the world's population (CDC, 2011). Among the other lethal killers globally due to a single infectious agent, TB is second after human immunodeficiency virus (HIV) / acquired immune deficiency syndrome (AIDS) (WHO, 2014b). In 2008, World Health Organization (WHO) reported that approximately 9.2 million new TB cases and 1.7 million deaths occurred within the year while in 2010, WHO stated that a total of 8.8 million new cases of people infected with TB and around 1.4 million TB-related deaths.

In recent fact sheets, WHO (2014b) reported a total of 9 million new TB cases and 1.5 million TB-related deaths occurred globally in 2013. Figure 1 showed the estimated TB incidence rates worldwide for year 2013 (WHO, 2014a). This disease however undoubtedly remains outstanding globally in spite of the decline of its incidence within industrialized nations over the course of recent decades (Be *et al.*, 2009). Although the declining of the estimated number of TB incidence is very slow each year, the world is still concomitant in achieving the Millennium Development Goal (MDG) which to reverse the spread of TB by 2015 (WHO, 2014b).

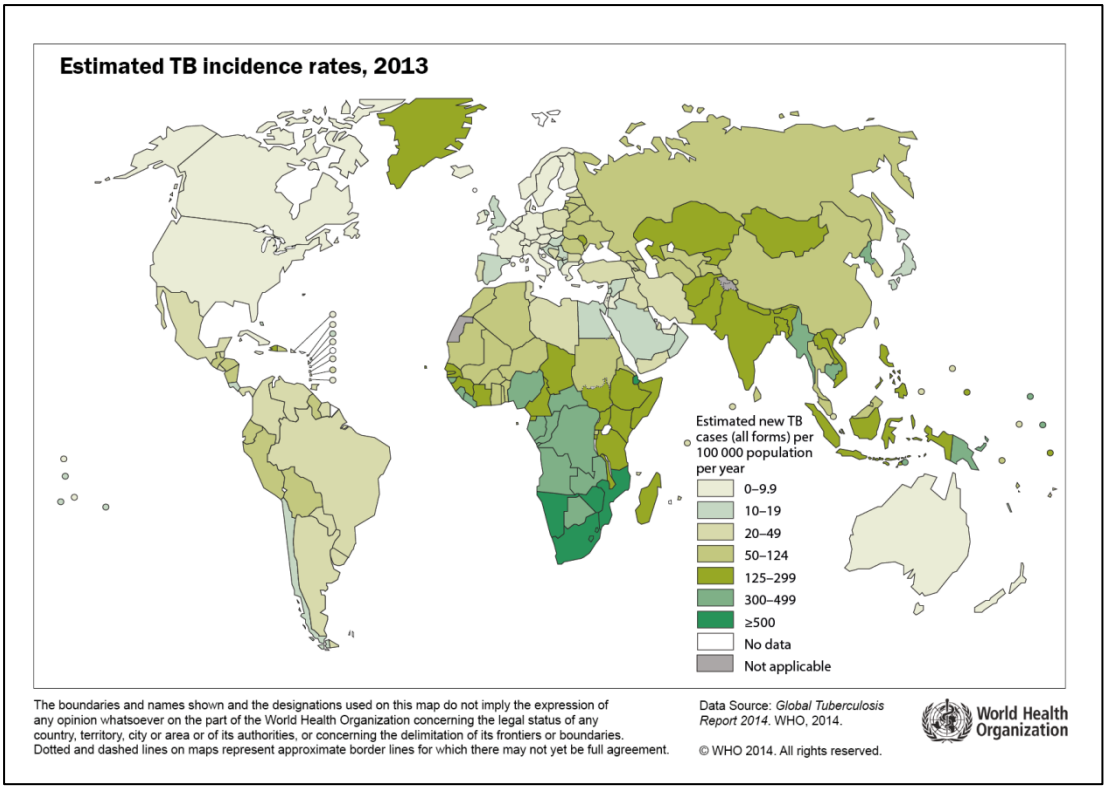


Figure 1: Global Estimated TB Incidence Rates for year 2013

(Source: Global TB Report 2014 (WHO, 2014a))

To date, Stop TB Strategy and supporting Global Plan to Stop TB are the actions perform by WHO to dramatically reduce the burden of TB and halve TB death rates by 50% relative to 1990 and TB prevalence by 2015 (WHO, 2012; WHO, 2015a). The Global Plan to Stop TB founded in 2001 was a roadmap for a five-year period in combating against TB (WHO, 2015a). Currently, the updated Global Plan to Stop TB 2011-2015 is the third plan in progress which targeted by 2050, concomitant with the MDGs and supported by the Stop TB Partnership to eliminate TB as a public health problem (one case per million populations) (WHO, 2015b).

Global trends in estimated rates of TB incidence, prevalence and mortality from year 1990-2015 was shown in Figure 2 (WHO, 2014a). By definition,

tuberculosis is a bacterial disease caused by a bacterium called *Mycobacterium Tuberculosis* (MTB) that usually presents in the lungs as pulmonary TB and also capable to manifest in any part of the body such as the kidney, spine and brain through the lymphatic and blood vessels which known as extra-pulmonary TB. It spread very efficiently from person to person, via airborne which commonly by coughing and sneezing from the throat and lungs of people with the active respiratory disease (WHO, 2012).

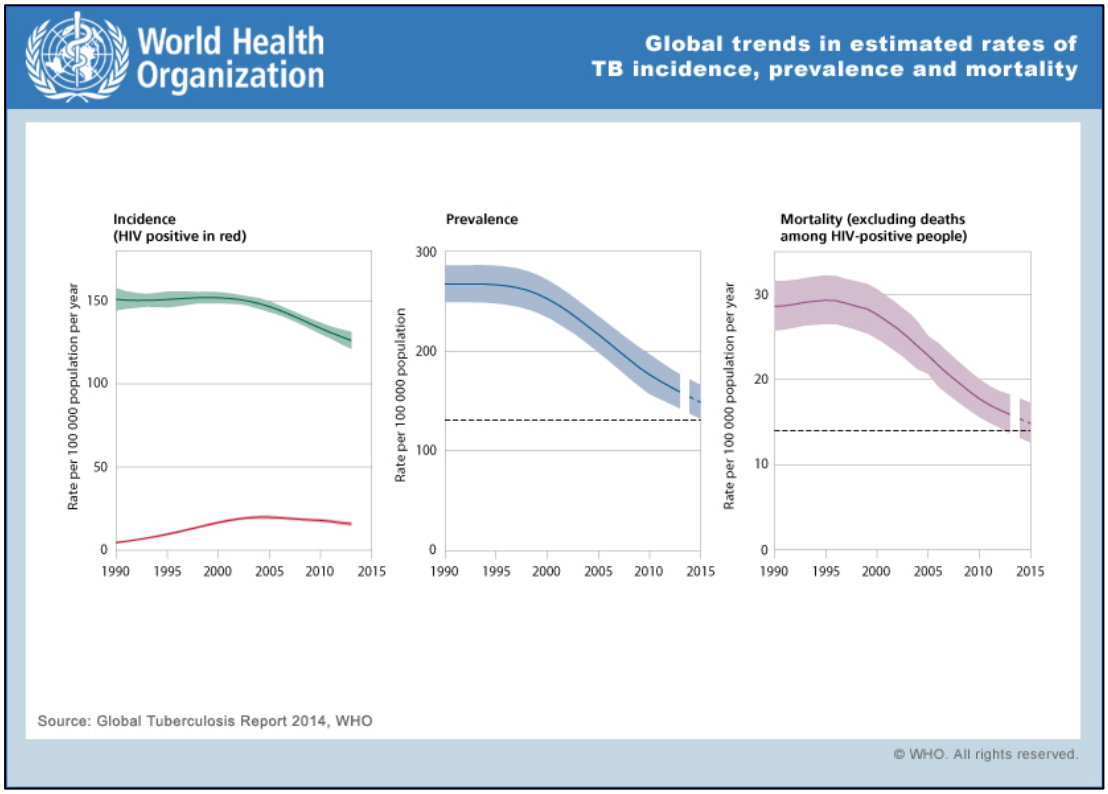


Figure 2: Global Trends in Estimated Rates of TB Incidence, Prevalence and Mortality

(Source: Global TB Report 2014 (WHO, 2014a))

WHO (2014b) stated that the rate of TB-related deaths between 1990 and 2013 have decreased by an estimated 45% and mostly (over 95%) occurred in low- and middle-income countries while TB prevalence rate has dropped by an estimated 41%. For year 2013, the global estimated TB mortality rates excluding TB deaths

among HIV-positive cases were shown in Figure 3 (WHO, 2014a). In addition, most cases of the deaths were reported in the high-burden and less-developed countries which generally, high of incidence in Asia, Africa and South America (Norhayati, 2009, November 16). Bacay-Domingo & Ong-Lim (2009) found that Southeast Asia carries the biggest burden of the disease in terms of the number of cases while in economically-underprivileged countries, parasitic diseases, malnutrition, ignorance, superstition and overcrowding were the other contributing factors for the rise in the number of TB cases.

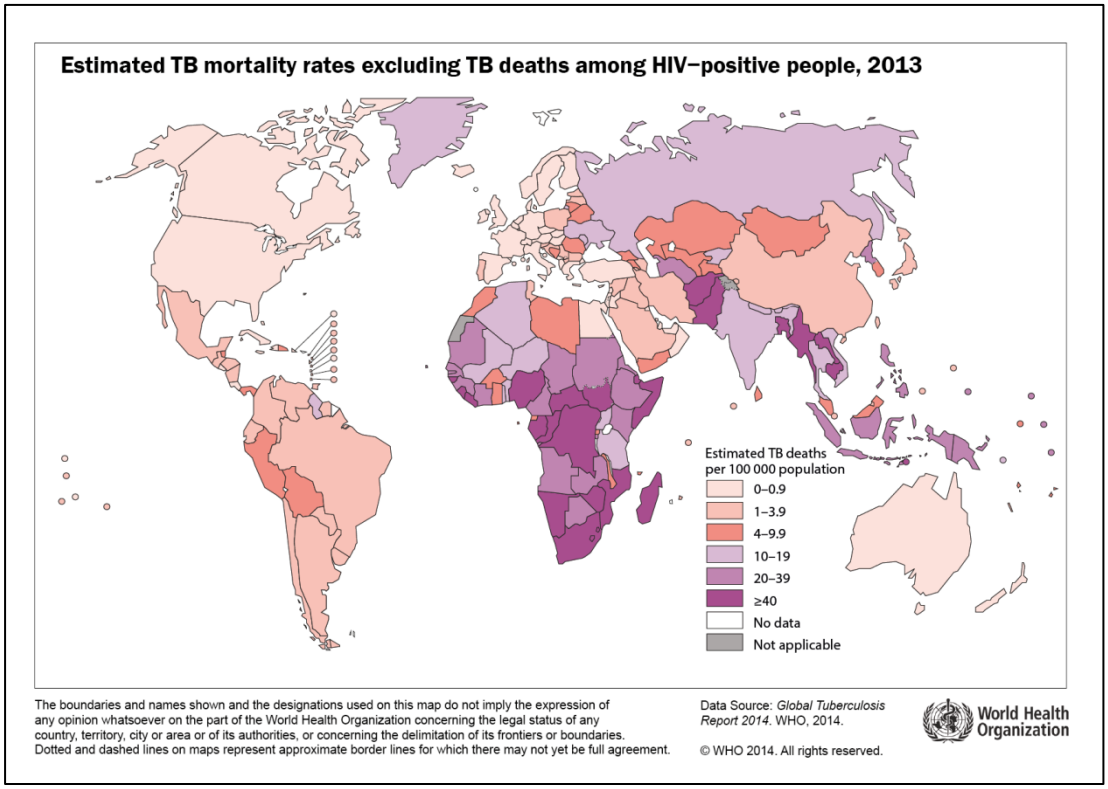


Figure 3: Global Estimated TB Mortality Rates excluding TB deaths among HIV-positive people for year 2013

(Source: Global TB Report 2014 (WHO, 2014a))

Tuberculosis (TB) of central nervous system (CNS) which mainly caused by bacterium called *Mycobacterium tuberculosis* is a rare, yet highly awfully manifestation of tuberculosis disease (Rock *et al.*, 2008; Chatterjee, 2011). The CNS

has been the second commonest site of involvement within 15% of all TB cases which occur outside the respiratory system (extra-pulmonary TB) although 85% of the cases occur in the lungs commonly known as pulmonary TB (Algahtani *et al.*, 2014). CNS tuberculosis which is the most serious form of infection with *Mycobacterium tuberculosis* constitutes approximately 5%–15% of the extra-pulmonary tuberculosis cases (Hernandez Pando, 2011). CNS tuberculosis particularly in cases of meningitis accounted only one to 10% of all TB cases but carries a high mortality and distressing level of neurological morbidity (Yang *et al.*, 2007; Chatterjee, 2011).

Harris & Morris (2007) found that as many as 10% of persons with pulmonary TB will develop CNS tuberculosis, which can manifest as meningitis or lesions of the brain or spine. Isabel & Hernandez Pando (2014) has revealed that 30% from the cases of CNS tuberculosis end up with fatality while 50% of the survival cases need further treatment sequels and in six to twelve months prior to the detection of neurological symptoms, at least 75% of the patients had experienced with pulmonary TB which has been reported by some other studies. However, there were also cases of CNS tuberculosis accounted roughly 25-30% of the cases which do not have any association with active cases of pulmonary TB (Isabel & Hernandez Pando, 2014). In general, CNS tuberculosis has two state of presentation either in diffuse forms, like basal exudative meningitis, or in localized forms, like tuberculoma, abscess or cerebritis (Bernaerts *et al*., 2003*;* Algahtani *et al.*, 2014).

Gropper *et al.* (1995) reported that cases of *Mycobacterium tuberculosis* infection of the CNS are scarce and even cases of TB itself are uncommon in the

industrialized countries. The cases of CNS tuberculosis found generally resulted from an infection from other organ system in which commonly related with military TB. Gropper *et al.* (1995) also has found that 600 out of 4000 cases of extra-pulmonary TB in the USA in 1979 were the cases of meningitis. The number of CNS tuberculosis cases keep increased in most developed countries where in 1991, 8 million new cases of TB were reported in which the cases of CNS tuberculosis were denoted by 400 000 cases or 5% of the total.

CNS tuberculosis is associated with significant morbidity and mortality which predominantly affecting very young children in high TB prevalence countries and affecting adults in low TB prevalence countries (Thwaites *et al.*, 2009; Chatterjee, 2011). Aside from affecting children, this disease also affected human immunodeficiency virus (HIV)-infected individuals (Rock *et al.*, 2008). More than half die or are disabled of those who receive treatment for this disease and the others if left untreated; CNS tuberculosis is fatal (Harris *et al.*, 2007). Furthermore, Rock *et al* .(2008) reported that, a study in Spain documented that out of TB deaths in 1993, CNS tuberculosis accounted for 3.2% while in a large study in Taiwan, CNS tuberculosis attributed 1.5% of TB deaths for year between 1997 until 2001. However, little attention have been received towards the pathogenesis, diagnosis and treatment of CNS tuberculosis compared to pulmonary TB, which investigation intensively have been done in numerous clinical trials (Yang *et al.*, 2007).

1.2 Tuberculosis in Malaysia

In Malaysia, TB is still a major public health problem compared to CNS tuberculosis despite the implementation of preventive and control measures with its incidence rate in the last ten years has been stagnant at around 58.7 to 65.5 per 100,000 populations (Rafiza *et al.*, 2011). Malaysia is classified as a country with an intermediate TB burden (Rundi, 2010). Out of all TB cases, pulmonary TB accounted 91% while TB lymphadenitis, bone and joint TB and miliary TB are the most common extra-pulmonary TB seen in Malaysia (Jetan *et al.*, 2010). To date, WHO (2014a) in its global TB report stated that in Malaysia for year 2013, there were 24, 071 TB cases notified with incidence rate to be 80.24 per 100,000 populations (refer to Figure 4). As compared with number of TB cases notified in 2012 (22,710 cases), number of TB cases notified in 2013 had increased by 6% (MOH, 2012a; WHO, 2014a). Jetan *et al.* (2010) found that TB was the number one cause of death in Malaysia in the early 1940s and 1950s.

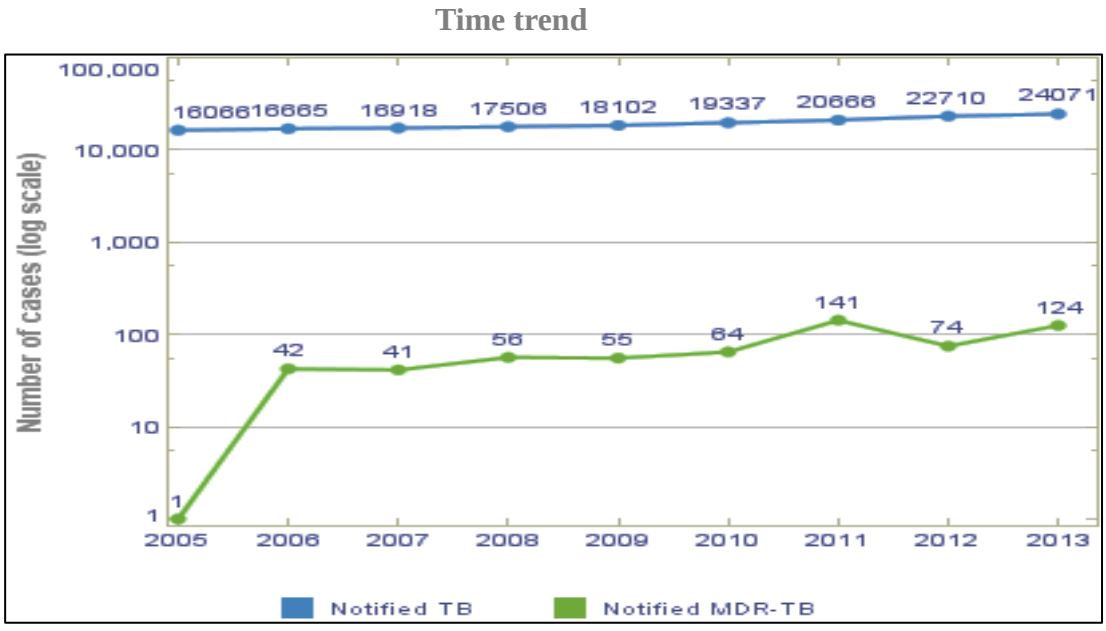


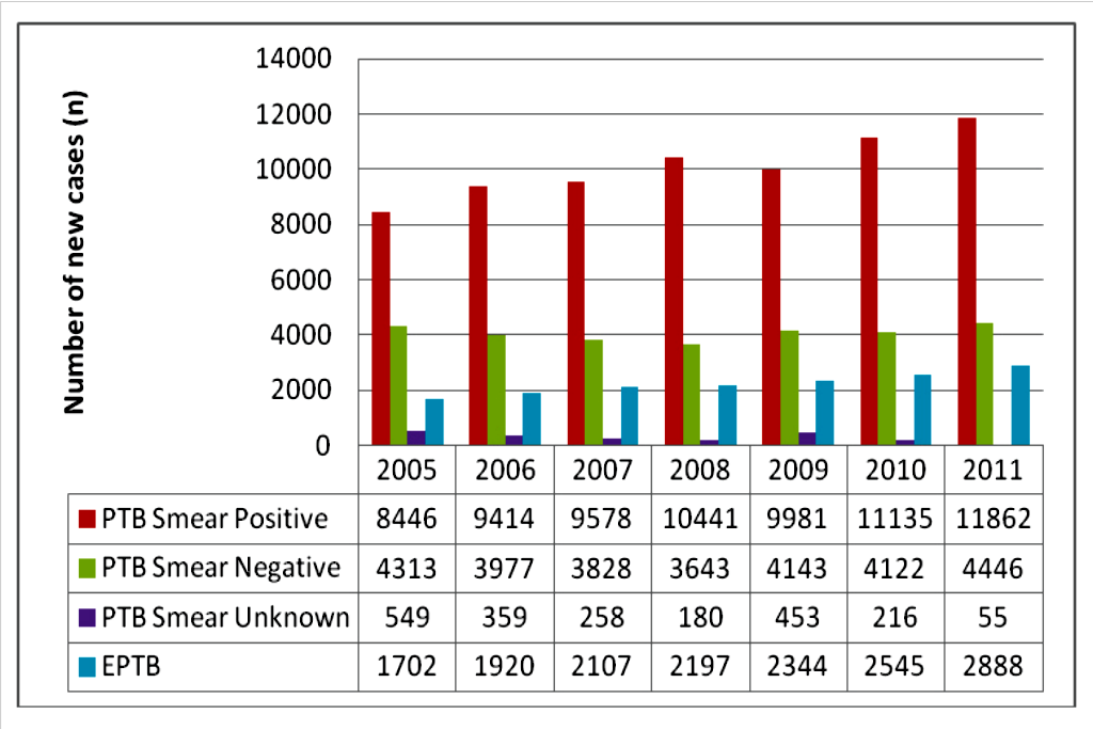
Figure 4: Notification of TB and MDR-TB cases in Malaysia for year 2005-2013

(Source: Global TB report 2014 (WHO, 2014a))

Besides, many sanatoriums in various parts of the country received patients with TB infection and were managed by surgical means. National TB Control Programme (NTP) then was launched in 1961 by Malaysian government after realizing its seriousness which later in 1994 integrated into the general health services (Venugopalan, 2004; Jetan *et al.*, 2010). The headquarters of the NTP was The National TB Centre situated in Kuala Lumpur which now has been known as The Institute of Respiratory Medicine while the state general hospitals with their chest clinics have been assigned as the state board of directors (Iyawoo, 2004). The Public Health Division of the MOH then has taken over the national TB directorate since 1995 and currently is under the Director of Disease Control (Iyawoo, 2004). TB problem in Malaysia between 1970 and 1990 declined significantly as like other developed and industrialized countries (Aziah, 2004). The establishment of NTP in 1961, enhancement in nutrition and housing, improved ventilation of homes and workplace, improved health set up, and isolation of highly infectious TB cases in sanatoria were the factors towards significant declining of TB problem between year 1970-1990 (Aziah, 2004).

However, Aziah (2004) also reported that the incidence of TB in Malaysia slowly increased from early 1995 till 2002. In 2001, TB has been the second most communicable disease in Malaysia (Jetan *et al.*, 2010). Increasing TB/HIV co-infection, poor implementation of the TB control programme and a massive influx of immigrants were among the postulated reasons of the increasing TB cases (Aziah, 2004; Venugopalan, 2004). In 2007, TB in Malaysia is endemic with a notification rate among smear-positive patients of 36 per 100,000 (Rundi, 2010). Notification of new TB cases in Malaysia for year 2005 until 2011 has been shown in Figure 5

(MOH, 2012c). In 2011, 72% of new pulmonary tuberculosis (PTB) patients have smear positive rate (refer to Figure 5). However, in developing countries including Malaysia, the risk of TB infection and disease among healthcare workers has not been well defined (Tan & Kamarulzaman, 2006).



	2005	2006	2007	2008	2009	2010	2011
PTB Smear Positive	8446	9414	9578	10441	9981	11135	11862
PTB Smear Negative	4313	3977	3828	3643	4143	4122	4446
PTB Smear Unknown	549	359	258	180	453	216	55
EPTB	1702	1920	2107	2197	2344	2545	2888

Figure 5: Notification of new TB cases in Malaysia for year 2005-2011

(Source: Management of TB (Third Edition) 2012 (MOH, 2012c))

1.3 Problem statement

Predominantly affecting young children, CNS tuberculosis is a serious, often fatal form of TB. According to Harris and Morris (2007), although CNS tuberculosis may be a rare complication of TB, it is essential especially for healthcare workers to keep CNS tuberculosis in the differential when evaluating neurological issue since it can be a dreadful omission for the patient. Christopher *et al.* (2010) have found that healthcare workers attributed 5.8% estimation of median annual incidence of TB

infection in low and middle income countries. CDC data recorded that 6.3% of extra-pulmonary cases (1.3% of total TB cases) had CNS tuberculosis, while up to 10% of cases showed CNS involvement reported in a study from an American epidemiological study of extra-pulmonary tuberculosis (Cherian & Thomas, 2011). In general, the incidence of CNS tuberculosis is directly proportional to the prevalence of TB infection (Garg, 1999). It also has been reported that the incidence of CNS tuberculosis cases without the involvement of pulmonary TB are very rare (Parekh *et al.*, 2014).

By examining knowledge, attitude and practice (KAP) of healthcare workers (HCWs), this will reveal their self-sufficient knowledge perception on the prevention of CNS tuberculosis. Thus, the needs which to be covered in continuing the medical education sessions on TB as a whole in the future could be identified (Ayaya *et al*., 2003). In Malaysia, the numbers of cases of TB incidence among healthcare workers have been reported continuously increasing (MOH, 2012b). There is no previous study has been performed to evaluate the KAP regarding CNS tuberculosis prevention especially among healthcare workers. This research therefore, aims to determine level of knowledge, attitude and preventive practices of CNS tuberculosis among healthcare workers and to identify factors that influence the healthcare workers towards CNS tuberculosis prevention specifically at Hospital Universiti Sains Malaysia (USM), Kelantan and Hospital Kuala Lumpur (HKL), Kuala Lumpur.

1.4 Justification of study

The healthcare workers who manage patients with CNS tuberculosis are expected could efficiently prevent themselves from getting the disease by using their knowledge. At the same time, they should be able to care and manage the patients and know how to manage the ones who are suffering with the complications. This study is vital for the healthcare workers to take precaution steps when attending to the patients who are suffering from CNS tuberculosis. Although majority of the reported cases among healthcare workers are more on the general TB, however several studies revealed that the incidence of CNS tuberculosis is interrelated with the incidence of TB. Finding from this study can provide information regarding the level of knowledge, attitude and preventive practices on CNS tuberculosis among the local healthcare workers. The finding will also allow appropriate actions to be taken especially by the ministry of health to improve any detectable unsatisfactory area in the healthcare settings based on the healthcare workers' responses.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview of CNS tuberculosis

According to Hernandez Pando (2011) regarding modelling of cerebral tuberculosis, the beginning of CNS tuberculosis is believed with respiratory infection like any other forms of TB which then followed by early haematogenous dissemination to extra-pulmonary sites. Highly oxygenated regions of the body, including the brain were the most frequently regions that this haematogenous seeding occurred (Rock *et al.*, 2008). The early comprehension towards pathogenesis of CNS tuberculosis came from Rich and McCordock (cited in Be *et al.*, 2009; Hernandez Pando, 2011) upon their basis of clinical and experimental observations. They suggested that the development of CNS tuberculosis have two phases which initially, begins with development of small tuberculous lesions (Rich foci) then later one or more of the small lesions will rupture or further growth causing the development of several types of CNS tuberculosis (Hernandez Pando, 2011).

Rich and McCordock also revealed that the meninges, the subpial or subependymal surface of the brain or the spinal cord can be the locations of the early developed tuberculous lesions which may stay inactive for a long time (Hernandez Pando, 2011; Shahina *et al.*, 2012). Later, Rich and McCordock found that meningitis which is the most common form of CNS tuberculosis may occurred once the bacteria of TB disseminated into subarachnoid space or into the ventricular system due to the rupture of the small tuberculous lesions (foci) (Be *et al.*, 2009;

Hernandez Pando, 2011; Shahina *et al.*, 2012). Figure 6 below showed the pathogenesis and immune response of CNS tuberculosis. Primarily, a number of studies has described that tuberculous meningitis is the most frequent manifestation of CNS tuberculosis followed by tuberculoma, tuberculous brain abscess, cerebral miliary tuberculosis, tuberculous encephalopathy, tubercular encephalitis and tuberculous arteritis (Rock *et al.*, 2008; Isabel & Hernandez Pando, 2014).

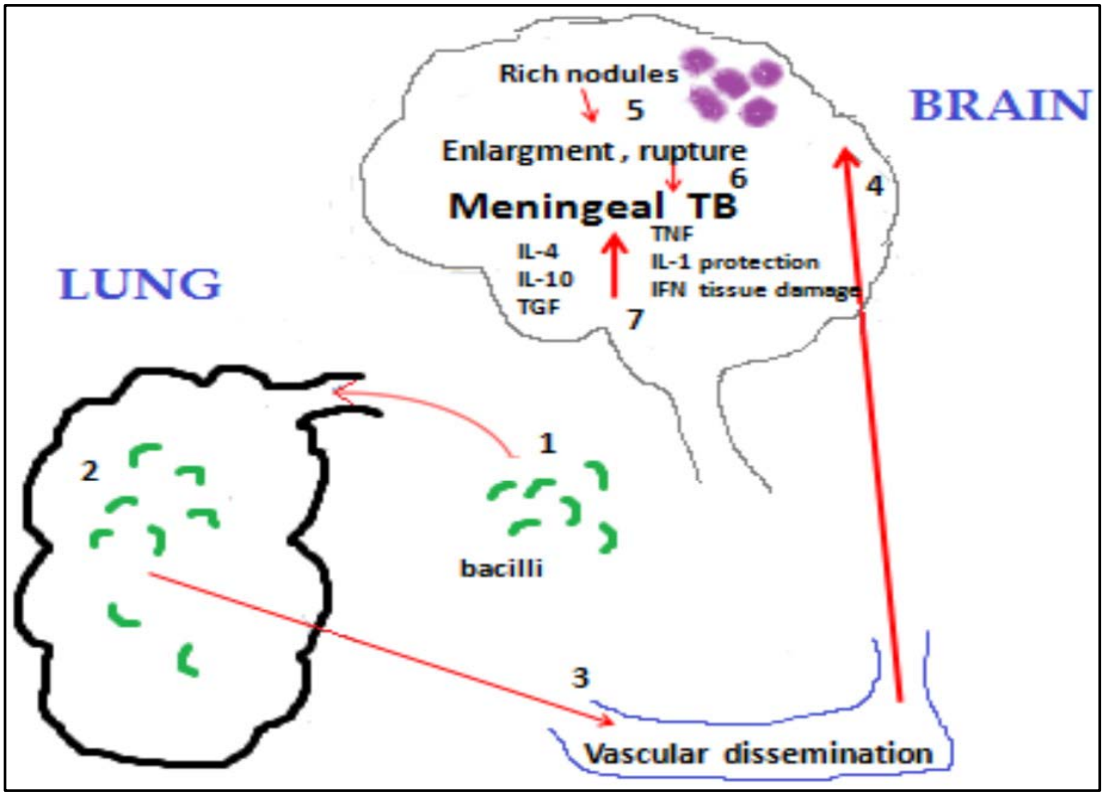


Figure 6: Pathogenesis and immune response of CNS tuberculosis

(Source: The image of the pathogenesis and immune response of cerebral TB (Isabel & Hernandez Pando, 2014))

Figure 7 showed the meninges of the CNS which consists of three types; the dura mater (the thickest), arachnoid mater and pia mater (the thin layers). The word "Lepto" from leptomeninges which were the combination of the arachnoid and pia mater which means "thin or fine", comes from the Greek word while the word "dura" means tough (Samuel, 2011). In addition, according to Khoo et al. (2003), TB

involving the leptomeninges in most patients is also thought to spread from a primary source outside the CNS like the lung or gastrointestinal tract through haematogenous dissemination.

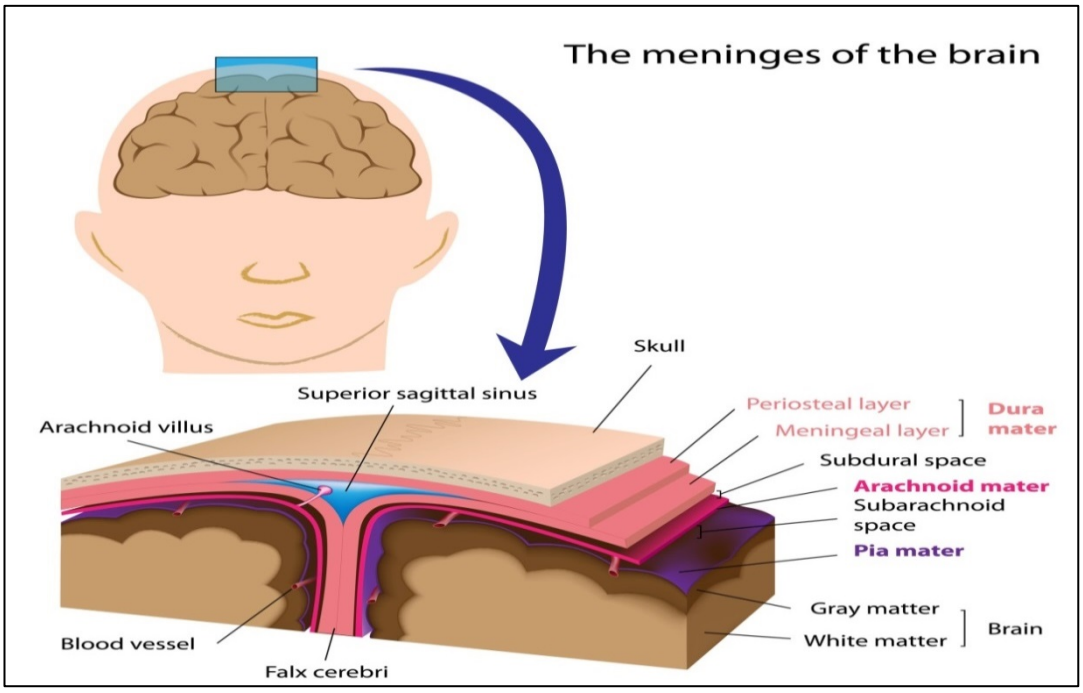


Figure 7: The Meninges of the Central Nervous System

(Source: The image of the meninges of the brain (Samuel, 2011))

Chatterjee (2011) has stated that the virulence of the bacteria and the immune resistance of the host can determine the lesions specification which results from discharge of the bacilli into the cerebrospinal fluid (CSF). The circulation of CSF in brain was shown in Figure 8 (Antranik, 2011). Observation towards vaccinated and well-nourished patients was done since they tend to develop more localized involvement of the brain and meninges (Gauba & Varma, 2005). The classification of different types of CNS tuberculosis has been shown in Table 1 below (Garg, 1999; Chatterjee, 2011). Since intracranial and intraspinal involvement commonly concomitant therefore, neuroimaging procedures should include both the brain and spine (Gauba & Varma, 2005).

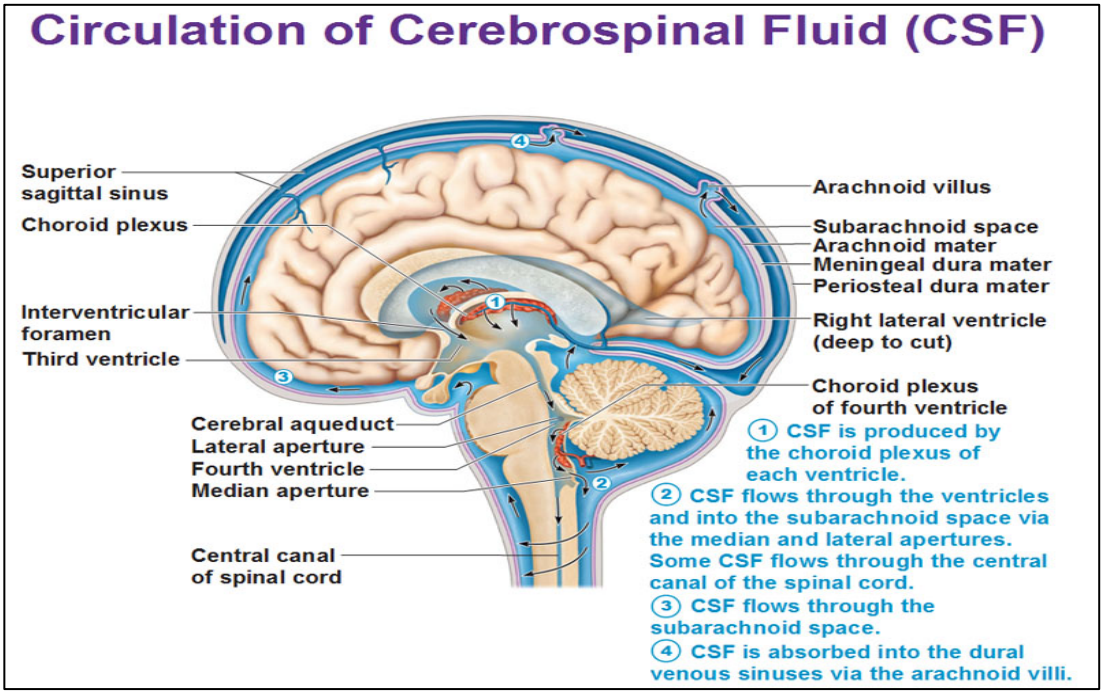


Figure 8: The Circulation of Cerebrospinal Fluid (CSF)

(Source: The image of the Circulation of Cerebrospinal Fluid (Antranik, 2011))

Table 1: Classification of CNS Tuberculosis

Classification of CNS Tuberculosis
Intracranial ➢ Tuberculous meningitis (TBM) ➢ TBM with miliary tuberculosis ➢ Tuberculous encephalopathy ➢ Tuberculous vasculopathy ➢ Space-occupying lesions: • Tuberculoma (single or multiple) • Multiple small tuberculoma with miliary tuberculosis • Tuberculous brain abscess *Spinal* ➢ Pott's spine and Pott's paraplegia ➢ Tuberculous arachnoiditis (Myeloradiculopathy) ➢ Non-osseous spinal tuberculoma ➢ Spinal meningitis

(Source: Garg, 1999; Chatterjee, 2011)

The most common presentation of CNS TB, **tuberculous meningitis (TBM)** accounting 70-80% of cases which predominantly in young children and adolescents (Gauba & Varma, 2005). Direct meningeal seeding and proliferation has caused meningitis during a tuberculous bacillemia which is the condition where there presence of bacilli in the circulating blood, either at early infection time, or resulted from an old pulmonary focus breakdown, or resulted from an old parameningeal focus (ear and sinus infections) breakdown with rupture into subarachnoid space (American Thoracic Society, 2000). Figure 9 below showed the pathogenesis of CNS tuberculosis and followed by the occurrence of TBM (Be *et al.*, 2009).

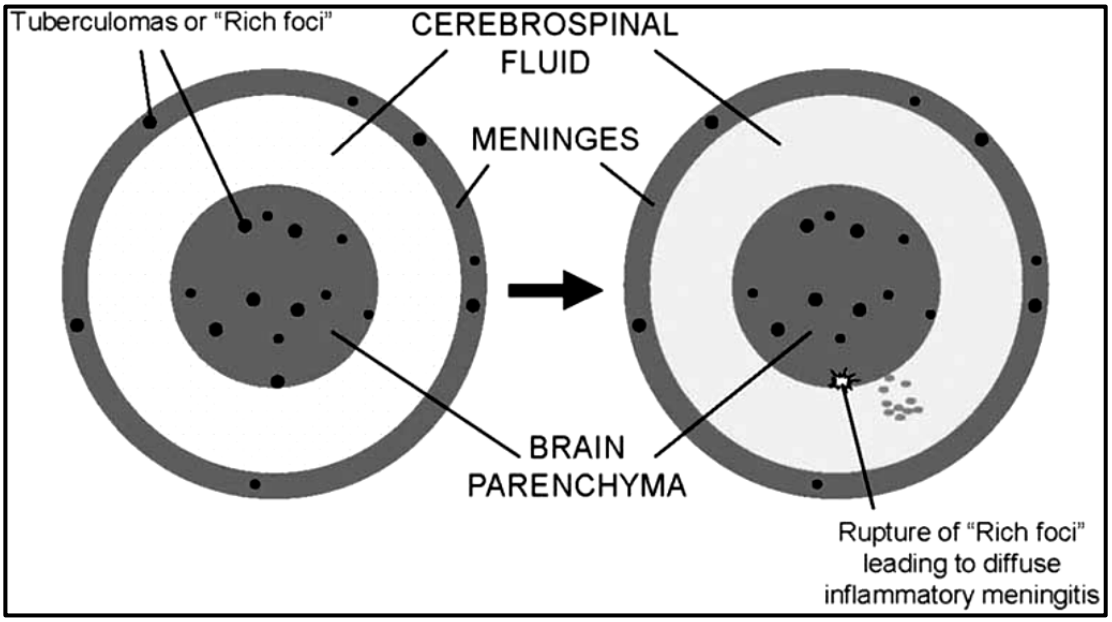


Figure 9: Pathogenesis of Central Nervous System Tuberculosis

(Source: The image of the pathogenesis of CNS tuberculosis and subsequent tuberculous meningitis (Be *et al.*, 2009))

Furthermore, a dense gelatinous exudate develops after the release of tubercle bacilli from the granulomatous lesions (Rock *et al.*, 2008; Chatterjee, 2011). Diffused meningitis or localized arteritis forms as a result of subarachnoid space contamination which is happened primarily at the base (basal portions) of the brain (American Thoracic Society, 2000; Gauba & Varma, 2005). The tuberculous lesions

(the Rich Foci) typically are located both in the meninges and in the brain parenchyma by following the vascular pattern (Rock *et al.*, 2008).

Other manifestations of CNS tuberculosis is **tuberculous granuloma (tuberculoma)** which is also the most common parenchymal form of CNS tuberculosis and in the developing world, constitute about 5-40% of intracranial space occupying lesions (Gauba & Varma, 2005). They can occur with or without TBM but commonly more often in the absence of the TBM (Gauba & Varma, 2005; Rock *et al.*, 2008). Firm, avascular, spherical masses (contains necrotic areas of caseation where tubercle bacilli may be found) with size varying between 2cm and 10cm in diameter are the characteristics of tuberculomas (Chatterjee, 2011). Rock *et al.* (2008) have expressed that when there is enlargement of tubercles in the brain parenchyma without rupturing into the subarachnoid space, this is when the tuberculomas start to arise.

Generally, patients with miliary pulmonary TB commonly have tuberculomas which neurologically asymptomatic (Gauba & Varma, 2005). The most commonly affected regions are the frontal and parietal lobes especially on the left side probably as a result from haematogenous spread and greater blood flow to the dominant hemisphere (Gauba & Varma, 2005). Aside from TBM and tuberculoma, **tuberculous brain abscess** is a rare and uncommon complication of CNS tuberculosis which could develops from parenchymal tubercular granulomas (tuberculomas) or by the Rich Foci which spreading from the meninges in patients with TBM (Gauba & Varma, 2005; Rock *et al.*, 2008).

Fever, headache, meningismus (stiff neck), focal neurological deficits, behavioural changes and decreased level of consciousness were among the classic symptoms of tuberculous meningitis while as in children, they often present with fever, neck stiffness, seizures and abdominal symptoms like nausea and vomiting (Rock *et al.*, 2008). During the course of the TBM, 20-30% of patients sometime developed focal or generalized convulsions, 17-70% of them presence with cranial nerves involvement and 4-35% of cases presented with partial or complete loss of vision (Gauba & Varma, 2005). As for cerebral tuberculoma, most patients presented with fever, headache and weight loss while the commonest symptoms are focal and generalized seizures (Thwaites *et al.*, 2009). Gauba & Varma (2005) and Chatterjee (2011) also mentioned focal neurological signs, intracranial hypertension and papilledema as the presenting signs and symptoms of tuberculomas.

Individual aged less than 40 years, HIV infection and certain ethnic populations have been clinically identified as the risk factors of CNS tuberculosis (Hernandez Pando, 2011). Thwaites *et al.* (2009) reported that other risk factors include very young children (high TB prevalence countries), immigrants (low TB prevalence countries), alcoholism, diabetes mellitus, malignancy and patients with corticosteroid treatment therapy aside from age and immune status. Miliary TB has been closely interrelated with the occurrence of CNS tuberculosis in children where haematogenous dissemination has been posited to increase the likelihood of the Rich foci development (Rock *et al.*, 2008). Furthermore, in relation to primary pulmonary infection, the timing and frequency of development of the small tuberculous lesions is dependent on age and immune status. Dissemination in children commonly occurs early and they are in highest risk group in getting CNS tuberculosis in the first year

following infection which predominantly effects very young children (<3years) in countries with high TB prevalence (Thwaites *et al.*, 2009). In contrast, majority of cases in low TB prevalence countries are in adults, and often immigrants from areas of high TB prevalence.

Clinically, diagnosis of CNS tuberculosis through cerebrospinal fluid (CSF) examination has been the mainstay of diagnosis of the disease apart from radiological examination via computerized tomography (CT) scans and magnetic resonance imaging (MRI) (Chatterjee, 2011). Samples of CSF for the examination could be taken by lumbar puncture process (conventional method) or by cisternal and ventricular process (Rock *et al.*, 2008). American Thoracic Society (2000) found that lumbar puncture or spinal tab is done when there is the presence of meningeal signs during physical examination. Thwaites *et al.* (2009) mentioned that lumbar puncture and examination of CSF is the best in diagnosing CNS tuberculosis especially the TBM. The used of large volumes of CSF to be cultured especially in ventricular fluid could resulted to the sensitivity of over 90% of the CSF specimens in detecting the organism (Garg, 1999). Several previous studies have reported that the process of identifying of tuberculous bacilli in CSF either through smear examination or bacterial culture affects the final conclusive diagnosis of CNS tuberculosis disease (Garg, 1999; Chatterjee, 2011).

In other perspective, more insight of CNS tuberculosis progression as well as its prognostic and diagnostic information could be discovered with the emergence of CT scan and MRI regards to the enhancement on the diagnostic accuracy results (Modi & Garg, 2013). CT scan of the head should be done before the lumbar

puncture when there are focal findings during physical examination or when there are suggestions of increased intracranial pressure (ICP) (American Thoracic Society, 2000). The scan for TB meningitis may seem normal but it may also show diffuse oedema or obstructive hydrocephalus which is a common complication of TBM while for tuberculoma, ring-enhancing mass lesions may be seen (American Thoracic Society, 2000). As for MRI which assessing meningeal and parenchymal abnormalities, the results of contrast-enhanced scanning is better compared to CT scan as well as better indicator on the involvement of the spinal cord and cranial nerves (Chatterjee, 2011; MOH, 2012c).

Treatment of CNS tuberculosis is an intensive or initial phase of treatment which then followed by a continuation or maintenance phase similar with the model of short course chemotherapy of the most common TB; pulmonary tuberculosis (Thwaites *et al.*, 2009). WHO has declared that directly observed therapy, short course (DOTS) has become one of its strategies for combating TB effectively since the worldwide re-emergence of TB and corresponding of drug resistant in the 1990s (Modi & Garg, 2013). Implementation of DOTS strategy in Malaysia has been driven by its five elements for its success which included the government commitment towards the NTP, the supervision of drugs administration should be directly observed by health personnel or trained individuals and regular documentation of each dose of medication taken by the patient under supervision but however the supervision of treatment does not confined only to the health care facilities (MOH, 2002a).

Generally, before any conclusive diagnosis confirmed by CSF cultures or other means of microbiological identification obtained, the treatment usually is started beforehand (Gauba & Varma 2005). Infectious Diseases Society of America, Centers for Disease Control and Prevention (CDC), and American Thoracic Society guidelines have authorized a standard approach for antibiotic therapy of anti-TB drugs for treatment of CNS tuberculosis which can be seen in details in Table 2 (Rock *et al.*, 2008). The recommended chemotherapy for initial phase began with anti-TB drugs of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB) followed by the discontinue of PZA and EMB after two months while INH and RIF were continued for another seven to ten months which known as maintenance phase (Modi & Garg, 2013).

Table 2: Guidelines for the treatment of CNS tuberculosis

Drug	Daily Dose		Duration (mo)	CNS penetration
	Children	Adults		
First-line therapy				
Isoniazid	10-15 mg/kg (300 mg)	5 mg/kg (300 mg)	9-12	Yes
Rifampicin	10-20 mg/kg (600 mg)	10 mg/kg (600mg)	9-12	Yes, with inflammation
Rifabutin	Unknown	5 mg/kg (300 mg)	9-12	Yes, with inflammation
Pyrazinamide	15-30 mg/kg (2.0 g)	15-30 mg/kg (2.0 g)	2	Yes
Ethambutol	15-20 mg/kg (1.0 g)	15-20 mg/kg (1.0 g)	2	Yes, with inflammation
Second-line therapy				
Cycloserine	10-15 mg/kg/day (1.0 g/day)	10-15 mg/kg/day (1.0 g/day)	18-24	Yes
Ethionamide	15-20 mg/kg/day (1.0 g/day)	15-20 mg/kg/day (1.0 g/day)	18-24	Yes
Streptomycin	20-40 mg/kg/day (1.0 g)	15 mg/kg/day (1.0 g), 10 mg/kg/day in patients >59 yr of age (750 mg)	6	Yes, with inflammation
Amikacin-kanamycin[a]	15-30 mg/kg/day (1.0 g)	15 mg/kg/day (1.0 g), 10 mg/kg/day in patients >59 yr of age (750 mg)	6	Yes, with inflammation
Capreomycin[a]	15-30 mg/kg/day (1.0 g/day)	15 mg/kg/day (1.0 g), 10 mg/kg/day in patients >59 yr of age (750 mg)	6	Yes, with inflammation
p-Aminosalicylic acid	200-300 mg/kg/day in 2 to 4 divided doses (10 g)	8-12 g/day in 2 or 3 divided doses	18-24	Yes, low levels
Levofloxacin	Unknown[b]	500-1000 mg	18-24	Yes, low levels
Moxifloxacin	Unknown[b]	400 mg	18-24	Yes, low levels
Gatifloxacin	Unknown[b]	400 mg	18-24	Yes, low levels

[a] Intravenous route only; maximum doses in parentheses.
[b] Long-term use of fluoroqunolones in children has not been approved.

(Source: Rock *et al.*, 2008)

As in Malaysia, there were five vital drugs used as the first-line therapy for the treatment of extra-pulmonary TB similar with the treatment regimen for PTB which were isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin but the duration of treatment should be completed at least 12 months for the cases of TBM as well as the use of steroids for the acute cases (MOH, 2002a). To date, Philip *et al.* (2015) have found that bacillus Calmette-Guerin (BCG) vaccination which commonly given to infants, is the only licensed vaccine for TB. In cases of extra-pulmonary TB, it also could protect young children aged below five while in adults, 75-85% of TBM cases reported could be shielded by BCG although it is more effective in the cases of pulmonary TB (PTB). Nevertheless, nutritional status has been reported by a number of studies that it could be the reason behind the beneficial effect of BCG on TBM and also only the onset of TBM could be delayed by the BCG vaccination (Philip *et al.*, 2015).

2.2 Tuberculosis among healthcare workers (HCWs)

TB caused by *Mycobacterium tuberculosis* since 1920s has been reported to be an occupational hazard for healthcare workers especially nurses and physicians (Sepkowitz *et al.*, 1995). TB disease threat towards occupational hazard receives little attention (Ramazan *et al.*, 2004). However, several outbreaks of TB in healthcare settings in the early 1990s have elevated concern about transmission to both patients and HCWs (Ramazan *et al.*, 2004). In 1999, WHO reported that based on recent studies performed in developing countries regarding the risk of transmission in health care settings (nosocomial transmission) of *M. tuberculosis*

(MTB), HCWs who care for infectious TB patients are at risk of the MTB infection and disease.

In HCWs, the risk of active TB disease is estimated two to three times greater than in the general population (Tudor *et al.*, 2014). A higher risk of acquiring TB disease was associated with certain work locations (inpatient TB facility, laboratory, internal medicine, and emergency facilities) and occupational categories (radiology technicians, patient attendants, nurses, ward attendants, paramedics, and clinical officers) (Joshi *et al.*, 2006). Costa *et al.* (2011) reported that working in inadequately ventilated spaces and performing procedures involving contaminated aerosols in settings that favour transmission from an active disease are the reasons which HCWs are at the higher risk group of MTB infection.

In other perspectives, high influx of immigrants from high TB burden countries, increasing number of HIV/AIDs cases, transmission within overcrowding settings and emergence of multi drug resistant TB could be the other reasons behind the re-emergence of TB cases as the exposure to HCWs will increase as the number of patients seeking for treatment at health facilities increased (Rafiza *et al.*, 2011). Jelip *et al.* (2004) thought that nosocomial TB transmission happened because of the improper implementation of infection control measure as the risk of TB infection was about four times greater towards a HCW who is sitting in proximity to TB case. However, different occupational groups and their working conditions varying the risk of infection widely (Nassaji & Ghorbani, 2012).

A study of TB among HCWs by Baussano *et al.* (2011) revealed that the occurrence of TB among HCWs was on average of 34 (IQR 18-108) with 12,689 (IQR 2,979-57,279) persons-years infected on average which came from countries with low, intermediate and high TB incidence that accounted 67 cases/ 100,000 persons, 91/100,000 persons and 1,180/100,000 persons respectively. The study also revealed that exposure in health care settings is associated with the incidence of TB cases among the HCWs. Besides, a systematic review towards HCWs in low- and middle-income countries conducted by Joshi et al. (2006) also supported that nosocomial exposure attributed to the risk of TB disease among HCWs with a range of 25 to 5,361 per 100,000 annually.

Joshi *et al.* (2006) revealed that the prevalence of latent tuberculosis infection (LTBI) among HCWs was on average, 54% (range 33-79%) with a range of 69 to 5,780 per 100,000 of the annual risk of incidence among HCWs. Besides, a study of TB among HCWs by Baussano *et al.* (2011) revealed that the occurrence of LTBI among HCWs was on average 23 with 731 persons infected annually on average. Tudor *et al.* (2014) also reported the estimation of LTBI globally is more than 50% among HCWs; however the cases of active TB disease were less well documented among HCWs. Moreover, recent study conducted by Borotto (2011) revealed that the LTBI prevalence among HCWs in Santiago was 15.4% and among the HCWs, physicians has the highest prevalence (21.8%) then followed by nurses (19.6%).

Ministry of Health (2012) Malaysia defines HCWs as group of people who work in health care facilities which include nurses, physicians, nursing and medical students, dental workers, laboratory workers and others. Over the past five years, the