World Journal of Medical Sciences 10 (3): 285-294, 2014
ISSN 1817-3055

DOI: 10.5829/idosi.wjms.2014.10.3.837

Prevalence and Associated Factors with Transmission of Latent Tuberculosis among Household Contacts of Multi-Drug Resistant Tuberculosis Patients in Malaysia

[1]Omar Salad Elmi, [2]Habsah Hasan, [1]Sarimah Abdullah,
[3]Mat Zuki Mat Jeab, [4]BA Zilfalil and [1]Nyi Nyi Naing

[1]Unit of Biostatistics and Research Methodology, School of Medical Science,
Universiti Sains Malaysia, Health Campus 16150, KubangKerian, Kelantan, Malaysia
[2]Department of Medical Microbiology and Parasitology, School of Medical Science,
Universiti Sains Malaysia, Health Campus 16150 KubangKerian, Kelantan, Malaysia
[3]Respiratory Unit, Department of Medicine,
Hospital Raja Perempuan Zainab II Kota Bharu, Kelantan, Malaysia
[4]Department of Paediatrics, School of Medical Science, Universiti Sains Malaysia,
Health Campus, 16150 KubangKerian, Kelantan, Malaysia.

Abstract: Contact investigations are extremely important components that involved effectiveness of tuberculosis (TB) control programs. Close contacts of multi-drug-resistant tuberculosis (MDR-TB) cases, such as household members, are most likely to become infected because of intense and/or prolonged exposure to index cases. Thus, these contacts are highly recommended to be diagnosed. This study was designed to determine the prevalence and associated factors with the transmission of latent TB infection among household contacts of index cases in Malaysia. A cross-sectional study was conducted among household contacts of index cases who attended at three Respiratory Specialist Clinic and those who warded at six Hospitals in Peninsular West Malaysia. Blood samples were collected using QFT-G tubes. An ELISA machine was performed for tests and the result was calculated using QFT-GIn-Tube software. Data were analyzed by multivariate analysis. A total of 139 participants were enrolled in this study, comprised 69 index cases and 70 household contacts. The index cases comprised 46 (66.7%) males and 23 (33.3%) females, with mean age and SD of 41.78 (17.1 years. By contrast, the household contacts include 38 (54.3%) females and 32 (45.7%) males, with mean age and SD of 36.12 (16.88) years. The overall prevalence of LTBI was 52.8% (95%CI, 0.405 and 0.649). The significant associated factors with LTBI transmission were sputum smear positive (forAFB) [AOR:6.09,95% CI:(1.40, 26.45), (P<0.016)] and cough presence [AOR: 0.15,95%CI:(0.03, 0.62), (P<0.009)]. The prevalence of LTBI among the household contacts of index cases in Malaysia is relatively high. Cough presence and sputum smear positive were significant factors associated with LTBI transmission among household contacts. The strengthening of infection control is very crucial and should be immediately adopted to prevent or reduce TB transmission within the community

Key words: Prevalence · LTBI · Factors Associated · Mdr-Tb Or Xdr-Tb · Malaysia

INTRODUCTION

Multi-drug-resistant tuberculosis (MDR-TB) is the major public health problem worldwide and it is a significant concern of national tuberculosis control programs in both developed and developing countries [1] In Malaysia, the re-emergence of MDR-TB or XDR-TB and TB/HIV co-infection is increasing because of TB transmission. Similar to other developing countries, TB is still a great public health concern in

Corresponding Author: Omar Salad Elmi, Unit of Biostatistics and Research Methodology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
Tel: +60173721347, Fax: +609-7653370.

Malaysia and the second most frequent cause of death despite preventive and control measures have been taken [2, 3].

The incidence rate of TB in Malaysia has increased by around 58.7 to 65.6 per 100,000 people in the last decade. The number of TB cases detected annually is relatively higher than the reported incidence of HIV in Malaysia. In addition, the Malaysian Ministry of Health reported an average of 18,500 cases between 2007 and 2010 and about 20,666 new TB cases were registered in 2011 [4].

Latent TB infection (LTBI) is a condition in which a person is infected with *Mycobacterium tuberculosis* but does not have any clinical or radiographic evidence of an active disease [5]. The organism resides within the host in a clinically inactive or latent state, contained by the host immune response but is at risk of progression to active disease [6, 7].The risk of LTBI and active TB in household contacts is well established,household contacts and healthcare workers are still recognized as a high-risk group for LTBI [8].For persons with untreated LTBI and intact immunity, the estimated risk of developing TB is 5% to 10% over a lifetime, with about 50% to 80% of that risk occurring during the first two years following infection. For persons who are immunocompromised by HIV co-infection, the risk of developing the disease increases by 5% to 10% per year [9].

Contact investigation is recommended as a strategy by the International Union Against Tuberculosis and Lung Disease and the World Health Organization and is a valuable tool for identifying new TB cases and preventing disease transmission among household contacts [10-12].LTBI is detected by a standardized intradermal skin test called tuberculin skin test (TST) or by a blood test (QuantiFERON-Gold®, Gold In-Tube, or T-Spot TB). For decades, TST has been the gold standard for screening LTBI, which is both advantageous and disadvantageous, is well documented [13, 14]. QuantiFERON-TB Gold In-Tube (QFT-G) is a new tool for screening LTBI and recommended for use in low- and medium-income countries [15, 16]. WHO has been published recommendations against their used in low- and medium-income countries as an aid for detecting LTBI and active TB [16].

Therefore, the individual household contacts of index cases that are newly or previously diagnosed with MDR-TB or XDR-TB and considered to be a high-risk group infected with the disease should be screened. Identifying the factors associated with TB transmission and treating those at higher risk of TB are recommended, which play a key role in the identification of LTBI and essential for the elimination of TB. Detecting LTBI is fundamental to infection control programs in a community.

Determining LTBI provides an opportunity to treat and prevent the reactivation of latent infection, which leads to an active disease. This process may also aid in the early diagnosis and prevention of further TB transmission [9]. However, published data on LTBI in Malaysia using QFT-G are still insufficient. Therefore, this study was aimed to determine the prevalence and associated factors with LTBI transmission among household contacts of index cases in Malaysia

MATERIALS AND METHODS

Study Population: A cross-sectional study was conducted among household contacts of MDR-TB or XDR-TB index cases who were wardedat six Hospitals and those who were attended at three respiratory specialist chest clinics from six states in peninsular West Malaysia: Kelantan, Perak, PulauPinag, Johor Baru and Wilayah Persekutuan (Kuala Lumpur). Study recruitment was conducted between May 2012 and April 2013.

Case Identification and Data Collection: In Malaysia, all MDR-TB or XDR-TB index cases are required to be reported to the MDR-TB registry of the TB and respiratory specialist chest clinic or hospitals under the Tuberculosis Information System (TBIS). A list of all index cases with pulmonary and extra-pulmonary MDR-TB or XDR-TB was obtained from the National Public Health Laboratory Center (NPHL) in Sungai Buloh, Selangor, Malaysia. The NPHL is a national referral laboratory and the only laboratory in Malaysia that performs drug susceptibility testing (DST) against first- and second-line anti-TB drugs. All cases were confirmed to have MDR-TB or XDR-TB by culture positive as in the DST.This list was cross-checked with the TBIS MDR-TB registry.

Definition of Operational Term:

***LTBI*:** Was defined as positive QFT-G in the absence of TB, with no previous or current treatment of TB.

The degree of *household contact* was defined as family or friends, who live in the same house, slept on the same bed, stayed in the same room, or usually shared meals with index cases.

***MDR-TB*:** Was defined as a strain of *M. tuberculosis* resistant to at least two of the most effective first-line drugs (Isoniazid and rifampicin) the most effectiveness ant-TB drug.

***Extensive Drug Resistant-Tuberculosis (XDR-TB)*:** Was defined as TB caused by the strain of *M. Tuberculosis* that is resistant to at least two first line drug and second line fluoroquinolone and among a second line injectable drugs either (Amikacin, kanamycin or capreomycin).

***Index Cases*:** Was defined as MDR-TB or XDR-TB confirmed cases.

The index cases included in this study were cases diagnosed from January 2010 to May 2012 were treated at three respiratory specialist chest clinic and/or those admitted to six hospitals within peninsular Malaysia.

All cases who were under treatment, defaulted treatment, defaulted follow-up, or died during the period of study were included. Exclusion criteria included unconfirmed cases based on laboratory testing, those who were not registered in TBIS and those treated at a private hospital or clinic. Data was collected using a newly structured data form questionnaire that covered the scope of the study.

Socio-demographic characteristics, such as age, gender, race, marital status, level of education, living condition, occupation, monthly income and information on whether the index cases were recipients of comprehensive social security allowance, were documented. Information retrieved from the medical records of index cases includes history of previous TB infection, contact with TB patients, individuals with COPD and smoking status. Information on clinical risk factors associated with the development of LTBI of the index status, such as cavitation status, HIV infection, sputum smear status, culture status, cough presence and duration of cough, was documented.

Identification of Household Contacts and Data Collection: The household contacts of the index cases were identified via the medical records of the index cases and through interviews. All household contacts, such as family and friends who live in the same house with the index cases, were included in the study. Unrelated household contacts, such as those who came for a visit and/or were not staying in the same house with the index cases, were excluded from the study. Household contacts who had other medical conditions or serious illness that might affect the results of the study (QuantiFERON-TB Gold test), such as those who had end-stage renal failure, organ transplantation, advanced-stage cancer, systemic lupus erythematous, advanced heart diseases (e.g., heart failure and myocardial infarction) and frequent anemia, were also excluded from the study.

Eligible household contacts who agreed to participate in the study were requested to visit the nearest specialist chest clinic or hospital. Participation in this study was on a voluntary basis. All household contacts were informed about the study. Written informed consent was obtained from all the participants who were willing and confirmation was obtained before enrolment in the study. In the case of children, parental consent was obtained.

All available household contacts were asked to provide, blood samples for LTBI test. Peripheral blood (3 cc) was drawn from the participants by a professionally qualified staff from hospitals.

Interferon Gamma Assay (IFN-γ Assay): QuantiFERON®-TB Gold In-Tube (Cellestis Limited, Carnegie,Victoria,Australia was used it). The QFT-G was purchested from ALLEIGH company branch in Malaysia.Principle: The test was based on the release of interferon gamma by sensitized lymphocytes when exposed to antigen of mycobacterium tuberculosis [13].

Steps of Protocol: Blood collection: Blood samples was collected via three different QuentiFERON TB gold in tube, which included a TB antigens (ESAT-6, CFP-0 and TB 7.7) tube, a mitogen (phytohemagglutinin) tube and a negative control tube. The content of each tube was mixed by shaking the tubes vigorously for 5 seconds or 20 times to ensure that the entire inner surface of the tube is coated with blood. Afterward, within a maximum of 6 hr of collection, all samples were immediately brought to the microbiology laboratory. The tubes were incubated at 37°C for 16 h to 24 h. The tubes were centrifuged and plasma was collected and frozen at -70°C or -80°C. After sample collection, the samples were tested in batches of 28 samples per plate by an ELISA machine and interpreted by QFT-G software analysis according to the manufacturer's protocol.

Tuberculin Skin Test: (TST) was done by trained health care workers according to International guidelines (17). All the household contact were traced and asked to come to the nearest health care centrs or hospitals and home visit was done for participants who did not return for TST reading principlally.

Purified protein derivative (PPD), a solution of protein derivative of *Mycobecterium. Tuberculosi*is injected into inner surface of the for earm. Then the delayed-type hypersensitivity response to the PPD is measured at from 48 to 72 hours after injection. Of protocol: 0.1 ml of PPD containing 5 tuberculin units is injected into the inner surface of the forearm, normally in

an area free of lesion and away from veins. After 72 hours of injection, the reaction was read based on the area of duration around the site of injection. LTBI infection is defined as positive skin test: 10 mm is regarded as positive.

All important demographic characteristics were collected from all adults and children living in the same household who agreed to participate in this study. The relationship and close proximity of the household contacts with the index cases and other related variables of TB transmission were also identified. All necessary information was retrieved by a single researcher.

Age, gender, race, marital status, level of education, living condition, occupation, monthly income, whether they were recipients of comprehensive social security allowance and, BCG vaccine were documented. Closeness and information related to the household contacts of the index cases included relationship to the index (spouse/child or others), sharing of the same bedroom but not the same bed, sleeping in different rooms, the number of people living in the same house, the number of rooms in the house and gender of contact were recorded.

Statistical Analysis: Data analysis and entry was done by using Statistical Package for Social Sciences (SPSS) version 20.0. Descriptive analysis was presented as mean and SD and For categorical variables, the data was presented as frequency (n) and percentage (%). Pearson chi-square test or Fisher's exact test was applied to determine the differences of proportion for both group between close proximity of household contact and index cases. Univariable and Multivariable analysis were used to determine the potential factors associated with development of LTBI transmission among huosehold contacts. The results were presented by appropriate tabulations based on the determined variables, regression with coefficient, crude or adjusted odds ratio with 95% confidence interval (CI) and its corresponding p-values.

Ethical Approval: The ethical clearance was obtained from the Human Ethics Committee at Hospital Universiti Sains Malaysia and the Medical Research Ethics Committee (MREC) in the Ministry of Health Malaysia. Confidentiality and privacy of information of the study participants were essured.

RESULTS

A total of 85 index cases were recruited to this study. However, only 69 participants were included in the final analysis because four cases travelled out of state during the study recruitment and 13 cases were either homeless or their household contacts refused to participate in the study. Table 1 showed the demographic characteristics of the index cases. The mean age and SD was 41.78 (17.13) years. Index cases comprised 46 (66.7%) males and 23(33.3%) females. Most of the index cases were Malay 40(58.0%), followed by foreigners 16(23.2%). The highest education was secondary school 22 (31.9%), 26 (37.7%) participants were unemployed and the family income of 33 (47.88%) participants was less than RM 675. Participants with history of TB infection, history of contact with someone infected with TB, smoking status and individuals with COPD were 34 (49.3%), 34 (49.3%), 34 (49.3%) and 10 (14.5%), respectively.

Table 2 showed the demographic characteristics of the household contacts. A total of 78 household subjects were contacted and invited to participate in this study, but only 70 household contacts participated. However, eight household contacts refused to provide blood samples and withdrawn from the study.

A total of 38 (54.3%) females and 32 (45.7%) males were included, with mean age and SD were 36.12 (16.88) years. The highest education was secondary school 22 (31.9%), 26 (37.7%) were unemployed participants and 33 (47.8%) household contacts have family income less than RM 675.The overall prevalence of LTBI among the household contacts of index cases was 52.8 % (95%CI, 0.405%, 0.649%), whereas that of the non-LTBI was 38.5% (95% CI, 0.272%, 0.495%). An undetermined result of this study was 4.0% (95% CI, 0.15% and 0.139%) with non-LTBI and 2.0% (95% CI, 0.003% and 0.077%) with LTBI patients. The majority of LTBI cases had no previous diagnosis of TB, 24.0% (95%CI 0.034, 0.099) for non-LTBI and 38% (95%CI 0.089%, 0.120%) for LTBI. Most of the LTBI cases had received BCG vaccination 31% (95%CI 0.03%, 0.09%).

The relationship between closeness with the index cases and the development of LTBI among the household contacts was presented in Table 3. Spouses and children 32(82.1%) with close relationships with the index cases were positive with QFT-G. Contacts who shared the same bedroom with the index cases were likely to be positive with QFT-G 33 (84.6%). The poor living conditions and

Table 1: Demographic characteristics of MDR-TB index cases (n= 69)

Variable	MDR-TB index cases n (%)	Mean SD
Age *		41.78(17.13)
Gender		
Female	23(33.3)	
Male	46(66.7)	
Race		
Indian	6(8.7)	
Chinese	7(10.1)	
Foreign	16(23.2)	
Malay	40(58.0)	
Marital Status		
Single	19(28.4)	
Married	47(70.1)	
Widowed	1(1.4)	
Educational level		
No formal education	5(7.2)	
Primary	5(7.2)	
Secondary	22(31.9)	
Diploma	7(10.1)	
Degree and above	5(7.2)	
Illiterate	1(1.4)	
Occupational level		
Government employee	5(7.2)	
Private employee	7(10.1)	
Self-employee /own account work	12(17.4)	
House wife	4(5.8)	
Unemployed	26(37.7)	
Income level		
≤RM 675	33(47.8)	
RM 675 to <RM1000	1(1.4)	
RM 1000 to < RM 2000	4(5.8)	
RM 2000 to <RM 3000	1(1.4)	
≥RM 3000	3(4.3)	
Living alone		
Did not live alone	56(94.9)	
Lived alone	3(5.1)	
Previous history of TB		
Absent	35(50.7)	
Present	34(49.3)	
Known TB contact		
Absent	35(50.7)	
Present	34(49.3)	
Smoking		
Did not smoke	35(50.7)	
Smoked	34(49.3)	
COPD		
Absent	59(85.5)	
Present	10(14.5)	

*Mean and SD

crowding of the people living in the same household as the contacts were observed in the majority. Houses had at least two rooms. However, no statistically significant correlation was observed among these variables.

Table 2: Demographic characteristics of LTBI and no LTBI among household contact of index case (n =70)

Variable	Non LTBII n (%)	With LTBI n (%)	*P*-Value
Gender			
Female	15(48.4)	23(59.0)	0.377[a]
Male	16(51.6)	16(41.0)	
Race			
Indian	2(6.5)	4(10.3)	0.913[b]
Chinese	3(9.7)	5(12.8)	
Foreign	13(41.9)	15(38.5)	
Malay	13(41.9)	15(38.5)	
Marital Status			
Single	8(25.8)	14(35.9)	0.266[a]
Married	23(74.2)	25(64.1)	
Widowed	0	1(2.7)	
Divorced	0	1(3.1)	
Educational level			
No formal education	3(9.7)	6(15.4)	0.715[b]
Primary	8(25.8)	10(25.6)	
Secondary	12(38.7)	17(43.6)	
Diploma	6(19.4)	3 (7.7)	
Degree and above	2(6.5)	2(5.1)	
Religious schooling only	0	1(2.6)	
Occupational level			
Government employee	2(6.5)	1(2.6)	0.930[b]
Private employee	9(29.0)	14(35.9)	
Self-employee /own account work	4(12.9)	4(10.3)	
House wife	5(16.1)	6(15.4)	
Unemployed	11(35.5)	14(35.9)	
Income level			
≤RM 675	20(64.5)	22(56.4)	0.973[b]
RM 675 to< RM1000	6(19.4)	7(17.9)	
RM 1000 to < RM 2000	3(9.7)	5(12.8)	
RM 2000 to <RM 3000	0	3(7.7)	
≥RM 3000	2(6.5)	2(5.1)	
QFT-G test[c]			
Positive	52(88.1)	38(94.5)	0.001[b]
Undetermined	4(12.9)	2(5.1)	
Previous history of TB			
Present	7(22.6)	1(2.6)	0.009[a]
Absent	24(77.4)	38(97.4)	
BCG[d]Scan Present			
Present	31(79.5)	21 (67.7)	0.264[a]
Absent	10(32.3)	8(20.5)	

[a]P -value For Chi- Square test was applied [b] P-value for Fisher Exact test was applied [d]QFT-G QuantiFERON-TB Gold In-Tube, [c]BCG, Bacillus Calmette–Guérin

Table 4 Simple logistic regression analysis and Multiple Logistic regression showed significant predictor variables, such as cough presence [OR: 0.03 95% CI: (0.05, 0.86), (P<0.030)] sputum smear positive for (AFB) [OR: 4.06 95% CI: (1.97, 16.91), (P<0.004)] and culture positive [OR: 5.25 95% CI: (1.00, 27.45), (P<0.049)].

Table 3: Relationship between theclose proximity characteristics with index case and development of LTBI (n= 70)

Variable	QFT-G Negative for LTBI n (%)	QFT-G Positive for LTBIn (%)	*P*-Value
Relationship to index patients			
Others	5(16.1)	7(17.9)	0.841[a]
Spouse / Child	26(83.9)	32 (82.1)	
Gender of Contact			
Female	10(32.3)	12(30.8)	1.000[b]
Male	20(64.5)	25(64.1)	
Both	1(3.2)	2(5.1)	
Contact share same bedroom			
Shared	23(74.2)	33(84.6)	0.279[a]
Did not shared	8(25.8)	6(15.4)	
Contact shared same bed			
Shared same bed	12(38.7)	12(30.8)	0.487[a]
Did not shared	19(61.3)	27(69.2)	
Contact slept in different bedroom			
Different	6(19.4)	9(23.1)	0.706[a]
Not different	25(80.6)	30(76.9)	
Number of people in the same house			
1	5(16.1)	3(7.7)	0.128[b]
2-3	2(6.5)	10(25.6)	
3-4	7(22.0)	10(25.6)	
>4	17(54.8)	16(41.0)	
Number of rooms in the house			
≤2	18(58.1)	26(65.7)	0.613[b]
2-3	7(22.6)	10(25.6)	
3-4	4(12.9)	2(5.1)	
≥4	2(6.5)	1(2.6)	

[a]P -value For Chi- Square test was applied

[b]P -value for Fisher Exact test was applied.

LTBI Latent Tuberculosis Infection

Table 4: Comparison between Simple logistic and Multiple Logistic Regression analysis an associated factor with development of LTBI among household in relation with clinical characteristics of index case (n=69)

		Simple Logistic Regression			Multiple Logistic Regression	
Variable	(b)	Crude OR (95%CI)	P- Value	(b)	Adjusted OR (95%CI)	*P*-Value
Sputum Smear Status[a]						
Negative	0	1	0.004	0	1	0.016
Positive	1.40	4.06(1.97, 16.91)		1.81	6.09(1.40, 26.45)	
Cough present						
Present	0	1	0.049	0	1	0.009
Absent	1.56	0.03(0.05, 0.86)		-1.92	0.15(0.03,0.62)	
Culture Status						
Negative	0	1	0.030			
Positive	1.66	5.25(1.00, 27.45)				

•Backward Step wise LR Multiple Logistic Regression was applied

•Multicolinearity and interaction term were checked and not reported.

•Hosmer - Lemeshow test, (p= 0.069) classification table (Overall correctly classified percentage (71.4%) and area under ReceiverOperating Characteristics (ROC) curve (70%) was to check the fit of the model.

•Regression Equation = Log (p/1-p)= $b_{0+} b_1*x_1+b_2*x_1$

[a] Odd Ration (OR)

[b] Regression coefficient

The most significant factors associated with LTBI transmission to household contacts. Multiple logistic regression analysis showed that sputum smear positive [AOR:6.09,95% CI:(1.40, 26.45), (P<0.016)] and cough presence [AOR: 0.15, 95%CI:(0.03, 0.62) (P<0.009)] were significantly associated factors with the LTBI transmission among the index cases.

DISCUSSION

Several studies have supported the strong effects of age and sex on the global incidence of TB [18, 19]. Young people were commonly affected by LTBI among household contacts. The present study also found that the mean age of the participants was 36.12 [16.88], consistent with a study that assessed LTBI among close household contacts of MDR-TB patients in central Taiwan [20]. A similar study was also reported among the household contacts of TB-infected cases in Uganda [21].

Gender difference was associated with TB infection and females were more likely to be infected with TB among the household contacts. However, males were more likely to develop MDR-TB than females, in case of MDR-TB woman was seen to be compliance with MDR-TB treatment [22]. The finding of this study noted that the female household contacts are the most affected, with similar studies reported in Taiwan among household contacts of MDR-TB and household contacts of TB cases in Uganda [20, 21].

TB is considered a disease of poverty because is associated with low-income population. However, the association between specific socio-economic factors and TB remains unclear [23]. Studies on these factors had been conducted among household contacts in Laos [24] and among adolescents in a high-burden region in South Africa [25]. Low socio-economic status, such as low-level of education, unemployment and low family income, is associated with LTBI transmission among household contacts. Also these factors have been found in greater proportion in this study, although it was notstatistically significant.

The present study interestingly observed that the overall prevalence of LTBI among the household contacts of index cases in Malaysia was 52.8 % (95%CI, 0.405%, 0.649%), whereas that of the non-LTBI was 38.5% (95% CI, 0.272%, 0.495%). Another study used TST and reported an LTBI prevalence of 26% to 36% among children living with TB patients, with lower prevalence compared to present results [25]. The proportion of LTBI among the household contacts in the current study is higher than that reported in a systematic review of studies in high- and middle-income countrieswherethe pooled prevalence was 47.2% (95% CI, 30.0% to 61.4%) [26]. Also lower prevalence rate (47.8%) was reported in Thailand [27]. By contrast, higher rates have been reported among the household contacts in Chang Rai (55.6%) [10] and the Philippines (69.2%) [28].

The following factors may have caused the low rates in our study: (i) low population density; (ii) low HIV prevalence; and (iii) other countries have higher rates of TB burden compared with Malaysia which is considered an intermediate TB burden country. Most previous studies have used TST to detect LTBI. However, TST had poor sensitivity to LTBI, especially in contacts with prevalence of HIV co-infection and vaccinated population. Our study used QFT-G, which is more sensitive and more specific than TST in LTBI detection. Low socio-economic status could be another factor associated with high LTBI.

The risk of TB infection depended on the duration of contact and the extent of exposure. TB infection usually depended on the following: length, frequent travelling and proximity of exposure; concentration of organisms expelled into the air from an infected person or index cases to the contacts; and the virulence of the organism. Therefore, household contacts whohadthese factors have a higher prevalence of LTBI.

This study demonstrated the associated factors with the development of LTBI among the household contacts of index cases and index status in Malaysia. The high prevalence of LTBI was associated with factors such as the close proximity (Such as spouse or children) between index and household contact. TB transmission occurs by contact, such as by sharing the same bedroom or sleeping in the same bedwith the index case. These factors were not found to be statistically significant in this study. This is may be due to small sample size.

Poor socio-economic living conditions and crowding are important factors for TB transmission in underdeveloped and developing countries [29]. In Guinea- Bisssau, adult overcrowding is a risk factor for TB [30]. In the current study, we used the number of persons per room as a measure of overcrowding and found that it was not a significant risk factor for LTBI among the household contacts of the index cases, contrary to previous reports in which overcrowding was reported as a significant factor for TB. The difference could be attributed to the different economic statuses of the countries.

Housing density as well as other environmental factors and TB incidence has been previously reported [31]. Clark *et al.* [31]suggested that TB incidence is high in communities with high average housing density. Communities with overcrowded housing also experience a high prevalence of LTBI. Risk factors associated with LTBI transmission and overcrowded housing conditions could increase the exposure of susceptible people to those with infectious respiratory diseases and the probability of transmission. Close proximity increase the probability for these individuals to come into contact with air contaminated with the bacteria that cause the infection [31, 32].

Multivariate analysisshowed that the significant factors associated with LTBI transmission among the household contacts in the present study were sputum smear positive(for AFB)[AOR:6.09,95% CI:(1.40, 26.45), (P<0.016)] and cough presence [AOR: 0.15, 94%CI:(0.03, 0.62) (P<0.009)]. The presence of AFB and cough in the index case were associated with a higher risk of LTBI infection among household contacts. A similar result has been reported elsewhere25]. However, smear positive has long been perceived as factor for TB transmission. Index cases with greater bacillary burdens as indicated by a positive sputum smear were more likely to transmit the infection and the risk of infection was particularly high among close contacts of infectious patients [6]. Patients with a smear positive can infect around 10 persons with the disease annually. Studies focused on TB transmission and identification of LTBI among contacts have found greater transmission of TB infection from patients with AFB positive, coughpresence, culture positive and TB/HIV co-infection.[33-36].Similar results were reported in a systematic review and meta-analysis [37].

The present study is primarily limited by its small data set and may not be representative of the whole Malaysian population as big as it. This condition was due to the low MDR-TB prevalence in the country. Additionally, examination of household contacts only at the time of diagnosis of the index patient already presents high risk of TB infection. Some data were missing from the clinical records of MDR-TB, suggested that proper documentation is highly important. Multivariable analysis showed a large confidence interval and a high odds ratio, perhaps it might be due to small sample size. Despite these limitations, the finding of this study suggests the crucial importance of contact investigation in filling the gap between the expected and diagnosed numbers of household contacts of index cases and in the identification of high-priority candidates of LTBI transmission and treatment in Malaysia. Adult's household contacts had a 10% to 15% chance of developing the disease in their lifetime. Therefore, given the insufficiency of data, this study explores the prevalence of LTBI among household contacts of index cases in Malaysia using QFT-G.

CONCLUSION

The prevalence of LTBI among household contacts of index cases in the present study was found to be high. Also the cough presence and sputum smear positive were significant factors associated with LTBI transmission among household contacts. Our study provides further arguments that contact tracing for TB control in developing countries is beneficial.Therefore, it is suggested that contact investigation among high risk group such as household contacts with index cases should be prioritized. Furthermore, increasingawareness of the infectiousness of TB within household contacts as well as the community and the general population is urgently needed. Index cases should be isolated from household contacts and immediate contact tracing should be conducted to prevent or reduce the transmission cycles and spread of the disease within the contacts and community.

Conflict Interest: All authors have declared that there is no any potential conflict of interest.

ACKNOWLEDGEMENT

The authors of this study wish to thank the Ministry of Health, Malaysia, particularly the officers and staff and all the Multi-Centre Healthcare /or Hospitals and Respiratory Specialist Chest clinics, in Peninsular Malaysia for their assistance during this study.. We would like to convey our deepest appreciation to all the participants who took part in this study. We would like to express our sincerest gratitude and thanks to Adamu Ahmed Rufa'i for his help in the completion of the proofreading for the final manuscripts. This study was supported by the Research University, Grant number 1001/PPSP812098 at the USM

REFERENCES

1. Huang, W.C., C.H. Chen, C.C. Huang, K.M. Wu, C.S. Chiou, C.F. Lin, J.H. Chen and G.H. Shen 2013. A reduction in anti-tuberculosis drug resistance after the implementation of the national "STOP TB" program in central Taiwan, 2003-2007. Jpn J. Infect. Dis., 66: 89-95.

2. MOH, 2008. Ministry of Health Malaysia. National tuberculosis control programme. Report Disease Control Division, Malaysia.
3. WHO, 2011. Global tuberculosis control.WHO report. 2011.
4. MOH, 2011. TB Surveillance report, 2011. in the Ministry of Health Malaysia.
5. Yamashita, Y., Y. Hoshino, M. Oka, S. Matsumoto, H. Ariga, H. Nagai, M. Makino, K. Ariyoshi and Y. Tsunetsugu-Yokota 2013. Multicolor flow cytometric analyses of CD4+ T cell responses to Mycobacterium tuberculosis-related latent antigens. Jpn J. Infect Dis., 66: 207-215.
6. Hauck, F., R.B.H. Neese, A.S. Panchal and W. El-Amin, 2009. Identification and management of latent tuberculosis infection. Am. Fam. Physician, 79: 879-86.
7. Taylor, Z., C.M. Nolan and H.M. Blumberg, 2005. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC and the Infectious Diseases Society of America.MMWR and CDC rep, l: 54, 1.
8. WHO, 2007. Chapter 4: childhood contact screening and management. Int. J. Tuberc. Lung. Dis., 11: 12-5.
9. CDC, 2013. Latent tubercuLosis infection: a Guide for Primary HeaLtH care Providers. CDC, pp: 3-35.
10. Morrison, Janina, Madhukar Pai and Philip C. Hopewell, 2008. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. The Lancet Infectious Diseases, 8: 359-368.
11. Denkinger, C.M., K. Dheda and M. Pai 2011. Guidelines on interferon-gamma release assays for tuberculosis infection: concordance, discordance or confusion? Clin Microbiol Infect 17: 806-814. DOI: 10.1111/j.1469-0691.2011.03555.x
12. Underwood, B.R., V.L. White, T. Baker, M. Law and J.C. Moore-Gillon 2003. Contact tracing and population screening for tuberculosis--who should be assessed? J. Public Health Med., 25: 59-61.
13. Mazurek, Gerald H., John Jereb, Phillip Lo Bue, Michael F Iademarco, Beverly Metchock and Andrew Vernon, 2005. Guidelines for using the QuantiFERON-TB Gold test for detecting Mycobacterium tuberculosis infection, United States. MMWr recomm rep 54: 49-55.
14. Takayanagi, K., M. Aoki, K. Aman, S. Mitarai, N. Harada, K. Higuchi, M. Okumura, T. Yoshiyama, H. Ogata and T. Mori 2011. Analysis of an interferon-gamma release assay for monitoring the efficacy of anti-tuberculosis chemotherapy. Jpn J. Infect. Dis., 64: 133-138.
15. Mori, T., M. Sakatani, F. Yamagishi, T. Takashima, Y. Kawabe, K. Nagao, E. Shigeto, N. Harada, S. Mitarai, M. Okada, K. Suzuki, Y. Inoue, K. Tsuyuguchi, Y. Sasaki, G.H. Mazurek and I. Tsuyuguchi, 2004. Specific detection of tuberculosis infection: an interferon-gamma-based assay using new antigens. Am J Respir Crit Care Med 170: 59-64. doi: 10.1164/rccm.200402-179OC.
16. Brock, I., K. Weldingh, T. Lillebaek, F. Follmann and P. Andersen, 2004. Comparison of tuberculin skin test and new specific blood test in tuberculosis contacts. Am J Respir Crit Care Med 170: 65-69. doi: 10.1164/rccm.200402-232OC.
17. Arnadottir, T., H.L. Rieder, A. Trebucq and H.T. Waaler, 1996. Guidelines for conducting tuberculin skin test surveys in high prevalence countries. Tuber Lung Dis., 77(Suppl 1): 1-19.
18. Crampin, A.C., J.R. Glynn, S. Floyd, S.S. Malema, V.K. Mwinuka, B.M. Ngwira, F.D. Mwaungulu, D.K. Warndorff and P.E. Fine 2004. Tuberculosis and gender: exploring the patterns in a case control study in Malawi. Int J. Tuberc Lung Dis., 8: 194-203.
19. Holmes, C., B.H. Hausler and P. Nunn, 1998. A review of sex differences in the epidemiology of tuberculosis.Int. J. Tuberc. Lung. Dis., 2: 96-104.
20. Huang, Y.W., G.H. Shen, J.J. Lee and W.T. Yang 2010. Latent tuberculosis infection among close contacts of multidrug-resistant tuberculosis patients in central Taiwan. Int J. Tuberc Lung. Dis., 14: 1430-1435.
21. Uwatudde, D., M. Nakakeeto, E.C. Jones-Lopez, A. Maganda, A. Chiunda, R.D. Mugerwa, J.J. Ellner, G. Bukenya and C.C. Whalen, 2003. Tuberculosis in household contacts of infectious cases in Kampala, Uganda. American Journal of Epidemiology, 158: 887-898.
22. Drobniewski, F., I. Eltringham, C. Graham, J.G. Magee, E.G. Smith and B. Watt, 2002. A national study of clinical and laboratory factors affecting the survival of patients with multiple drug resistant tuberculosis in the UK. Thorax, 57: 810-816.
23. Harper, M., F.A. Ahmadu, J.A. Ogden, K.P. McAdam and C. Lienhardt, 2003. Identifying the determinants of tuberculosis control in resource-poor countries: insights from a qualitative study in The Gambia. Trans R Soc. Trop. Med. Hyg., 97: 506-510.

24. Mahomed, H., T. Hawkridge, S. Verver, L. Geiter, M. Hatherill, D.A. Abrahams, R. Ehrlich, W.A. Hanekom and G.D. Hussey, 2011. Predictive factors for latent tuberculosis infection among adolescents in a high-burden area in South Africa. Int J. Tuberc Lung Dis., 15: 331-336.
25. Nguyen, T.H., P. Odermatt, G. Slesak and H. Barennes, 2009. Risk of latent tuberculosis infection in children living in households with tuberculosis patients: a cross sectional survey in remote northern Lao People's Democratic Republic. BMC Infect Dis., 9: 96. doi: 10.1186/1471-2334-9-96.
26. Shah, N.S., C.M. Yuen, M. Heo, A.W. Tolman and M.C. Becerra, 2013. Yield of Contact Investigations in Households of Patients With Drug-Resistant Tuberculosis: Systematic Review and Meta-Analysis. Clin Infect Dis., doi: 10.1093/cid/cit643.
27. Tornee, S., J. Kaewkungwal, W. Fungladda, U. Silachamroon, P. Akarasewi and P. Sunakorn, 2004. Risk factors for tuberculosis infection among household contacts in Bangkok, Thailand. Southeast Asian J. Trop. Med. Public Health, 35: 375-383.
28. Salazar, G.E., T.L. Schmitz, R. Cama, P. Sheen, L.M. Franchi, G. Centeno, C. Valera, M. Leyva, S. Montenegro-James, R. Oberhelman, R.H. Gilman and M.J. Thompson, 2001. Pulmonary tuberculosis in children in a developing country. Pediatrics, 108: 448-453.
29. Liu, J.J., H.Y. Yao and E.Y. Liu, 2004. Relationship between tuberculosis prevalence and socio-economic factors in China.Zhonghua Liu Xing Bing Xue Za Zhi, 25: 1032-4.
30. Gustafson, P., V.F. Gomes, C.S. Vieira, P. Rabna, R. Seng, P. Johansson, A. Sandstrom, R. Norberg, I. Lisse, B. Samb, P. Aaby and A. Naucler 2004. Tuberculosis in Bissau: incidence and risk factors in an urban community in sub-Saharan Africa. Int. J. Epidemiol., 33: 163-172. DOI: 10.1093/ije/dyh026.
31. Clark, M.P. Riben and E. Nowgesic, 2002. The association of housing density, isolation and tuberculosis in Canadian First Nations communities. Int. J. Epidemiol., 31: 940-5.
32. Sepkowitz, K.A., 1996. How contagious is tuberculosis. Clin. Infect. Dis., 23: 954-62.
33. Wells, C.D. and L.J. Nelson, 2004. New international efforts in childhood tuberculosis: proceedings from the 2002 Workshop on Childhood Tuberculosis, Montreal, Canada, 6-7 October 2002. Int. J. Tuberc. Lung. Dis., 8: 630-5.
34. Kritsk, A., 1996. Management of TB contacts in Brazil: is it a priority? Symposium. Investigation of Contacts to Tuberculosis Cases. Department of Public Health Bureau of TB Control.New York City, l: 7-8.
35. Shaw, J.B. and N.Wynn-Williams, 1954. Infectivity of pulmonary tuberculosis in relation to sputum status.Am. Rev. Tuberc., 69: 724-32.
36. Snider, D.E. Jr., G.D. Kelly, G.M. Cauthen, N.J. Thompson and J.O. Kilburn, 1985. Infection and disease among contacts of tuberculosis cases with drug-resistant and drug-susceptible bacilli.Am. Rev. Respir. Dis., 132: 125-32.
37. Morrison, J.M. Pai and P.C. Hopewell, 2008. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. Lancet. Infect. Dis., 8: 359-68.