A Review of Tuberculosis Research in Malaysia

Swarna Nantha Y, MRCGP

Outpatient Department, Klinik Kesihatan Seremban, Jalan Rasah 70300, Seremban.

SUMMARY

One hundred seventy four articles related to tuberculosis were found in a search through a database dedicated to indexing all original data relevant to medicine published in Malaysia between the years 2000-2013. One hundred fifty three articles were selected and reviewed on the basis of clinical relevance and future research implications. Topics related to epidemiology, clinical presentation, detection methods and treatment were well researched. However, limited information was available on screening and behavioural interventions. The younger population were more vulnerable to tuberculosis infection and had higher prevalence of risk factors that reactivate tuberculosis infection. Screening of tuberculosis was conducted primarily on healthcare workers, tuberculosis contacts, prisoners and foreign workers. Data on the clinical presentation of pulmonary and extrapulmonary tuberculosis was comprehensive. There was a general focus on related risk factors such as HIV and diabetes mellitus. A great degree of information was available on the treatment and various detection methods to identify tuberculosis. The efficacy and the practicality of investigative methods was analysed in this review. In conclusion, the direction of research should be aimed at novel preventive and control measures of tuberculosis. There should be emphasis on the screening of high risk groups (other than HIV) within the population namely diabetic patients, smokers and immunosuppressed individuals. The design of health policies should be guided by information gathered from research evaluation of community-based behavioural interventions.

KEY WORDS: *Pulmonary tuberculosis, extra pulmonary tuberculosis, latent tuberculosis, risk factors, HIV, diabetes mellitus*

SECTION 1: REVIEW OF LITERATURE

EPIDEMIOLOGY

Pulmonary tuberculosis

There is a rise in the incidence of tuberculosis cases in the country between the year 2011 and 2012[1]. Within that same time frame, there was also a concurrent rise in rate of relapse[1]. In 2001, tuberculosis was the second most commonly notified communicable disease in Malaysia[2]. A third of the national tuberculosis cases were from the state of Sabah[2]. In a survey, 83% (172/ 207) of patients were diagnosed to have pulmonary tuberculosis[3].

The incidence of tuberculosis in Manjung was 49.5/100000 population[4]. Smear positive tuberculosis rate amongst the population in Manjung was at 64% of the total tuberculosis cases in Perak[4]. Close to 98% (102/104) with pulmonary tuberculosis were detected in the moderate to advance stages of the disease[5].

Extra pulmonary tuberculosis

Ten percent (20/195) to 11% (22/207) of tuberculosis cases at a tertiary level chest clinic were classified as extra pulmonary tuberculosis[3,6]. About 14% (8/57) of pulmonary tuberculosis patients also had extra pulmonary involvement[7].

Twenty percent (30/149) of HIV-infected tuberculosis cases have been diagnosed with extra pulmonary tuberculosis[8]. In populations with risk factors for the reactivation of tuberculosis (HIV or diabetes mellitus, 7% (109/1548) of patients were confirmed cases of tuberculous lymphadenitis[9].

Population with risk factors related to tuberculosis

The population with diabetes mellitus is a major factor in the reactivation of tuberculosis, followed by smoking, chronic kidney disease/end stage renal failure and age related factors[10].

Diabetes mellitus

The prevalence of diabetes among tuberculosis patients at tertiary centres range between 14-33% [14% (25/173), 15% (53/352), 27% (338/1267), 30% (60/200) and 33% (68/207)][3,11-14] Patients with diabetes mellitus (DM) were more likely to have pulmonary tuberculosis (OR=2.079, $p<0.001$)[13]. The evidence for this was seen in large scale studies[15]. A greater percentage of pulmonary tuberculosis patients (91%, 1509/1651) were in the TB-DM group[15]. Four smaller scale studies had conflicting evidence on this matter. A study supporting this view discovered 82% (107/131) of patients diagnosed with pulmonary tuberculosis suffering from either diabetes mellitus, hypertension, ischaemic heart disease or all three conditions[16]. Three other studies revealed the prevalence of tuberculosis among diabetics between the range of 18 and 30%[7,17,18].

Little data was available on the prevalence of a specific extra pulmonary tuberculosis among diabetic population. One study found 16% (17/109) of patients with tuberculous lymphadenitis had diabetes mellitus[9].

Smokers

The prevalence of tuberculosis was higher in a smoking population[10]. In Malaysia, smoking prevalence rate is high amongst tuberculosis patients[19]. It was estimated that 40% (70/176) to 50% (102/207) of tuberculosis patients were smokers[3,11]. Smoking was prevalent in 57% (135/237) of pulmonary tuberculosis patients[18] while only 21% (41/195) of extra pulmonary tuberculosis patients had either smoking and/or drinking habits[6].

Most TB-HIV patients were smokers[20]. In a study assessing resurgence of tuberculosis in immunosuppressed patients, a

Corresponding Author: yogarabin@gmail.com

large number of HIV/AIDS patients with tuberculosis were smokers (61%, 177/290)[21]. A similar trend was seen in diabetic patients with tuberculosis where 46% (91/200) of this population were smokers[14].

Prevalence rates in tuberculosis patients who have been continuously smoking was higher than current and ex-smokers [(54%, 54220/100 000) vs (40% (329/817) and (14% (114/817)][19].

HIV
In an assessment designed to identify the frequency of opportunistic infections, tuberculosis was the most common cause of AIDS-defining illnesses (48%)[22].

In a two-year multi-centred study, the prevalence of HIV amongst tuberculosis patients was estimated at 7.7% (15/200)[14]. Higher prevalence rate was seen (15.9%) in a three-month survey[23]. A lower prevalence rate was recorded (2.4%) in a one-year study at an urban centre (5/207)[3]. A two-year study at a rural setting revealed a prevalence rate of 14% (25/176), comparable to findings at urban centres[11]. Hence, the combination of population density and duration of the study seem to yield different prevalence rates.

The prevalence of inpatients being diagnosed with concomitant HIV and tuberculosis was at 1.5% (2/131) in a seven-year survey[16]. Twelve percent (57/1857) of HIV positive patients at drug rehabilitation centres and prisons had tuberculosis co-infection[24]. Prisoners comprise 50% (13/25) of all HIV-infected tuberculosis patients receiving treatment at a tertiary centre chest clinic[23].

HIV patients had greater rates of pulmonary tuberculosis (68-79%) and lesser rates of extra pulmonary tuberculosis (20-22%)[25,26]. In large scale studies, prevalence rates ranged between 79% (117/149) and 86% (249/290)[8,27]. However, in a smaller study, only 11% (6/57) of pulmonary tuberculosis cases were detected to have HIV co-infection[7].

In patients with AIDS, pulmonary tuberculosis was the most common infection (29%, 37/128), followed by Pneumocystis carinii pneumonia (PCP) (28%, 36/128) and extra pulmonary tuberculosis (12%, 15/128)[28].

In one study, tuberculous lymphadenitis was the most common form of extra pulmonary tuberculosis[26]. About 10% (11/109) of tuberculous lymphadenitis patients had HIV infection[9].

Fifty two percent (16/176) of the mortality of tuberculosis cases were related to HIV infection[11]. Fifty one percent of notified TB deaths were associated with HIV co-infection amongst prisoners[24].

Other factors related to immunosuppression
Age and chronic kidney disease/end-stage renal failure (CKD/ESRF) were found to be related to the reactivation of tuberculosis[10]. Long term utilisation of steroids contributed to 2% (1/57) of pulmonary tuberculosis cases[7].

Healthcare workers (HCW)
The average notification of tuberculosis amongst healthcare workers in the five years studied was twice as high than that of the general population (280.4/100 000 vs 153.9/100 000)[29].

The incidence of TB amongst healthcare workers was 280.4 per 100 000 population from the year 1999 to 2004[29]. Incidence of latent tuberculosis infection in healthcare workers was 9.9 per 100 workers per year[30].

Intravenous drug users (IVDU)
The common mode of transmission of HIV in patients with tuberculosis was via intravenous drug injection (74%, 110/149)[25]. There was a significant association between HIV infection via intravenous drug abuse and the incidence of tuberculosis infection ($p<0.05$)[22]. Thus, it was not uncommon that almost 74% (19/25) of the HIV-infected tuberculosis patients were indeed IVDUs[23].

There was a predominance of pulmonary tuberculosis when compared to extra pulmonary tuberculosis amongst IVDUs. Seventy seven percent (191/290) of HIV-infected pulmonary tuberculosis patients were IVDUs27 while only 5% (10/195) of extra pulmonary tuberculosis patients were seen in this population[6].

Smaller numbers of IVDUs [1.5% (2/131)] were inpatients with tuberculosis[16]. A larger number of IVDUS (15%) received outpatient pulmonary tuberculosis treatment[31].

Hepatitis C virus (HCV) infection
HIV-infected patients with pulmonary tuberculosis were strongly associated with HCV infection[20].

Latent tuberculosis infection
Studies involving the prevalence of latent tuberculosis infection (LTBI) were limited to only specific groups in the community (prisoners, healthcare workers and tuberculosis contacts).

Prisoners
There was a high prevalence of LTBI [88% (234/266)] amongst prisoners consisting of both HIV and non HIV population[32]. Screening of LTBI in prisoners with HIV using interferon-ϒ-release assay (IGRA) detected a 12% (15/125) of previously undiagnosed active pulmonary TB[33].

Healthcare worker (HCW)
One study conducted at four hospitals revealed an 11% prevalence rate of LTBI among HCWs[34].

Contacts
Thirty percent (12/40) of the contacts of HIV positive pulmonary tuberculosis patients had positive tuberculin skin test (TST) compared to 53% (47/94) of the contacts of HIV negative patients [OR= 0.41, 95% CI 0.07-0.87; p=0.016][35].

Drug resistance rates
No multidrug-resistant tuberculosis (MDR-TB) cases were found amongst 252 HIV patients with tuberculosis in a study conducted at the National Tuberculosis Center[36]. At one tertiary setting, 1.9% (4/207) of patients had drug resistant tuberculosis[3].

Adverse events
The majority of patients (85%, 111/131) did not complain of side effects from anti-TB treatment16 while in a separate study, only 8.3% (9/109) of patients had adverse effects from anti TB treatment[37]. One study analysing the adverse effects of anti-TB treatment found the prevalence of drug-induced hepatitis to be at 9.7%[38].

Treatment regimens seem to influence the incidence of adverse drug reactions. Eleven percent (19/176) developed adverse drug reaction; 11 were from the 2SHRZ/4SHR2 category[11].

Demographics

Gender, Age and Ethnicity
Tuberculosis was predominant in a male population[11,16,24,39]. The majority of pulmonary tuberculosis cases were also males[3,7,17,39]. Males also had a higher preponderance of TB-related deaths[40].

Taking into account risk factors related to tuberculosis, there were higher rates of male HIV-infected tuberculosis patients when compared to females[8,20,21,25,26,36,41]. Males formed a large proportion of HIV patients with pulmonary tuberculosis (97%, 241/290)[27]. In contrast, one study had a significant female distribution in the TB-DM group ($p<0.05$)[20]. However in four other prevalence studies, there were more males than females with tuberculosis and diabetes[12,14,15].

Majority of non HIV-infected extra pulmonary tuberculosis patients were females (50%, 96/195)[6]. Miliary (5%, 13/263) and tuberculosis of the lymph nodes (11%, 29/263), were commonly found in foreign-born female patients[39]. Spinal tuberculosis (70%, 37/52)[42] and pleural effusion due to tuberculosis was significantly higher in males ($p=0.048$)[43].

Table I shows different types of TB and their association with age. Table II shows different types of TB and their association with ethnicity.

Education level
Fifty two percent (108/207) of tuberculosis cases had secondary education3. Seventy eight percent (76/97) of TB/HIV patients had completed secondary or tertiary education[7,23,41].

Socioeconomic status
The increase in the incidence of tuberculosis was more predominant amongst the socioeconomically deprived[44]. Foreign-born single males (48%, 125/263) and married females (71%, 187/263) had a greater percentage of tuberculosis infection[39].

In a survey involving pulmonary tuberculosis patients, married patients constitute about 67% (37/57) of detected cases while 65% (37/57) were unemployed(35%,18/57)[7]. Fifty percent (96/195) of non HIV-infected patients with extra pulmonary tuberculosis were unemployed[6].

In the HIV-infected tuberculosis category, being single and unemployed was a recurring theme[8,16,20,21,23,25,27,41]. When employed, HIV-infected tuberculosis patients often held non-professional occupations[41]. In HIV-infected tuberculosis patients, there were significant associations with age, family member to room ratio, sex and marital status[41].

SCREENING

Pulmonary tuberculosis
Only specific groups of the population were involved in studies pertaining to pulmonary tuberculosis screening. These groups were contacts of HIV patients, foreign workers and prisoners with HIV[33,35,49].

Contacts of HIV positive patients were less likely to contract pulmonary tuberculosis[35]. Only 30% (12/40) of contacts of HIV positive PTB patients had a positive TST when compared to 53% (47/94) of the contacts of HIV negative patients [OR= 0.41, 95% CI 0.07-0.87; $p=0.016$][35].

Pulmonary tuberculosis was the second most commonly detected disease during pre-employment medical examination of Indonesian domestic helpers at a private clinic[49].

Using a new nucleic acid amplification technology (through polymerase chain reaction), the screening of HIV-infected male and female prisoners detected 12% (15/125) of previously undiagnosed active pulmonary tuberculosis[33].

Latent tuberculosis
The focus of screening of LTBI was directed towards healthcare workers (HCWs), contacts of tuberculosis patients and drug abusers[30,34,50,51].

Screening of HCW revealed that the prevalence of latent tuberculosis infection in Malaysia was relatively low for an intermediate TB burden country[34]. There was a high incidence of TB exposure at the emergency department amongst HCWs screened with IGRA[30]. Working at the emergency department was significantly associated with TB infection[30].

At a tertiary centre, a positive TST (≥ 10mm) was seen in 4% (38/1024) of patients who were screened based on contact tracing records[50]. The yield (active tuberculosis cases) of contact tracing was low at 0.5% possibly due to the utilisation of a less accurate test and poor prioritisation of patients[50]. There is a need for a more accurate test such as IGRA[50].

A positive TST was seen in 87% of drug abusers who were screened for LTBI at a voluntary drug treatment centre[51].

RISK FACTORS

Diabetes mellitus
A greater number of tuberculosis patients (91%, 1509/1651) are diabetics[15]. The reactivation of tuberculosis seem to occur at least four years after the initial diagnosis of diabetes[14]. Age was a significant predictor of tuberculosis infection in patients with diabetes when compared to non-diabetic patients($p<0.05$)[15]. Tuberculosis patients with diabetes or HIV infection usually present with cough with or without sputum, fever and loss of appetite and/or weight[20]. The duration of symptoms was longer in non-diabetic tuberculosis patients[14]. Diabetes increased the mortality rate (7.5%) of diabetic patients compared to patients with only TB or diabetes[14].

Diabetes increased the likelihood of contracting pulmonary tuberculosis[14,16,18]. Diabetes is a strong risk factor for the development of pulmonary tuberculosis (30%, 71/237)[18]. When comparisons were made, diabetic patients were more likely to develop pulmonary tuberculosis (89%, 178/200) than non-diabetic tuberculosis patients (59%, 118/200)[14,16].

Smoking
Risk of activation of latent tuberculosis infection in smokers is two-fold than that of a non smoking population[10]. Smokers were found to be significantly associated with advanced tuberculosis disease on diagnosis[5].

HIV
Tuberculosis is a common cause of AIDS defining diseases[52,53]. It is also the leading cause of morbidity and mortality in AIDS patients[52]. HIV was the most common co-infection and was implicated in 15% of tuberculosis deaths[40]. Patients with TB/HIV with three or more opportunistic infections are closely associated with death[48].

Bacillus Calmette–Guérin (BCG) vaccination was ineffective in this group[20]. This was evidenced by the significant presence of BCG vaccination amongst HIV-infected group who had tuberculosis ($p<0.05$)[20].

The presentation of tuberculosis in HIV infected patients might be influenced by reduced CD4 counts[53]. This could also explain why HIV-infected patients with tuberculosis are less infectious to their contacts than HIV-negative patients[35]. However, in an isolated finding amongst prisoners, tuberculosis symptoms were similar between HIV infected and non HIV infected individuals[32].

In general, HIV-infected tuberculosis patients commonly present with cough, fever, with or without sputum production, lymphadenopathy, chest infiltrations, loss of appetite and/or loss of weight[8,20,21,25].

Cough and hemoptysis are the most common presenting symptoms in HIV patients[36]. HIV co-infection in tuberculosis patients was also significantly associated with fever and lymphadenopathy ($p<0.05$)[20]. AIDS patients with tuberculosis had a significant association with fever, cough, sputum or hemoptysis ($p<0.05$)[54]. The CD4 cell level played a significant role in tuberculosis ($p<0.05$)[54]. HIV patients with unsuccessful treatment outcome were associated with intravenous drug use, lymphadenopathy (OR 2.01; 95% CI 1.09-3.72) and low serum albumin (OR 4.61; 95% CI 1.73-12.27)[55].

A history of IVDU in HIV patients was directly linked to the incidence of tuberculosis infection ($p<0.05$)[22]. HIV-related tuberculosis with IVDU was associated with unemployment ($p<0.05$)[22]. There was a significant association between occupation or mode of HIV transmission and tuberculosis infection ($p<0.05$)[54].

Pulmonary tuberculosis was the most common form of tuberculosis found in both HIV and diabetic groups (90%, 62/67)[20,36]. It was also the most common pulmonary opportunistic infection amongst AIDS patients at a hospital setting[56]. Close to 86% (249/290) of HIV-infected patients had pulmonary tuberculosis 21. There was significant association between patients with HIV infection from IVDU and pulmonary tuberculosis ($p<0.05$)[27]. Cough and hemoptysis were significantly related to pulmonary tuberculosis amongst HIV patients[26,36]. TB-HIV group with pulmonary tuberculosis was significantly associated with HCV infection ($p<0.05$)[20].

Extra pulmonary tuberculosis in HIV patients was associated with CD4 counts less than 100[57]. There is significant association between HIV and extrapulmonary tuberculosis (summary OR: 1.3; 95% CI 1.05-1.6)[57]. Close to 14% (41/290) to 56% (140/252) of HIV patients had extra pulmonary, miliary or disseminated tuberculosis[20,21,36]. In one study, lymph nodes were commonly involved[53]. There were also higher rates of TB meningitis, pleural TB and TB pericarditis[53].

As part of routine monitoring of anti-tuberculosis treatment, HIV infection was a significant risk factor in the development of TB drug-induced hepatitis ($p<0.005$)[38].

Healthcare workers (HCWs)

From a demographic perspective, factors such as age, gender, history of tuberculosis contact outside the work place, duration of service and failure to use respiratory protection were considered risk factors for the development of tuberculosis among healthcare workers[29]. Ethnicity, designation, family contact and TB related knowledge did not significantly contribute to risk of contracting tuberculosis[29]. Working at the emergency department was significantly associated with the risk of TB infection[30].

Risk of LTBI was higher in HCWs who were aged 35 years and older [9.46 (CI: 2.22; 40.50)], and who had a history of living in the same house with close family members or friends with active tuberculosis [8.60 (CI: 1.36; 10.02])[34].

Immunosuppression

The development of prostatic tuberculosis was linked to an immunocompromised state[58]. Extensive steroid therapy led to the development of pulmonary tuberculosis which was identified through tracheal aspirate sample[59].

Prisoners

Factors correlated with tuberculosis symptoms amongst prisoners were increasing age (aOR 1.07, 95%CI 1.01-1.13), lower body mass index (aOR 0.82, 95%CI 0.7-0.96) and TST-reactive status (aOR 3.46, 95%CI 1.20-9.97)[32]. Undiagnosed active pulmonary tuberculosis among HIV infected prisoners was associated with longer duration of drug use[33].

CLINICAL FEATURES

Out of the 90% (209/232) of patients who had previous medical consultations for suspected tuberculosis, chest radiographs or sputum examination were not performed in 40% (93/232) of these patients[17]. Hence, appropriate care should be given to suspected tuberculosis patients as delay by healthcare providers was associated with advanced disease on diagnosis[5].

Most Malaysian inpatients with tuberculosis had a cluster of prolonged productive cough, night sweats, fever, anorexia, and weight loss (57%, 75/131)[16]. The rest had hemoptysis (34%, 45/131) and few had diarrhoea and dysphagia (9%, 12/131)[16]. The presentation was different amongst foreigners. Male foreign-born workers with tuberculosis were associated with fever (70%, 184/263), cough (91%, 239/263) and positive BCG vaccination status whereas females had higher predilection to lymphadenopathy (22%, 58/263)[$p<0.05$][39].

Patients with advanced features of tuberculosis had higher chances of death[40] and were usually malnourished or had loss of appetite[5].

Socioeconomic status did not affect the severity of disease[5]. Most patients had no history of contact with tuberculosis patients (72%, 41/57)[7].

Gender

The female gender was significantly associated with delay in the diagnosis of pulmonary tuberculosis[60].

Duration

Majority of newly diagnosed pulmonary tuberculosis patients had clinical symptoms for many years[61]. In one study, nearly half (45%, 104/232) of tuberculosis patients had symptoms for more than one year[17]. Patients with pulmonary tuberculosis had symptoms more than two weeks before hospital admission (OR 25.10; 95 CI 4.63-136.05; $p<0.001$)[62].

Common symptoms

Cough was the most common symptom in pulmonary tuberculosis (92%, 218/237)[18]. Only 8% (19/237) to 22% (51/232) had typical symptoms of cough, fever, loss of appetite and loss of weight[17,18]. However, pulmonary tuberculosis patients were more malnourished than normal people[63] and had significant history of night sweats (OR 5.43; 95% CI 1.10-

26.79; p=0.038)[62]. Hemoptysis was only seen in 4% (6/160) of patients with tuberculosis[64]. Risk factors for pulmonary tuberculosis include diabetes mellitus (18%, 42/232), positive family history of tuberculosis (17%, 39/232) and previous tuberculosis infection (5%, 12/232)[17]. The most common location for AIDS with tuberculosis was the pulmonary region (85%, 104/123)[54].

Tuberculous effusion
The most common cause of exudative pleural effusion was tuberculosis (44%, 82/186), followed by malignancy (30%, 56/186)[65]. Conversely, in a smaller study the most common cause for pleural effusion was malignancy (34%, 38/111), followed by tuberculosis (23%, 26/111) and parapneumonic effusions (19%, 21/111)[66].

Tuberculous effusions were frequent in the first five decades (73%, 60/82) of life and were the most common type of pleural effusion in this age group (70%, 60/86)[65]. However, a statistical significant association was found between a younger median age and tuberculous effusion (34.5 years) (mean age 34.5 years; p<0.001)[65,67]. Tuberculous and malignant lung effusions had more predominance on the right side of lung[67] and were smaller than malignant pleural effusions (p<0.001)[67].

Atypical presentations
Clinical and radiological manifestations of pulmonary tuberculosis may be atypical[17]. Five percent (17/163) of non immunocompromised inpatients were initially suspected to have community-acquired pneumonia and were later diagnosed to have pulmonary tuberculosis[62]. In one case report, a patient with upper lung collapse was given the provisional diagnosis of submucosal tumour but was discovered to have tuberculosis after a second attempt at bronchocopy[68]. Pulmonary cryptococcosis in a non-HIV infected person could present in a similar manner as tuberculosis or lung cancer[69]. There was a rare case report of a pneumatocoele which was due to TB pneumonia at two weeks of age[70].

A HIV-infected patient had no systemic symptoms of pulmonary tuberculosis but was confirmed through bronchoalveolar lavage, an elevated ESR level and a strongly positive IGRA test[71].

Pulmonary tuberculosis with concomitant extra pulmonary presentation
Fifteen percent (35/232) of pulmonary tuberculosis patients presented with extrapulmonary diagnosis[17]. Concurrent pulmonary and spine tuberculosis were seen in 67% of patients (22/33)[46].

Empirical treatment to identify pulmonary tuberculosis
Out of 107 patients who were empirically treated as smear negative pulmonary tuberculosis, only 11% (11/107) of patients were eventually diagnosed as 'non-TB' based on absence of both clinical and diagnostic findings or discovery of another cause of the pulmonary condition[37].

Extrapulmonary tuberculosis
The most common sign amongst extra pulmonary tuberculosis patients was lymphadenopathy (46%, 90/195)[6]. Patients also had previous history of tuberculosis (4%, 8/195) and contact with tuberculosis patients (9%, 18/195)[6]. Patients with extrapulmonary tuberculosis were also at significant risk of developing anti-TB drug-induced hepatitis (p<0.008)[38].

Spine
More than half [52% (17/33)] of patients with tuberculosis of the spine had neurological manifestations[46]. Other common presentations were backache (94%, 50/52), abscess (45%, 25/53) neurological deficit (44%, 23/53) and gibbus deformity (22%, 12/52)[42]. A high percentage of spinal tuberculosis did not have BCG scar (82%, 43/52) and 18% (10/52) had evidence of concurrent pulmonary tuberculosis[42]. In some cases, there is difficulty in differentiating spinal tuberculosis from a metastasis[72].

Vertebral involvement and complications
The most common vertebra involved was the 9th vertebra and the least common was the 3rd vertebra[42]. The average number of vertebra affected was 342. Most lesions involved the thoracic level (48%, 14/31) with 65% involving the pedicle region[73]. Disc collapse, prevertebral abscess and kyphosis were more severe in the pedicle group[73].

A case of Pott's disease of the spine with psoas abscess had been reported[74].

Tuberculous lymphadenitis
Cough and fever were the common symptoms found amongst patients with tuberculous lymphadenitis[9]. Lymph node involvement was seen in 46% (90/195) of extra pulmonary tuberculosis patients6. Lymphadenopathy (34%, 84/252) was the most common sign in HIV patients with extra pulmonary tuberculosis[36].

Genitourinary
Genitourinary tuberculosis in developing countries comprises approximately 15-20% of extrapulmonary cases of tuberculosis[58]. Seventy eight percent (7/9) of patients with tuberculosis of the genital tract had ascites, vague abdominal distension, weight loss[75]. These cases were misdiagnosed as ovarian carcinoma[75].

Atypical presentation
An atypical genitourinary tuberculosis could mimic a cervical carcinoma[76]. High degree of suspicion should be practised in HIV patients with symptoms similar to acute prostatitis. A case report diagnosed a case of prostatic tuberculosis through biopsy[58].

Complication
A spontaneous perforation of the bladder was due to tuberculosis[77].

Gastrointestinal tuberculosis (GITB)
In general, GITB presents with right iliac fossa pain (26%, 9/34), bowel obstruction (26%, 9/34), diarrhoea (18%, 6/34) and ascites (12%, 4/34) 47. Sites of TB involvement includes caecum (38%, 13/34), ileum (29%, 10/34), mesenteric lymph nodes (26%, 9/34), small intestines (21%, 7/34) and ascending colon (18%, 6/34)[47].

Abdominal tuberculosis
Ileocaecal regions, peritoneum and hepatobiliary system were the most commonly affected sites[78]. Clinical presentation include abdominal pain (62%, 21/34), anorexia (44%, 15/34), weight loss (56%, 19/34), fever (41%, 14/34) and abdominal distention (29%, 10/34)[78].

Tongue tuberculosis
Tuberculosis of the tongue presented with the symptoms of sore throat and dysphagia for three months[79].

Intestinal tuberculosis
Patients with intestinal tuberculosis often present with perianal fistula, appendicitis, ascites, rectal, intestinal or gastric 'growth', 'ulcerative colitis' or recurrent anaemia[80]. Patients could also present with sub-acute intestinal obstruction resembling Crohn's disease[81].

Tuberculous peritonitis
In a patient with abdominal pain and fever for two weeks and poor response to broad spectrum antibiotics, CT scan was the best modality in detecting tuberculous peritonitis[82].

Gallbladder tuberculosis
Symptoms of jaundice and right hypochondrial led to the use of CT scan to confirm gallbladder empyema. The diagnosis of gallbladder tuberculosis was confirmed by biopsy results[83].

Oesophageal tuberculosis
Oesophageal tuberculosis were first suspected as malignancies but was eventually diagnosed as tuberculosis[84].

Knee joint
Clinical presentation includes diffuse swelling of the knee, involvement of small joints of hand, fever, loss of appetite and weight[85-87]. In all three cases, the diagnosis was obtained through biopsy[85-87]. Magnetic resonance imaging (MRI) of the knee was helpful in two of the cases and was inconclusive in the other[85-87].

Bone

Tuberculosis of the talus
A swelling over antero-medial aspect of foot with irregular lytic lesion on x-ray was subjected to aspiration of fluid and curretage[88]. Histopathological examination of the bone grafting confirmed the diagnosis of tuberculosis[88].

Tuberculosis of the distal radius
A lesion with the features of suspected giant cell tumour was resected from distal radius. The histopathological report confirmed the lesion was tuberculosis[89].

Cervical tuberculosis
An elderly patient presented with one month of worsening neck pain and progressive upper and lower limb weakness was confirmed as cervical tuberculosis[90].

Atypical presentation
Ewing's sarcoma had similar presentation as tuberculosis in a young patient[91].

Hepatic system

Tuberculous liver abscess
Tuberculous liver abscess was seen in a young male patient who was diagnosed with Burkholderia pseudomallei and acid fast bacilli abscess of liver[92].

Bile duct tuberculosis
A HIV patient presented with biliary peritonitis due to spontaneous common bile duct perforation was later confirmed to be tuberculosis[93].

Abdominal tuberculosis
Most commonly affected sites were the ileocaecal regions, peritoneum and hepatobiliary system[78].

Vascular
The treatment of tuberculous vasculitis had good results from endovascular stenting of a stenotic subclavian artery[94].

A patient with persistent backache after the completion of treatment for spinal tuberculosis was diagnosed as pseudoaneurysm of infrarenal aorta[95].

Ocular

Clinical features in adults
Central retinal vein occlusion like signs and symptoms were seen in two case reports[96,97]. There were cases with redness and mucopurullent discharge of the eye[98] or headache and blurring of vision[99].

Out of the six case reports in adults, four case reports of ocular tuberculosis had a positive Mantoux and/or IGRA test[97-100]. Majority of these cases had no positive finding on chest x-ray, systemic blood screening, or sputum analysis[96,97,99,100]. In two case reports, anti-tuberculosis treatment was commenced based on Mantoux and IGRA test results[97,99]. The decision to commence anti-tuberculosis treatment in the remaining two cases of ocular tuberculosis depended on the analysis of vitreous fluid and conjunctival biopsy[97,99].

Clinical features in children
An immunocompetent child had bilateral optic neuritis[101]. Ocular tuberculosis was diagnosed based on a positive Mantoux test and a raised ESR[101]. All other blood tests and imaging were normal[101].

The other case report involves an immunocompetent patient with a reactivation of ocular tuberculosis after anti-tuberculosis treatment[102].

Splenic tuberculosis
A case of splenic tuberculosis was seen in a patient with prolonged fever and hepatosplenomegaly[103].

Endocrine
An adrenal tuberculosis infection presented as an egg-shell calcification of the adrenals[104]. Pancreatic tuberculosis was diagnosed in a HIV patient with nonspecific symptoms of pancreatic disease[105].

Others
Miliary and pleural involvement in extra pulmonary tuberculosis patients were at 20% (39/195) and 13% (25/195) respectively[6].

Clinical presentation in latent tuberculosis infection (LTBI)
Working at a tertiary centre had an increased risk for tuberculosis infection and was significantly associated with the level of occupational tuberculosis exposure[106]. This was seen in a study where medical ward HCWs were at significantly higher risk of positive TST reaction/LTBI (odds ratio, 2.18; 05% CI, 1.44 to 3.57; p= 0.002)[106]. Employment of more than one year and working as a nurse were significantly associated with positive TST reaction at a cut-off point of 15mm or greater[106].

Clinical presentation in non tuberculous mycobacterium infection (NTMI)
A case report documents an NTMI in a smoker with shortness of breath and loss of weight. Patient was diagnosed based on a positive Mantoux test and responded well to anti-tuberculosis treatment[107].

Complications

Majority of patients with tuberculosis had no complications due to the disease (65%, 85/131)[16]. However, few very common complications were detected namely pleural effusion, pneumothorax and pulmonary fibrosis[16].

DIAGNOSIS

Pulmonary and extrapulmonary tuberculosis

Tuberculin sensitivity test (TST)

Tuberculin sensitivity test reactions amongst the Malaysian population seem to range between 10-15mm[108]. Seventy two percent (74/103) and 57% (59/103) of tuberculosis patients had TST cut-off points of 10mm and 15mm respectively[108]. Tuberculin sensitivity test reading of 10mm had a higher sensitivity than a 15mm result[108].

Tuberculin sensitivity test results were significantly linked to the severity of a co-morbidity in a patient[108]. Tuberculin sensitivity test results were frequently negative in patients with higher levels of comorbidities (10mm cut-off, p=0.003; 15mm cut-off, p=0.012)[108].

In the assessment of the influence of post exposure infection of tuberculosis amongst contacts, only 30% (12/40) of contacts of HIV-PTB patients had positive TST compared to 53% (47/94) of the contacts of HIV negative patients [OR= 0.41, 95% CI 0.07-0.87; p=0.016][35].

Sputum/blood culture

Both culture methods (BACTEC MGIT 960 and BACTEC 460 TB) managed to detect Mycobacterium tuberculosis in 15% (42/279) specimens (respiratory and non respiratory) 109. Eighty percent (37/42) was detected by BACTEC MGIT 960 method while 83% (35/42) was detected by radiometric BACTEC 460 TB[109]. The BACTEC MGIT 960 technique was found to be more rapid, as sensitive and less labour intensive than the 'gold standard' BACTEC 460[109].

CD4 counts

In most HIV-infected tuberculosis cases, CD4 counts were less than 200 cells/mm^3 [21,36]. The TB-HIV deaths were associated with CD4 counts <200 cells/mm^3 and increase for every 10^3 cells per microliter unit increase in total white blood cell[48].

Pulmonary tuberculosis

Chest x-ray

Sixty nine percent (90/131) of inpatients with tuberculosis at a tertiary centre had positive chest x-ray finding[16]. At initial presentation, 46% to 73% (173/237) of pulmonary tuberculosis patients had advanced chest x-ray findings[7,18]. Larger proportions of patients without co-morbidities had typical presentation on chest x-ray[17]. Sixty two percent (144/232) of pulmonary tuberculosis patients had typical changes on chest x-rays while 39% (88/232) were not typical[17].

Tuberculous and malignant lung effusions had more predominance on the right side of the lung[67]. Tuberculous effusions (12%) were smaller than malignant pleural effusions (44%)(p<0.001)[67].

Tuberculosis among community acquired pneumonia (CAP) inpatients were significantly associated with chest radiograph showing upper lobe involvement (OR 8.23; 95% CI 1.59-42.53; p=0.012) or cavitary infiltrates (OR 19.41; 95% CI 2.94-128.19; p=0002)[62].

1. HIV patients

Only half of HIV-infected tuberculosis patients had pulmonary lesions on chest x-ray (55%, 82/149)[25]. Eighty four percent (67/80) of HIV patients had atypical clinical and investigative findings[110]; 5.4% (8/149) had pleural lesions while another 5.4% (8/149) had either hilar or perihilar lymph node lesions25. Sixteen percent (13/80) of HIV/TB cases had post primary pattern with opacities distributed at the upper zones with or without cavitation[110].

When comparisons were made in relation to CD4 counts, only one (out of 80) patient with CD4 counts less than 200 had typical pattern on chest x-ray[110]. Patients with CD4 counts more than 200 had typical pattern on chest x-ray[110].

Severity of tuberculosis chest x-ray was moderate to severe in sputum negative HIV patients[26].

2. Diabetic patients

A comparison between TB-DM and a non-diabetic group showed no difference in radiological findings[15]. However, opacity or cavity of the upper lobe involvement was lower in the TB-DM group than the non-diabetic group (89% and 91% respectively)[15].

Tuberculin sensitivity test

Seventy four percent (42/57) pulmonary tuberculosis cases had a positive Mantoux test[7]. Patients with concurrent HIV and tuberculosis infection had a lesser chance of a reactive TST[26]. These patients also had a stronger positive tuberculin skin test results (p<0.05)[20]. No correlation was found between TST results and sputum culture or chest x-ray severity in this group of patients[26]. On the other hand, post TST indurations of 52% and 26% amongst HCWs were of ≥ 10mm and 15mm greater respectively[106].

Sputum AFB

Almost 58% (37/57) - 89% (117/131) of pulmonary tuberculosis cases had a positive sputum AFB smear[5,7,16,18]. Only one study contradicted the findings described above by showing that only 23% (58/232) of pulmonary tuberculosis patients were tested positive for AFB sputum smear[17]. In the same study, another 11% of tuberculosis cases (26/232) were diagnosed via a positive sputum culture result[17]. Sputum results may even be negative in patients with typical clinical symptoms and chest radiograph changes[17]. Only 17% (33/237) of the pulmonary tuberculosis patients tested smear negative while 44% (104/237) were weakly positive for AFB and 25% (59/237) heavily positive sputum for AFB[18].

Although chest x-rays had typical findings, 40% (21/52) of newly diagnosed pulmonary tuberculosis patients did undergo previous investigations for tuberculosis[61]. In others, the diagnosis was excluded solely due to a negative sputum smear result[61].

1. HIV patients

Tuberculosis patients with HIV positivity often present with negative sputum smear for AFB (p<0.05)[23,26]. In line with these findings, only 51% (76/149) of HIV-infected tuberculosis patients had positive sputum smears[8,25].

2. Diabetic patients

The only study was carried out to analyse this issue found 74% (148/200) of diabetic patients having positive AFB smears compared to non-diabetic patients (51%, 102/200)[14].

Sputum culture

Culture results of pulmonary samples helped identify

tuberculosis in 11% (12/109) of patients who were treated empirically as smear negative PTB[37]. This is important in the treatment of HIV-infected tuberculosis where there were greater rates of smear negative sputum and sputum positive cultures[26].

Newer techniques of sputum culture has been assessed with Lowenstein-Jensen (LJ) culture as the gold standard[111]. The BBL MGIT had higher sensitivity and specificity than AFB smear microscopy[111]. A total of 20% (101/510) specimens were positively detected by BBL MGIT, 12% (60/510) by primary LJ medium culture and 6% (31/510) through direct smear examination[111]. The mean time to detection was significantly shorter for BBL MGIT than for LJ culture ($p<0.0001$)[111].

Blood
Immunocompromised CAP inpatients with concomitant tuberculosis infection were significantly associated with total white blood cell count on admission of 12 x 109/L or less (OR 6.28; CI 1.21-32.52; p=0.029) and lymphopenia (OR 4.73; 95% CI 1.08-20.85; p=0.040)[62].

The mean CD4 counts in HIV-infected tuberculosis patients were significantly lower[110]. Fifty three percent of all patients with AIDS-defining illness (mainly tuberculosis) had CD4 counts less than 200 cells/mm^3 at the time of diagnosis[22]. AIDS patients with CD4 counts less than 200 were more likely to produce normal chest x-rays, middle and lower zone parenchymal changes and mediastinal lymphadenopathy[110]. Lower levels of serum albumin ($p<0.023$) and higher levels serum globulin ($p<0.025$) were associated with drug-induced hepatitis on anti-TB treatment[38].

Interferon-Ɣ-release assay (IGRA)
Reversion and conversion occurred frequently amongst healthcare workers[30].

Polymerase chain reaction (PCR)
Single Xpert assay accurately detected only eight previously undiagnosed TB cases out of 15 culture positive TB cases[33]. This resulted in a sensitivity, specificity, positive predictive value and negative predictive value of 53%, 100%, 100% and 94%[33]. However, the assay managed to only detect 7% (1/15) of active TB cases among HIV patients[33].

In the analysis of pleural fluid for tuberculosis, PCR outperformed AFB staining and LJ medium methods112. It had a 19%, 96%, 67% and 72% in sensitivity, specificity, positive predictive value and negative predictive value respectively[112].

Bronchocopy and pleuroscopy
Between 40-49% of pulmonary tuberculosis cases were diagnosed from specimens obtained from bronchoscopy[17,66]. The value of bronchocopic evaluation was seen in a case study involving HIV-infected patient[71]. Effusion fluid analysis did not reveal Mycobacterium tuberculosis on staining but IG-Ɣ levels were elevated[71]. A bronchoalveolar lavage revealed AFB on smear and culture[71].

In a region of high prevalence of tuberculosis, pleuroscopy aided in about 52% (32/62) of the cases of unexplained pleural effusion[43].

Effusion analysis
Microscopic analysis of tuberculous effusion showed a lymphocyte predominance, with higher lymphocyte percentage but lower red cell count and higher protein content[67]. The PCR analysis of pleural effusion identified 9% (6/67) of cases while AFB staining identified none and LJ medium identified 1.5% (1/67) 112. Pleural biopsy had a better yield (69%) in terms of identifying tuberculosis than Mycobacterium culture of effusion (24%) while pleural fluid staining was negative[71].

A combination of investigations (staining, sputum, pleural biopsy, lavage) yielded the diagnosis in 92% of patients with tuberculous effusion[66]. This was evidenced in a case study involving a HIV-infected patient where effusion fluid did not reveal Mycobacterium tuberculosis but a bronchoalveolar lavage revealed AFB on smear and culture[71].

Extrapulmonary tuberculosis
Histopathological studies seem to be the most useful diagnostic tool in diagnosing patients with extra pulmonary tuberculosis (52%, 101/195)[6]. X-rays were able to isolate findings attributable to tuberculosis in 42% (82/195) of patients with extra pulmonary tuberculosis[6].

Spine tuberculosis

1. Imaging
Tuberculosis of the spine occurred mostly at the thoracic vertebrae (30%, 10/33), followed by the lumbar vertebrae (27%, 9/33)[46]. The most common radiological lesion seen in spinal tuberculosis was of the paradiscal type (47%, 25/53)[42]. Close to 12% (4/33) of the spine tuberculosis cases had characteristic skip lesions[46].

2. Blood
In a study that analysed various modalities that could be used in diagnosing spinal tuberculosis, PCR had high specificity and sensitivity (94% and 100%)[113].

3. Erythrocyte sedimentation rate played a role in screening as well as assessing the neurological severity in patients with tuberculosis of the spine[46,114]. Erythrocyte sedimentation rate was normal only in 9% (3/33) of tuberculosis patients46. Erythrocyte sedimentation rate helped differentiate patients who had neural deficit from those who were neurologically normal[114].

4. Sputum smear and bacterial growth
Sputum smear results and bacterial culture growth for Mycobacterium are of limited value in the management of tuberculosis of the spine[114].

5. Histology
The percentage of patients with spinal tuberculosis diagnosed through histological examination was 44% (23/53)[42]. In diagnosing spinal tuberculosis, histopathogical examinations yielded 82% in sensitivity and 100% in specificity[113].

6. Culture
Lowenstein-Jensen culture had a sensitivity of 6% and a sensitivity of 100% in detecting spinal tuberculosis[113].

Tuberculous lymphadenitis
The most frequent specimen used in the diagnosis of extra pulmonary tuberculosis was lymph nodes (35%, 68/195)[6]. A high degree of positive results (83%, 90/109) were obtained in cases of tuberculous lymphadenitis through fine needle aspiration[9].

Gastrointestinal tuberculosis (GITB)
Patients with abdominal tuberculosis had significantly lower serum haemoglobin (p=0.036) than pulmonary tuberculosis cases[78]. Sixty eight percent (24/34) of GITB cases were confirmed through histopathological tissue studies[47]. Chest radiographs suggested TB in 47% of these cases (16/34)[47].

Table I: Age of population in various tuberculosis categories

Category	Age range or associated factors/Studies
Tuberculosis in general	• Mean age 33.3 years +/- 9.95, predominant in younger population (up to 34 years of age)[39] • Majority of patients in 20-60 years[11] • Highest frequency in 34-45 years[26] • Higher among >60 years24 • Increased incidence in elderly[44]
Tuberculosis death in general	• 24-44 years[40]
Tuberculosis in foreign-born	• Mean age of 14-72 years[39]
Tuberculosis amongst inpatients	• 21-60 years[16]
Delay and extreme delay in management of tuberculosis	• 30-39 years[45]
HIV-infected tuberculosis patients	• Mean age 34 years[8,25] • Mean age 36 years[41] • 18-75 years, mean age of 36.1 years[21] • 21-62 years[20] • Younger patients and unmarried patients[20] • 30-39 years[23] • Mean age for HIV/TB co-infection
Tuberculosis with diabetes	• More likely in 46-60 years[13] • 21-78 years[20] • Mean age of these patients was significantly higher than that of non-diabetic patients ($p<0.05$)[15] Married patients with diabetes had greater chances of contracting the disease ($p<0.05$)[20]
Tuberculosis+HIV+DM	• 29-73 years[12]
Pulmonary tuberculosis	• Majority in 45-64 years[7] • Predominant age group amongst HIV patients 35-44 years[27] • 35% (90/237) in the productive age group[18] • 46% (109/237) were more than 50 years of age[18]
Extra pulmonary tuberculosis in general	• Mean age 39 years, with the largest number of patients in the ages between 25-34 years[6] • 79% of patients were less than 50 years of age[6]
Tuberculous lymphadenitis	• Mean age 36.4 years[9]
Tuberculosis of the spine	• Mean age 40.2 years[42] • Mean age of 36.5 years (n=33) with a peak incidence in the second decade of life (27%, 9/33)[46] • 72% (24/33) of cases were males[46]
Gastrointestinal tuberculosis	• 30-40 years (58%, 20/34)[47].

In a case study, CT scan proved the best modality in detecting a case of tuberculous peritonitis[82].

Ocular tuberculosis
Most imaging, blood and sputum investigations had negative results. The detection and treatment of ocular tuberculosis relied on positive results of Mantoux and IGRA tests[96,97,99,100].

Splenic tuberculosis
Splenic tuberculosis was confirmed by a percutaneous splenic biopsy that revealed granuloma formation and Langhan's giant cells[103].

Endocrine
Endoscopic ultrasound, CT scan and ultrasound guided tissue biopsy was an essential tool in the diagnosis of pancreatic tuberculosis[105].

Non tuberculous mycobacterium infection (NTMI)
Patient with NTMI was diagnosed based on a positive Mantoux test and a positive response to anti-tuberculosis treatment[107].

Detection of latent tuberculosis infection

Tuberculin skin test
Tuberculin skin test had poor detection rate of tuberculosis amongst HIV infected prisoners[32]. The utilisation of TST and IGRA could be a viable option in the screening of diabetic patients with comorbidities for latent tuberculosis infection[10].

MANAGEMENT

Pulmonary tuberculosis

The commonly used treatment regime between the year 1998 and 2004 was the 2SHRZ/4SHR regime[3,7,11].

Only 17% of pulmonary tuberculosis patients were successfully treated with empirical anti-tuberculosis therapy that were based on clinical and radiological features[36]. However, empirical treatment of suspected tuberculous effusions led to clinical improvements in 65% (40/62) - 84% (81/109) of patients[37,115]. There were isolated clinical improvements in 13% (12/109) and radiological improvements alone in 3%

Table II: Influence of ethnicity and geography in various tuberculosis categories

Category	Ethnicity and related factors/Studies
Tuberculosis in general	• Majority were Chinese in ethnicity (56%, 116/207), followed by Malays (34%, 70/207)[3] • Predominantly of Malay ethnicity (96%, 169/176) and another 2.8% (5/173) were Chinese[11] • Highest tuberculosis incidence rates involved patients of Indian descent[24] • 43% (56/131) of patients admitted to UMMC with the diagnosis of tuberculosis were Malays followed by patients with Chinese ethnicity (22%, 29/131)[16] • High incidence of tuberculosis amongst the indigenous people but patients with Chinese descent comprise a larger number of infected cases[44]
Tuberculosis in foreigners	• Foreign nationalities contribute to 15% of all notified cases[24] • 87% of foreign-born patients with tuberculosis were from Southeast Asian countries (87%, 71/263)[39]
HIV-infected tuberculosis patients	• Majority were of Malay descent (94%, 140/149)[8] • Majority were of Malay descent (17%, 4/25)[23] • Majority were Malays at 47% (136/290)[21] • Majority were of Malay descent[25] • Majority were Malays (74%, 72/97)[41] • The majority were Malays[20]
Tuberculosis with diabetes	• The majority were Malays[20] • Chinese were more likely to be associated with diabetes mellitus (odds ratios [OR] = 1.401, P= 0.011)[13]
Pulmonary tuberculosis	• High percentage amongst the Malay population (95%, 54/57)[7] • Majority of HIV patients with pulmonary tuberculosis were Malays (48%, 118/290)[27]
Extrapulmonary tuberculosis in general	• Malay patients represented the majority of patients (49%, 96/195)
Tuberculous lymphadenitis	• Higher amongst Malays (41%, 45/1548) followed by patients who were of Chinese descent (34%, 37/1548)[9]
Spinal tuberculosis	• More common among Iban patients (50%, 26/52)[42]
Gastrointestinal tuberculosis	• Most cases involved Malays (74%, 25/34), followed by Chinese (12%, 4/34) and Indians (9%, 3/34)[47]
Tuberculosis mortality	• Indians showed the highest case fatality rate amongst patients treated for tuberculosis[40] • Death in TB-HIV co-infection was associated with being Malay (ahR 4.48; 95%CI 1.73-11.64)[48]

(3/109)[37,115]. Effusions with the size smaller than 1/10 were three times more likely to have complete resolution than larger effusions after commencing anti-tuberculosis treatment (p=0.04)[115].

Higher percentage of HIV patients with pulmonary tuberculosis (42%) were treated successfully with a short-course (six months) of anti-TB therapy[36].

Extra pulmonary tuberculosis

In contrast to the treatment of pulmonary tuberculosis, successful treatment of extra pulmonary infection in HIV patients (43%) required a longer duration of anti-tuberculosis therapy[36].

Spine tuberculosis

1. Surgery

Based on the findings of a study, the preferred surgical procedure was radical anterior debridement and fusion supplemented by anterior or posterior instrumentation of the spine if needed[46]. The radical surgical debridement and grafting rate was at 39%[46]. In 30 patients who received surgical treatment, there was a 4 degree correction in the kyphosis angle of the spine; after six months of treatment, 24 of them had excellent and good outcomes while six had a fair outcome [42].

Endoscopic, endonasal approach was the best approach in the surgical management of cranio-vertebral junction stenosis[116].

2. Chemotherapy

Anti-tuberculosis chemotherapy was still preferred as the cornerstone of treatment as opposed to surgical intervention[46]. However, it was discovered that in 23 patients treated conservatively with anti-TB, there was an increment of 8 degrees of kyphosis angle[42]. Twenty two others had a fair result and only one had poor outcome after six months of treatment[42].

Gastrointestinal tuberculosis (GITB)

Although most patients with GITB (34/34) responded well to anti-tuberculous treatment[47], abdominal tuberculosis had a higher rate of adverse events related to anti-tuberculous treatment (p<0.001)[78].

In one study, CT scan findings were a major predictor for the early initiation of anti-TB regime in tuberculous peritonitis[82]. The eventual diagnosis was confirmed later through histopathological studies obtained from a laparotomy[82].

Ocular tuberculosis

The effective treatment of ocular tuberculosis will require a combination of anti-tuberculous therapy and oral corticosteroids[100]. This was contradictory to another finding

seen in a case report where the resolution of symptoms in ocular tuberculosis was achieved after a six months therapy consisting of only anti-TB treatment[96]. Topical and systemic steroids were ineffective[96].

Genitourinary tuberculosis
Although anti-TB is the mainstay of treatment, surgical intervention might be needed in selected cases[76].

Vasculitis
There has been reports on the benefits and good outcomes of endovascular stenting of a stenotic subclavian artery in cases of tuberculous vasculitis[94]. The repair of a tuberculous aortic pseudoaneurysm with in situ silver-impregnated vascular in lay graft led to an uneventful post operative recovery[95].

Joint
After anti-tuberculosis treatment was commenced, a patient with tuberculous synovitis of the knee joint experienced improvements in symptoms and overall health[86].

Latent tuberculosis infection

Bacillus Calmette–Guérin vaccination prevents the risk of conversion of latent tuberculosis infection to clinical tuberculosis[117]. However, the evidence for mass BCG vaccination of healthcare workers remains controversial and inconclusive[117].

PROGNOSIS AND TREATMENT OUTCOME

A treatment success rate of 82% was seen amongst patients who were diagnosed at an outpatient and hospital setting[2]. Fifty two percent (95% CI 45.7-57.9) of patients sought treatment 30 days from the onset of symptoms[45]. Another 24% (95 CI 18.6-29.0) of patients received consultation after 90 days of developing the illness[45].

Pulmonary tuberculosis

Among the significant factors for the unsuccessful treatment outcome of pulmonary tuberculosis were age, gender, educational level, employment status, family incomes, co-existence of extra pulmonary TB, smoking, diabetes mellitus, HIV status, sputum cultures, chest x-ray findings and duration of delay for diagnosis[118].

Fifty four percent (31/57) of patients with pulmonary tuberculosis had completed treatment[7]. Twenty six percent (15/57) had died and 18% (10/57) had defaulted treatment7. Male foreign-born patients with pulmonary tuberculosis had higher percentages of treatment completion at ≥ 6 (38%, 100/263) and ≥ 9 (13%, 34/263) months when compared to their female counterpart[39].

Extrapulmonary tuberculosis

Gender differences
Treatment success rate was higher amongst females with extrapulmonary tuberculosis (9%, 24/263)[39].

Tuberculous lymphadenitis
In the treatment of tuberculous lymphadenitis, 57% (62/109) patients were treated successfully while 5% (5/109) had died during treatment[9].

Spinal tuberculosis
Treatment of spinal tuberculosis resulted in an excellent outcome in 40% (24/53) of patients[42]. Fifty three percent (28/53) of patients had fair results and 2% (1/53) had poor result[42].

Abdominal tuberculosis
Abdominal tuberculosis (ATB) had a higher rate of adverse events of anti-tuberculosis treatment ($p<0.001$)[78].

Pancreatic tuberculosis
A patient with pancreatic tuberculosis experienced symptomatic improvement following commencement of anti-tuberculosis drugs[119].

Tuberculosis in HIV infected patients

Failure rate and loss to follow up
A higher percentage of failure rate was seen in HIV-infected tuberculosis patients (28%, 19/67)[20]. HIV-infected patients with tuberculosis had a 55% (160/290) to 57% (165/290) frequency of loss to follow up[21,27].

Survival rates
Upon commencement of treatment, the median survival weeks of HIV infected tuberculosis patients was at 13.5 weeks[25]. Survival at 2, 6, and 12 months after initiating tuberculosis treatment were 91%, 83% and 79% respectively[48].

In the treatment amongst immunosuppressed patients, the commonly used regimen for HIV-infected TB patients was EHRZ+B6[20]. The highest percentage of treatment success was at six months of anti-tuberculosis treatment[20]. Amongst HIV/AIDS + TB infected patients who survived, 11% (32/290) of patients who completed treatment fell in the six or more months treatment category while 21% (61/290) fell in the nine or more months treatment category[21].

Mortality rates
Death was seen in 0.8% (2/290) of HIV patients with pulmonary tuberculosis[27]. Twenty three percent (53/227) of patients with HIV/TB co-infection had died at the end of the study with 40% of deaths within two months of TB diagnosis48. Another study found 39% (58/149) of HIV infected tuberculosis patients have died after three years[8]. Also, not receiving HAART treatment was associated with death among TB/HIV co-infected patients[48]. Seventy four percent (110/149) of these patients had died without completing the six months anti-TB regime[8,25]. Out of those who survived, only 32% (93/290) were successfully treated for their illness[27].

Predictors of unsuccessful treatment
Unsuccessful treatment outcome among HIV-infected TB patients were associated with intravenous drug use (OR 2.72; 95% CI 1.44-5.16), not receiving antiretroviral treatment (OR 5.10; 95% CI 2.69-9.69), lymphadenopathy (OR 2.01; 95% CI 1.09-3.72) and low serum albumin (OR 4.61; 95% CI 1.73-12.27) 55. Males (OR=0.721, p=0.049) and patients with relapse of tuberculosis (OR=0.494, p=002) were less likely to have successful treatment outcomes[13].

Tuberculosis in diabetic patients

The treatment outcome was similar in tuberculosis cases with or without diabetes mellitus[13]. Better treatment results were seen in patients between the age 46-60 years (OR=1.567, p=0.001)[13]. However, one study showed TB/DM patients, primarily of the pulmonary type, had more treatment success with a longer duration of treatment of nine months (33%)[15]. Lower proportion of patients in the TB/DM group defaulted treatment (19.8%)[15].

The highest percentage of treatment success were in both groups at six months of anti- tuberculosis treatment[20]. Significantly higher percentage of success rate in treatment

(<0.05) was found in tuberculosis patients with diabetes (35%, 24/69) than TB/HIV patients (19, 13/67)[20]. A success rate of 22% (n=15) was seen in TB/DM patients with nine months of anti-tuberculosis, similar to patients with a 12 month regimen[20].

Smoking cessation

Patients receiving integrated treatment of smoking cessation and TB regime had significantly higher rate of success in quitting smoking when compared with those who received the conventional TB treatment alone (p=0.019)[120]. There were also higher rates of treatment default and failure in the conventional TB treatment group[120].

Prisoners

There was poor success rate in the implementation of preventive isoniazid treatment at correctional facilities[121]. Adverse consequences and treatment interruption ranged from 1 to 55%[121].

Adverse effects

Eleven percent (19/176) of patients developed adverse drug reaction at a tertiary centre, and 58% (11/19) were from the 2SHRZ/4SHR2 regime[11]. The most common adverse effects include nausea and vomiting (41%, 54/131), drug induced hepatitis[16,20], blurring of vision[16,20] and skin rashes[16,20]. There was a case report of ethambutol ocular toxicity in a patient with pulmonary tuberculosis treatment which resolved within two months after cessation[122].

Adverse drug reactions seem to be more common in patients with extra pulmonary tuberculosis[38,78]. The prevalence of drug-induced hepatitis was 9.7% and the significant risk factors were the presence of HIV infection and extra pulmonary tuberculosis[38].

Drug resistance

A study on the cases of tuberculosis at a tertiary centre reported no drug resistant cases within the study year[11].

The TB-DM group experience lower resistance to anti-tubercular (1.4%) therapy when compared to non-diabetics[15]. No cases of drug resistance or deaths were notified amongst the TB-HIV and TBDM patients[20].

PREVENTION AND CONTROL MEASURES

Based on the results of one study, the efficacy of BCG in preventing tuberculosis was low. About 64% (113/176) of the tuberculosis patients had BCG scars[11]. This brings to question the efficacy of the vaccine[11].

A Geographic Information System (GIS) application helps identify the geographical distribution and the trend of tuberculosis in a particular region[123]. This helps in tuberculosis surveillance activities[123].

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

EPIDEMIOLOGY

In general, there was a lack of prevalence data amongst population who were susceptible to LTBI and eventually primary progressive tuberculosis. There was also very little prevalence data from a primary care perspective. It is valid to call for mandatory health examination for all foreign workers arriving in Malaysia within one month of arrival regardless of whether or not they are certified fit in their countries of origin[49].

SCREENING

Healthcare workers are at high risk of contracting tuberculosis. Hence, it is recommended that they should also undergo TB screening at least once every two years[29]. The HCWs need to have an up-to-date knowledge of the pattern of health and disease and their determinants in each district[2]. They should emphasise the use of Directly Observed Therapy, Short-course (DOTS) in high risk populations[118]. Screening by age, chest x-rays and HIV status helps categorise patients who are vulnerable to unsuccessful treatment[118]. Implementation of TB screening for HIV patients is important to reduce TB mortality[40].

Tuberculin skin test may be replaced with a more accurate and specific method, interferon gamma release assay (IGRA) in highly prioritised group[10,50]. Tuberculin skin test and IGRA used in combination is an economical method to screen tuberculosis in high risk populations[10]. A TST cut-off of 15mm or greater may correlate better with Mycobacterium tuberculosis infection than a cut-off of 10mm or greater in a setting with high prevalence of BCG vaccination[106]. Polymerase chain reaction (single Xpert assay) improved TB case detection and outperformed AFB smear but yielded low sensitivity in screening prison HIV patients[33]. The PCR is a rapid method for the detection of Mycobacterium tuberculosis in pleural fluid but is a weak test in terms of sensitivity[112]. Hypertonic saline should be used to induce sputum and sputum culture should be done prior to commencing an anti-tuberculosis regime[124]. Pleuroscopy was a safe diagnostic procedure and sampling nodules was satisfactory[43].

DETECTION

The BBL MGIT system will be a suitable alternative to LJ culture for the routine diagnosis of pulmonary tuberculosis[111]. Fine needle aspiration is the most reliable diagnostic test for tuberculous lymphadenitis[9]. The PCR is a reliable method to identify spinal tuberculosis even after two weeks of anti-TB treatment[113]. The ESR could be used in the prediction of the evolution of paraplegia in spinal tuberculosis[114], and MRI could be used to detect early pedicle involvement in spinal tuberculosis[73]. A high index of suspicion is required to diagnose ocular tuberculosis when all other systemic investigations are negative, especially where TB is endemic[97].

TREATMENT AND PREVENTION

Educating and providing patients with more information about tuberculosis could lead to compliance to DOTS[125]. Healthcare workers are recommended to take extra precautions (wearing protective equipment) in the first ten years of service when performing procedures that are considered high risk in the development of tuberculosis infection[29]. Tuberculosis infection control need to be strengthened, especially at the Emergency Department where there was a large incidence of TB as evidenced by the study[30]. Specific guidelines on preventive measures for ambulatory care setting, including radiology clinics, should be developed to enable HCWs working in those areas to reduce the risk of infection[126].

Smoking has a negative impact on tuberculosis treatment outcomes[19]. The integrated approach of smoking cessation and tuberculosis treatment has shown benefits and might influence the future lung health of tuberculosis patients who quit smoking[120].

Empirical treatment of anti TB treatment is an acceptable practice if clinical suspicion is high in patients coming to our region[17,37,64]. Once confirmed, smaller effusions related to pleural tuberculosis can be given anti-tuberculosis treatment alone while larger effusions could benefit from thoracentesis[115].

In patients with drug-induced hepatitis with liver enzymes five times above normal, an alternative regimen of streptomycin, oxfloxacin and ethambutol should be commenced[127].

There was a higher percentage of HIV patients with pulmonary tuberculosis (42%) who were treated successfully with a short-course (six months) of anti-TB therapy[36] while extra pulmonary infection required a longer duration of treatment in order to be successful[36].

In cases of tuberculosis of the spine, surgery provides faster pain relief46. However, the decision to pursue surgical intervention should only be after careful patient selection in order to prevent morbidity and mortality[46]. The effective treatment of ocular tuberculosis will require a combination of anti-tuberculous therapy and oral corticosteroids[100,102]. A trial of anti-tuberculous drugs should be considered for patients with a high clinical suspicion of gastrointestinal tuberculosis[80]. In the assessment of a regional tuberculosis programme, healthcare workers were encouraged to examine each child for BCG scars and if it is not present by the age of three months, the child should be re-vaccinated[24].

SECTION 3: FUTURE RESEARCH DIRECTION

Future studies should focus on the analysis of LTBI in high-risk population such as diabetes mellitus, smokers, the elderly and CRF/ESRF patients[10]. Research at a primary care setting could uncover a 'hidden' reservoir of LTBI in diabetics, CRF/ESRF and elderly patients.The role of future research in the detection of LTBI in a Malaysian setting might be necessary to gauge the disease reservoir before implementing prophylactic measures for risk groups involved[10].

Multicentered and multidisciplinary initiatives are important to gauge research on the risk of LTBI amongst HCWs. There is a role for GIS in studying the top spots for diseases, mapping the spread of the disease with a focus on population or areas with higher density. There is the need to study treatment of latent TB infection such as who should be treated. Another area to study is the outcome of MDR TB.

There has been a call to not only focus on secondary prevention, but also primary prevention of tuberculosis[10]. With the rise of tuberculosis in the nation, the pressing issue of prophylactic treatment of high risk groups in the Malaysian society requires further evaluation[10].

ACKNOWLEDGEMENT

I would like to sincerely thank the Director-General of Health, Malaysia for his permission to publish this paper. I wish to thank Clinical Research Centre team for its contribution and support. I would also like to especially thank Dr. Lim Ai Wei (CRC) for her diligence in editing this article and rendering it to its current form.

REFERENCES

1. World Health Organization (WHO). Global health observatory data repository: Tuberculosis, incidence and case detection. [Internet]. WHO. 2014 [cited 2014 Apr 27]. Available from: http://apps.who.int/gho/data/node.main.1315?lang=en.
2. Dony JF, Ahmad J, Khen Tiong Y. Epidemiology of tuberculosis and leprosy, Sabah, Malaysia. Tuberc. 2004 ;84(1-2): 8–18.
3. Elfatih IE, Abdul Razak M, Mohamed Izham MI *et al.* A survey of tuberculosis cases in Penang Hospital: preliminary findings. Malaysian J. Pharm. Sci. 2004; 2(2): 1–8.
4. Muzaffar Z, Ling H, Sujinder S, *et al.* Improving the rate of acid fast bacilli sputumm screening: Sitiawan Health Clinic experience. J. Health Manag. 2012; 10(2): 20.
5. Hamimah S. The severity of pulmonary tuberculosis disease and the contributing factors, places visited and place of diagnosis for cases from Pendang District 2000. 2000;
6. Nissapatorn V, Kuppusamy I, Rohela M, *et al.* Extrapulmonary tuberculosis in Peninsular Malaysia: retrospective study of 195 cases. Southeast Asian J Trop Med Public Heal. 2004; 35(Suppl 2): 39–46.
7. Jamalludin AR. Review of pulmonary tuberculosis cases in Kuala Terenggany from 1998-2001. Int. Med. J. 2003;2(2).
8. Mohammad Z, Naing NN. Characteristics of HIV-infected tuberculosis patients in Kota Bharu Hospital, Kelantan from 1998-2001. Southeast Asian J Trop Med Public Heal. 2004; 35(1): 140–143.
9. Khan AH, Sulaiman SA, Muttalif AR *et al.* Tuberculous lymphadenitis at Penang General Hospital, Malaysia. Med Princ Pr. 2011; 20(1): 80–84.
10. Swarna Nantha Y. Influence of diabetes mellitus and risk factors in activating latent tuberculosis infection : a case for targeted screening in Malaysia. Med J Malaysia. 2012; 67(5): 465–470.
11. Siti Fatimah A, Syed Azhar SS, Mohamed Izham MI. Evaluation of the tuberculosis management at Dungun Hospital. Malaysian J. Pharm. Sci. 2004; 2(2): 35–36.
12. Gnanasan S, Ting KN, Wong KT, *et al.* Convergence of tuberculosis and diabetes mellitus: time to individualise pharmaceutical care. Int J Clin Pharm. 2011; 33(1): 44–52.
13. Sulaiman SA, Khan AH, Muttalif AR, *et al.* Impact of diabetes mellitus on treatment outcomes of tuberculosis patients in tertiary care setup. Am J Med Sci. 2013; 345(4): 321–325.
14. Syed Suleiman SA, Ishaq Aweis DM, Mohamed AJ, *et al.* Role of diabetes in the prognosis and therapeutic outcome of tuberculosis. Int J Endocrinol. 2012; 2012(645362): 1–6.
15. Nissapatorn V, Kuppusamy I, Jamaiah I, *et al.* Tuberculosis in diabetic patients: a clinical perspective. Southeast Asian J Trop Med Public Heal. 2005; 36(Suppl 4): 213–220.
16. Jetan CA, Jamaiah I, Rohela M, *et al.* Tuberculosis: an eight year (2000-2007) retrospective study at the University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. Southeast Asian J Trop Med Public Heal. 2010; 41(2): 378–385.
17. Ismail Y. Pulmonary tuberculosis - a review of clinical features and diagnosis in 232 cases. Med J Malaysia. 2004; 59(1): 56–64.
18. Abdul Razak M. Significance of symptoms and investigations in tuberculosis case finding. J. Pharm. Sci. 2004; 2(2): 29–30.
19. Awaisu A, Nik Mohamed, Abd Aziz N, *et al.* Tobacco use prevalence, knowledge, and attitudes among newly diagnosed tuberculosis patients in Penang State and Wilayah Persekutuan Kuala Lumpur, Malaysia. Tob Induc Dis. 2010; 8(1): 2–9625–8–3.
20. Nissapatorn V, Kuppusamy I, Josephine FP, *et al.* Tuberculosis: a resurgent disease in immunosuppresed patients. Southeast Asian J Trop Med Public Heal. 2006; 37(Suppl 3): 153–160.
21. Nissapatorn V, Kuppusamy I, Anuar AK, *et al.* Tuberculosis: clinical manifestations and outcomes. Southeast Asian J Trop Med Public Heal. 2003; 34(Suppl 2): 147–152.
22. Nissapatorn V, Lee C FQ *et al.* AIDS-related opportunistic infections in Hospital Kuala Lumpur from 1994 to 2001. Jpn J Infect Dis. 2003; 56(5-6): 187–192.
23. Mazlinah M. Sociodemographic characteristics and clinical manifestations of tuberculosis patients with and without human immunodeficiency virus at Chest Cclinic, Hospital Terengganu. Undocumented.
24. Venugopalan B. An evaluation of the tuberculosis control programme of Selangor state, Malaysia for the year 2001. Med J Malaysia. 2004; 59(1): 20–25.
25. Wan MZ, Syed Hatim N, Naing NN. Characteristics of HIV-Infected Tuberculosis Patietns In Kota Bharu Hospital, Kelantan From 1998 To 2001. Malaysian J. Pharm. Sci. 2004; 2(2): 20–20.
26. Velaiutham S, Abdul Razak M, Khatijah B. Characteristics of pulmonary tuberculosis in HIV seropositive patients in Chest Clinic, Penang Hospital. Malaysian J. Pharm. Sci. 2004; 2(2): 31.
27. Nissapatorn V, Kuppusamy I, Init I, *et al.* Pulmonary tuberculosis in HIV/AIDS patients. Trop Biomed. 2002; 19(1): 49–53.
28. Lian YL, Heng BS, Nissapatorn V, *et al.* AIDS-defining illnesses: a comparison between before and after commencement of highly active antiretroviral therapy (HAART). Curr HIV Res. 2007; 5(5): 484–489.
29. Jelip J, Mathew GG, Yusin T, *et al.* Risk factors of tuberculosis among health care workers in Sabah, Malaysia. Tuberc. 2004; 84(1-2): 19–23.

30. Rafiza S Rampal KG. Serial testing of Malaysian health care workers with QuantiFERON(R)-TB Gold-In-Tube. Int J Tuberc Lung Dis. 2012; 16(2): 163–168.
31. Mahmud M. Infectious disease among heroin addicts receiving outpatient treatment in Muar. Malaysian Anti-Drugs J. 2007; 1: 73–80.
32. Margolis B, Al-Darraji HA, Wickersham JA, *et al.* Prevalence of tuberculosis symptoms and latent tuberculous infection among prisoners in northeastern Malaysia. Int J Tuberc Lung Dis. 2013; 17(12): 1538–1544.
33. Al-Darraji HA, Razak HA, Ng KP, *et al.* The diagnostic performance of a single GeneXpert MTB/RIF assay in an intensified tuberculosis case finding survey among HIV-infected prisoners in Malaysia. PLoS One. 2013; 8(9): e73717.
34. Rafiza S, Rampal KG. Prevalence and risk factors of latent tuberculosis infection among health care workers in Malaysia. BMC Infect Dis. 2011; 11(19-2334): 11–19.
35. Mohammad Z, Naing NN, Salleh R, *et al.* A preliminary study of the influence of HIV infection in the transmission of tuberculosis. Southeast Asian J Trop Med Public Heal. 2002; 33(1): 92–98.
36. Nissapatorn V, Kuppusamy I, Sim BL, *et al.* Tuberculosis in HIV/AIDS patients: a Malaysian experience. Southeast Asian J Trop Med Public Heal. 2005; 36(4): 946–953.
37. Loh LC, Abdul Samah SZ, Zainudin A, *et al.* Pulmonary disease empirically treated as tuberculosis - a retrospective study of 107 cases. Med J Malaysia. 2005; 60(1): 62–70.
38. Marzuki OA, Fauzi AR, Ayoub S, *et al.* Prevalence and risk factors of anti-tuberculous drug induced hepatitis in Malaysia. Singapore Med J. 2008; 49(9): 688–693.
39. Nissapatorn V, Kuppusamy I, Wan-Yusoff WS et al. Clinical analysis of foreign-born patients with tuberculosis found in Malaysia. Southeast Asian J Trop Med Public Heal. 2005;36(3):713–721.
40. Venugopalan B, Rajendra P. A retrospective study of death among patients treated for tuberculosis in Klang Chest Clinic for the year 1999. Med J Malaysia. 2001; 56(1): 39–43.
41. Narwani H, Naing NN. Comparison of socio-economic and demographic characteristics of HIV and HIV-infected tuberculosis patients in Kota Bharu Hospital, Kelantan. J. Kesihat. Masy. 2004; 10: 38–40.
42. Ahmad hata R, Razak M, Ting FS. The pattern of spinal tuberculosis in Sarawak General Hospital. Med J Malaysia. 2001; 56(143-150).
43. Kannan SK, Lin WJ, Teck TS, *et al.* Pleuroscopy: early experience in an East Malaysian state with high tuberculosis prevalence. J Bronchol. Interv Pulmonol. 2009; 16(4): 250–253.
44. Noridah O, Hairul Izwan Ar, Hazlee AH. A review of tuberculosis in Kinta District. IMR Q. Bull. 2003; (54):2 4–28.
45. Christina R, Fielding K, Godfrey-Faussett P, *et al.* Delays in seeking treatment for symptomatic tuberculosis in Sabah, East Malaysia: factors for patient delay. Int J Tuberc Lung Dis. 2011; 15(9): 1231–1238.
46. Dharmalingam M. Tuberculosis of the spine-the Sabah experience. Epidemiology, treatment and results. Tuberc. 2004; 84(1-2): 24–28.
47. Radzi M, Rihan N, Vijayalakshmi N, *et al.* Diagnostic challenge of gastrointestinal tuberculosis: a report of 34 cases and an overview of the literature. Southeast Asian J Trop Med Public Heal. 2009; 40(3): 505–510.
48. Ismail I, Bulgiba A. Predictors of death during tuberculosis treatment in TB/HIV co-infected patients in Malaysia. PLoS One. 2013; 8(8): e73250.
49. Leong CC. Pre-employment medical examination of indonesian domestic helpers in a private clinic in Johor Bahru - an eight year review. Med J Malaysia. 2006; 61(5): 592–598.
50. Atif M, Sulaiman SA, Shafie AA, *et al.* Tracing contacts of TB patients in Malaysia: costs and praticality. Springerplus. 2012; 1: 40–1801–1–40.
51. Al-Darraji HA, Wong KC, Yeow DG, *et al.* Tuberculosis screening in a novel substance abuse treament center in Malaysia: Implications ofr a comprehensive approach for integrated care. J Subst Abus. Treat. 2013;
52. Nissapatorn V. Lessons learned about opportunistic infections in Southeast Asia. Southeast Asian J Trop Med Public Heal. 2008; 39(4): 625–641.
53. Tengku Saifudin TI, Lee C. HIV associated opportunistic pneumonias. Med J Malaysia. 2011; 66(1): 76–82.
54. Nissapatorn V, Lee C, Ithoi I, *et al.* Tuberculosis in AIDS patients. Malays J Med Sci. 2003; 10(1): 60–64.
55. Ismail I, Bulgiba A. Determinants of unsuccessful tuberculosis treatment outcomes in Malaysian HIV-infected patients. Prev Med. 2013; 57(Suppl): S27–S30.
56. Nissapatorn V, Lee CKC KA. Impact of pulmonary opportunistic infections among AIDS patients in General Hospital Kuala Lumpur, Kuala Lumpur, 2001. Trop Biomed. 2001; 18(2): 117–121.
57. Naing C, Mak JW, Maung M, *et al.* Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. Lung. 2013; 191(1): 27–34.
58. Lee PY, Ong TA, Dayangku Norlida AO. Tuberculous prostatic abscess in an immunocompromised patient. Malaysian Fam. Physician. 2010; 5(3): 145–147.
59. Saraswathi S, Noorizan AA, Yahaya H, *et al.* Tuberculosis development in a patient with chronic history of steroid abuse: a case report. Malaysian J. Pharm. Sci. 2004; 2(2): 34.
60. Chang CT, Esterman A. Diagnostic delay among pulmonary tuberculosis patients in sarawak, Malaysia: cross-sectional study. Rural Remore Heal. 2007; 7(2): 667.
61. Ismail Y. Tuberculosis - are we missing the diagnosis? Singapore Med J. 2002; 43(4): 172–176.
62. Liam CK, Pang YK, Poosparajah S. Pulmonary tuberculosis presenting as community-acquired pneumonia. Respirology. 2006; 11(6): 786–792.
63. Sharma G, Koley S, Sandhu JS *et al.* A study of changes in the body composition components in the patients with pulmonary tuberculosis. Med J Malaysia. 2008; 63(2): 118–121.
64. Wong CM, Lim KH, Liam CK. The causes of haemoptysis in Malaysian patients aged over 60 and the diagnostic yield of different investigations. Respirology. 2003; 8(1): 65–68.
65. Liam CK, Lim KH, Wong CM. Causes of pleural exudates in a region with a high incidence of pulmonary tuberculosis. Respirology. 2000; 5(1): 33–38.
66. How SH, Chin SP, Zal AR, *et al.* Pleural effusions: role of commonly available investigations. Singapore Med J. 2006; 47(7): 609–613.
67. Liam CK, Lim KH, Wong CM. Differences in pleural fluid characteristics, white cell count and biochemistry of tuberculous and malignant pleural effusions. Med J Malaysia. 2000; 55(1): 21–28.
68. Abdul Rani MF, Cheung HS, Sunita A. Endobronchial tuberculosis mimicking pulmonary neoplasm. Int. Med. J. 2002; 1(1).
69. How SH, Kuan YC, Ng TH, *et al.* An unusual cause of haemoptysis and headache: cryptococcosis. J Pathol. 2008; 30(2): 129–132.
70. Rohana J, Lau DS, Hasniah AL, *et al.* Pneumatocoele in a neonate with perinatal tuberculosis. Arch Dis Child Fetal Ed. 2013; 98(2): F121.
71. Khajotia R, Manthari K. An apparently healthy young man with a peculiar-looking chest radiograph. Can Fam Physician. 2011; 57(3): 311–313.
72. Zamzuri Z, Adham S, Shukrimi A, et al. Metastatic adenocarcinoma of the lung mimicking spinal tuberculosis. Int. Med. J. 2011; 10(2): 43–46.
73. Yusof MI, Hassan E, Rahmat N, *et al.* Spinal tuberculosis: the association between pedicle involvement and anterior column damage and kyphotic deformity. Spine (Phila Pa 1976). 2009; 34(7): 713–717.
74. Elnaim AL. Bilateral psoas abscess and extensive soft tissue involvement due to late presentation of Pott's disease of the spine. Indian J Surg. 2011; 73(2): 161–162.
75. Chow TW, Lim BK, Vallipuram S. The masquerades of female pelvic tuberculosis: case reports and review of literature on clinical presentation and diagnosis. J Obs. Gynaecol Res. 2002; 28(4): 203–210.
76. Lim PS, Atan IK, Naidu A. Genitourinary tuberculosis: an atypical clinical presentation. Case Rep Obs. Gynaecol. 2012; 2012: 727146.
77. Ho CCK, Siti Aishah MA, Praveen S, *et al.* Spontaneous bladder perforation: a rare complication of tuberculosis. Int J Infect Dis. 2010; 14(Suppl 3): e250–2.
78. Chong VH. Differences in patient profiles of abdominal and pulmonary tuberculosis: a comparative study. Med J Malaysia. 2011; 66(4): 318–321.
79. Hussaini J, Mutusamy S, Omar R, *et al.* Base of tongue tuberculosis: a case report. Acta Med Iran. 2012; 50(2): 151–152.
80. Ismail Y, Muhamad A. Protean manifestations of gastrointestinal tuberculosis. Med J Malaysia. 2003; 58(3): 345–349.
81. Praveen S, Razman J. The TB-Crohn's affair- a never ending dilemma. Med J Malaysia. 2008; 63(3): 259–260.
82. Karuppannan M, Noorizan AA, Abdul Razak M. Is computed tomography (CT) scan a rational indicator to initiate tuberculosis treatment in patient with tuberculous peritonitis? A case report. Malaysian J. Pharm. Sci. 2004; 2(2): 23.
83. Leong DK, Chan KW, Ramu P, *et al.* Tuberculosis of gallbladder with candidiasis, a rare entity. Med J Malaysia. 2011; 66(2): 146–147.
84. Momin RN CV. Oesophageal tuberculosis: rare but not to be forgotten. Singapore Med J. 2012; 53(9): e192–4.
85. Aminuddin CA, Samsudin OC, Shukur MH. Tuberculous bursitis around the knee mimicking benign tissue tumour. Int. Med. J. 2004; 3(1).

86. Mah ESL, Bux SI. Tuberculous synovitis of the knee with unusually thick synovial granulation tissue: a case report. Internet J. Orthop. Surg. 2007; 6(2).
87. Ong PS, Wahinuddin S. Osteoarticular tuberculosis mimicking rheumatoid arthritis. Mod Rheumatol. 2012; 22(6): 931–933.
88. Anand A, Sood LK. Isolated tuberculosis of talus without ankle and subtalar joint involvement. Med J Malaysia. 2002; 57(3): 371–373.
89. Pan KL, Ibrahim S. Tuberculosis of the distal end of the radius mimicking a giant-cell tumour. Med J Malaysia. 2000; 55(Suppl C): 105–106.
90. Rohana AG, Norasyikin AW, Suehazlyn Z, *et al.* A case of persistent hyponatremia due to reset thermostat. Med J Malaysia. 2006; 61(5): 638–640.
91. Shalini B, Wahinuddin S, Monniaty M, *et al.* Ewing's sarcoma mimicking tuberculosis - a case report. Malays J Med Sci. 2002; 9(1): 52–54.
92. Azali HY, Norly S, Wong LM, *et al.* Liver abscess caused by tuberculosis and meliodosis. Asian J Surg. 2007; 30(2): 138–140.
93. Jarmin R, Alwi RI, Shaharudin S, *et al.* Common bile duct perforation due to tuberculosis: a case report. Asian J Surg. 2004; 27(4): 342–344.
94. Guru K, Yahya M. It's aneurysmal, it's stenotic, its tuberculosis. Med J Malaysia. 2011; 66(5): 515–516.
95. Hussein H, Azizi ZA. Tuberculous aortic pseudoaneurysm treated with in situ silver-impregnated vascular inlay graft. Asian J Surg. 2008; 31(2): 87–89.
96. Mahyudin M, Choo MM, Ramli NM, *et al.* Ocular tuberculosis intially presenting as central retinal vein occlusion. Case rep Ophthalmol. 2010; 1(1): 30–35.
97. Ooi YL, Tai LY, Subrayan V, *et al.* Combined optic neuropathy and central retinal artery occlusion in presumed ocular tuberculosis without detectable systemic infection. Ocul Immunol Inflamm. 2011; 19(5): 370–372.
98. Hah YK, Ang EL, Zunaina E, *et al.* An uncommon presentation of ocular tuberculosis. Int. Med. J. 2006; 13(3): 199–201.
99. Nor-Masniwati S, Zunaina E, Azhany Y. Ocular tuberculosis with multiple cerebral abscesses. Case Rep Ophthalmol Med. 2012; 606741.
100. Kok HS, George TM, Bastion CM, *et al.* Two cases of retinal vasculitis in ocular tuberculosis involving different parts of the vascular system. Med. Health. 2006; 1(1): 91–93.
101. Norazizah MA, Wan Hazabbah, Rohaizan Y *et al.* Isolated optic neuritis secondary to presumed tuberculosis in an immunocompetent child. Med J Malaysia. 2012; 67(1): 102–104.
102. Norliza W, Muda W, Hashim SE, *et al.* Reactivation of ocular tuberculosis in a young immunocompetent patient. Int. Med. J. 2007; 14(1): 45–47.
103. Hamizah R, Rohana AG, Anwar SA, *et al.* Splenic tuberculosis presenting as pyrexia of unknown origin. Med J Malaysia. 2007; 62(1): 70–71.
104. Imisairi AH, Hisham AN. Adrenal tuberculosis: the atypical presentations of eggshell-like calcifications. ANZ J Surg. 2009; 79(6): 488–489.
105. Ketan SH. Pancreatic tuberculosis in HIV positive patient: a case report. Borneo J. Med. Sci. 2010; 4.
106. Tan LH, Kamarulzaman A, Liam CK *et al.* Tuberculin skin testing among healthcare workers in the University of Malaya Medical Centre, Kuala Lumpur, Malaysia. Infect Control Hosp Epidemiol. 2002; 10: 584–590.
107. Kasthoori JJ, Liam CK, Wastie ML. Lady Windermere Syndrome: an inappropriate eponym for an increasingly important condition. Singapore Med J. 2008; 49(e47-9).
108. Loh LC, Chan SK, Ch'ng KI, Tan LZ, Vijayasingham P, Thayaparan T. Influence of co-morbidity in the interpretation of tuberculin skin reactivity in multi-ethnic adult patients with tuberculosis. Med J Malaysia [Internet]. 2005 Oct;60(4):426–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16570703
109. Ganeswrie R, Chui CS, Balan S, *et al.* Comparison of BACTEC MGIT 960 syste and BACTEC 460 TB system for growth and detection of Mycobacteria from clinical specimens. Malays J Pathol. 2004; 26(2): 99–103.
110. Kooi ES, Mahayidin M. Pulmonary tuberculosis in HIV infection: the relationship of the radiographic appearance to CD4 T-lymphocytes count. Malays J Med Sci. 2001; 8(1): 34–40.
111. Fadzilah MN, Ng KP, Ngeow YF. The manual MGIT system for the detection of M. tuberculosis in respiratory specimens: an experience in the University Malaya Medical Centre. Malays J Pathol. 2009; 31(2): 93–97.
112. Salleh SA, Hussin S, Rahman MM. Nested PCR for the rapid detection of TB from pleural fluid at HUKM Malaysia. Pak J Biol Sci. 2008; 11(13): 1728–1732.
113. Ahmad Hata R, Ibrahim SF, Wong CC. The role of polymerase chain reaction (PCR) in diagnosis of spinal tuberculosis afer pre-operative anti-tuberculosis treament. Malaysian Orthop. J. 2011; 5(1): 8–12.
114. Tan SC, Harwant S, Selvakumar K, *et al.* Predictive factors in the evolution of neural deficit in tuberculosis of the spine. Med J Malaysia. 2001; 56(Suppl C): 46–51.
115. Selvarajah VS, Samudram S, Chua LT, *et al.* Efficacy of anti-tuberculosis treatment alone on reslution of tuberculosis pleural effusions. IeJSME. 2007; 2: 30–33.
116. Puraviappan P, Tang IP, Yong DJ, *et al.* Endoscopic, endonasal decompression of spinal stenosis with myelopathy secondary to cranio-vertebral tuberculosis: two cases. J Laryngol Otol. 2010; 124(7): 816–819.
117. Liam CK. Risk of tuberculosis to healthcare workers. Med J Malaysia. 2001; 56(1): 107–111.
118. Nik MR, Mohd NS, Wan Mohammad Z, *et al.* Factors associated with unsuccessful treatment outcome of pulmonary tuberculosis in Kota Bharu, Kelantan. Malaysian J. Pharm. Sci. 2011; 11(1): 6–15.
119. Redha S, Suresh RL, Subramaniam J, *et al.* Pancreatic tuberculosis presenting with recurrent acute pancreatitis. Med J Malaysia. 2001;56(1):95–97.
120. Awaisu N, Nik Mohamed MH, Mohamad Noordin N, *et al.* The SCIDOTS Project: evidence of benefits of an integrated tobacco cessation intervention in tuberculosis care on treatment outcomes. Subst Abus. Treat Prev Policy. 2011; 6: 26–597X–6–26.
121. Al-Darraji HA, Kamarulzaman A, Altice FL. Isoniziazid preventive therapy in correctional facilities: a systematic review. Int J Tuberc Lung Dis. 2012; 16(7): 871–879.
122. Tan AK, Mallika PS, Aziz S, *et al.* Ethambutol ocular toxicity in a patient with pulmonary tuberculosis - a case report. Malaysian Fam. Physician. 2008; 3(2): 87–90.
123. Azhar Shah S, Md Idris MN, Abdul Hadi HS *et al.* Usage of GIS application for tuberculosis control in Cheras, Kuala Lumpur, malaysia. Malaysian J. Public Heal. Med. 2002; 2(2): 15–26.
124. Vitus S, Dhanaraj P, Zaitun Y, *et al.* Is pulmonary tuberculosis case properly identified in Lahad Datu? A clinical audit in 2003. Malaysian J. Pharm. Sci. 2004; 2(2): 43.
125. O'Boyle SJ, Power JJ, Ibrahim MY, *et al.* Factors affecting patient compliance with anti-tuberculosis chemotherapy using the directly observed treatment, short-course strategy (DOTS). Int J Tuberc Lung Dis. 2002; 6(4): 307–312.
126. Tan L KA. Preventing tuberculosis in healthcare workers of the radiology deparment: a Malaysian perspective. Biomed Imaging Interv J. 2006; 2(1): e3.
127. Adyani MR, Noorizan AA, Yahaya H, *et al.* Sudden onset of anti-tubeculosis drug-induced hepatotoxicity in a critically ill patient. Malaysian J. Pharm. Sci. 2004; 2(2): 22.