TRANSMISSION AND RISK FACTORS FOR LATENT TUBERCULOSIS INFECTIONS AMONG INDEX CASE-MATCHED HOUSEHOLD CONTACTS

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Abstract. An understanding of the risk factors associated with acquiring and transmitting *Mycobacterium tuberculosis* (MTB) is required for controlling tuberculosis (TB). We aimed to determine the risk factors and transmission factors for latent tuberculosis infection (LTBI) in northeastern Thailand. Household contact persons ($n = 70$) and matched index patients with pulmonary TB ($n = 42$) who presented to Srinagarind Hospital, Khon Kaen, Thailand were interviewed from September 1, 2012 to March 31, 2014. LTBI was determined by positive results on both a tuberculin skin test and the QuantiFERON®-TB Gold In-Tube test. Multivariate analysis of host and environmental risk factors was performed. Among contact persons, being aged ≥20 years (adjusted OR=14.0; 95% CI: 1.2-159.5), having a family relationship with a TB subject such as being a spouse or parent (adjusted OR=24.9; 95% CI: 2.4-263.9) and exposure to a TB subject for ≥ 5 hours/day (adjusted OR=9.2; 95% CI: 1.4-58.1) were risk factors for LTBI. Having a high bacillary load (adjusted OR=2; 95% CI: 1.26-3.17) or a moderate bacillary load (adjusted OR=1.39; 95% CI: 1.04-1.84) among TB subjects correlated with increased transmissibility compared to having a low bacillary load. The type of dwelling and density of household members were not found to be risk factors for LTBI in our study. We conclude being aged ≥20 years and having a relationship with a TB patient as a spouse or parent were risk factors for acquiring LTBI, and having a higher bacillary load was a risk factor for transmitting TB.

Keywords: latent tuberculosis infection, transmission factor, risk factor, *Mycobacterium tuberculosis*, interferon-gamma release assay, Thailand

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB) and transmitted by aerosol droplets.

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An understanding of the factors that affect the transmission of MTB could inform TB prevention and control programs. Several studies have reported the risk factors for latent TB infection (LTBI) (Franchi *et al*, 2009; Nguyen *et al*, 2009; Ringshausen *et al*, 2009; Rafiza *et al*, 2011; Goswami *et al*, 2012). Healthcare workers and close patient contacts are the most frequently studied populations (Franchi *et al*, 2009; Nguyen *et al*, 2009; Ringshausen *et al*, 2009; Rafiza

et al, 2011; Goswami *et al*, 2012). However, few studies have analyzed the risk factors among TB subjects and their household close contacts and environmental factors simultaneously. Many studies in Thailand have determined risk factors for LTBI (Hiransuthikul *et al*, 2003; Tipayamong-kholgul *et al*, 2005; Tornee *et al*, 2005), but none of these studies have employed the interferon-gamma release assay (IGRA) to avoid false-positive results due to prior BCG vaccination.

The aim of this study was to determine the transmission factors for MTB among index cases and household close contacts using index case-matched close contact person analysis. Environmental factors associated with index cases and their close contacts were also analyzed.

MATERIALS AND METHODS

Study design and population

This was a cross sectional prospective study conducted between September 1, 2012 and March 31, 2014. One hundred twelve subjects with active pulmonary TB (*n* = 42) and their close contacts (*n* = 70), were selected from 154 subjects enrolled in the study. The subjects provided written informed consent and underwent a physical examination. Demographic data and host risk factors were collected using TB risk assessment forms. Blood samples were collected from the subjects for IGRA and a tuberculin skin test (TST) was performed. This study was approved by the Research Ethics Committee (HE551101) for Khon Kaen University.

Inclusion and exclusion criteria

Subjects with symptomatic pulmonary TB (having an abnormal chest x-ray consistent with TB and having a chronic cough or weight loss) who had positive sputum for acid-fast bacilli (AFB) or a positive Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA) on sputum or a sputum culture for MTB and who had not yet begun TB treatment or who had received treatment for ≤2 weeks were defined as "active TB subjects" (ATB subjects). A relative or household member who lived with an ATB subject for ≥2 weeks before and during TB treatment was defined as a "close contact" (CC). ATB subjects were excluded if they were HIV-positive or had received an immunosuppressive agent. CC were excluded if they progressed to ATB, became HIV-positive, received an immunosuppressive agent or tested positive on a TST within 3 weeks of recruitment.

Classification of bacillary load among TB subjects

ATB subjects were classified into three groups based on criteria published previously (Faksri *et al*, 2014). Briefly, the bacillary load was categorized as being low, moderate or high based on sputum AFB grading and chest x-ray findings. A sputum smear sample with 3+ AFB, a chest x-ray with miliary lesions or bilateral lesions on chest x-ray with a sputum smear sample with 1+ or 2+ AFB were categorized as having a high bacillary load. A sputum smear for AFB that was scantily positive or those with a negative sputum smear for AFB but who had a positive culture or PCR test for TB and minimal lesions on chest x-ray with no cavitary lesions were categorized as having a low bacillary load. Other positive findings for TB on chest x-ray or sputum AFB grading were categorized as having a moderate bacillary load.

Definitions of transmitting TB subjects and LTBI household contacts

A transmitting subject was defined as an ATB subject who caused at least one

CC to become infected with TB. A non-transmitting subject was defined as an ATB subject who caused no CC to become infected with TB. CC with positive IGRA and TST were defined as LTBI or infected cases. CC with negative IGRA and TST were defined as uninfected cases. CC with discordant IGRA and TST test results were excluded from the study.

IGRA and TST procedures

The QuantiFERON®-TB Gold In-Tube (QFT-GIT) IGRA was performed according to the manufacturer's instructions (Mazurek and Villarino, 2003). Briefly, venous blood samples were obtained from all study subjects and placed in three 1 ml tubes. The samples were mixed and incubated at 37°C for 21 hours. After incubation, the samples were processed and tested for interferon-gamma (IFN-γ) levels (IU/ml). The result was considered positive if the IFN-γ level in the MTB-specific antigen-exposed sample minus the value of the negative control was ≥0.35 IU/ml and ≥25% of the IFN-γ concentration in the negative-control sample.

The TST was performed following the Mantoux technique. Zero point one milliliter (5 TU) of purified protein derivative (RT23; Statens Serum Institute, Copenhagen, Denmark) was injected intradermally on the volar aspect of the forearm. At 48 hours, the diameter of the induration was determined by a trained nurse. The result was considered positive if the diameter of induration was ≥10 mm.

Data analysis

Comparison of parameters was conducted using the chi-square test or Fisher's exact test. Comparison of the average values between the groups was conducted using the Student's t-test. The risk estimation [crude odds ratio (OR)]was initially analyzed by univariate analysis. Multivariate analysis (adjusted OR) was performed using multiple logistic regression. A p-value < 0.05 was considered significant. SPSS, version 16 (SPSS, Chicago, IL) was used for statistical analysis.

RESULTS

Characteristics of ATB and CC subjects

One hundred fifty-four subjects (100 CC and 54 ATB subjects) were enrolled. Seventy CC and 42 ATB subjects met inclusion criteria. The mean age (±SD) of the ATB subjects was 50 (±15.4; range 17-74) years and the male to female ratio was 2.2:1. The mean duration of symptoms among ATB subjects prior to presentation was 36.5 (±15.4) days. Thirty-two of 42 ATB subjects (76.2%) were from Khon Kaen Province; 17/42 (40.5%) were farmers or laborers; 10/42 (23.8%) had a history of prior BCG vaccination; 23/42 (31%) drank alcohol; 17/42 (40.5%) smoked, and 19/42 (45.2%) had a poor or regular appetite. The mean BMI was 19.8 (±3.4). Nine of 42 subjects (21%) had scanty AFB or negative AFB on sputum smear but a positive culture or PCR-TB; 38% (16/42) had 1+ AFB, 17% (7/42) had 2+ AFB, and 24% (10/42) had 3+ AFB on sputum smear. On chest x-ray (CXR) 15/42 subjects (35.7%) had cavitary lesions and 16/42 (38.1%) had bilateral lesions. Eighteen of 42 ATB subjects (43%) were categorized as having a high bacillary load, 43% (18/42) were categorized as having a moderate bacillary load, and 14% (6/42) were categorized as having a low bacillary load. Most ATB subjects (34/42, 80.9%) lived in a detached house and 17/42 (40.5%) of patients had a house with 2 bedrooms. Most the ATB subjects (21/42, 50%) had 2-3 household contacts. The mean number of people per bedroom was 1.7±0.8. Twenty-eight of 42 subjects did not transmit TB and 14 did.

Table 1
Risk factors for latent TB infection of household close contacts.

Risk factors for LTBI among household contacts	Details of close contacts (n, %)		Crude odd ratios (95% CI)	Adjusted odds ratio (95% CI)
	Infected (n = 15)	Uninfected (n = 55)		
Female gender	12 (80.0)	37 (67.3)	1.95 (0.49-7.77)	1.69 (0.26-11.16)
Age ≥20 years	14 (93.3)	32 (58.2)	**10.06 (1.23-82.03)**	**14.02 (1.23-159.45)**
BMI ≥25	9 (60.0)	11 (20.0)	**6.00 (1.76-20.45)**	4.41 (0.92-21.12)
No prior BCG vaccination	1 (6.7)	8 (14.5)	0.42 (0.05-3.65)	0.1 (0.01-1.25)
Smoking	1 (6.7)	4 (7.3)	0.91 (0.09-8.81)	3.16 (0.16-62.18)
Alcohol consumption	4 (26.7)	13 (23.6)	1.18 (0.32-4.32)	0.47 (0.08-2.99)
Poor or regular appetite	1 (6.7)	6 (10.9)	0.58 (0.07-5.26)	1.28 (0.09-17.63)
Exposure to TB ≥5 hrs/day	12 (80)	28 (50.9)	3.86 (0.98-15.20)	**9.15 (1.44-58.05)**
Spouse or parent of TB patients	14 (93.3)	21 (38.2)	**22.67 (2.78-185.18)**	24.94 (2.36-263.91)

BMI, body mass index. Infected and uninfected status refers to TB household contact persons who were positive or negative on both TST and IGRA. Poor or regular appetite compared to good or excellent appetite as a reference. The bold numbers referred to statistically significant values. Multivariate analysis was performed by adjusting for all the factors except the relationship. The relationship was adjusted for all of the factors except age.

Of the 70 CC, the mean age (±SD) was 35.6±20.6 years (range 6 - 75). Ten of 70 CC (14.3%) were aged <10 years. The mean BMI among CC was 22.3 (±5.3). Thirty-five point seven percent (25/70) of CC were students; 92.9% (65/70) did not smoke; 75.7% (53/70) did not drink alcohol; 77.1% (54/70) were from Khon Kaen Province; 87.1% (61/70) had previously received a BCG vaccine and 90% (63/70) had a good or excellent appetite. Three percent of CC (2/70) had a history of diabetes mellitus (DM). Thirty-nine percent of CC (27/70) were spouses of ATB subjects, 27% (19/70) were daughters/sons, 11% (8/70) were parents, 17% (12/70) were nieces/nephews and 6% (4/70) were others. Fifty-seven percent of CC (40/70) were exposed to an ATB subject for $\geq$ 5 hours per day. Fifteen CC became infected and 55 did not infected.

Risk factors of among CC for developing LTBI

The mean age of CC who became infected with TB was significantly higher than those who did not (44.9±14.4 *vs* 33.1±21.5 years, respectively; *p* = 0.02). On univariate analysis CC aged ≥20 years were 10-fold (OR=10.06; 95% CI: 1.23-82.03) more likely to be infected than those aged <20 years (Table 1). The mean BMI of CC who became infected was significantly greater than those who did not (25.3±5.7 *vs* 21.5±5.0, respectively; *p* = 0.01). CC with a BMI ≥25 were six-fold (OR=6.0; 95% CI: 1.76-20.45) more likely to be infected than those with a BMI <25. CC subjects who were a spouse or a parent of an ATB subject were 23-fold (OR=22.67; 95% CI: 2.78-185.18) more likely to be infected than those with other relationships. None of the

Table 2
MTB transmission factors among pulmonary TB patients.

Transmission factors	Transmission rate by TB patients (*n*, %)		Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
	Transmitted (*n* = 14)	Non-transmitted (*n* = 28)		
Male gender	12 (85.71)	17 (60.7)	3.88 (0.73-20.79)	1.65 (0.19-14.44)
Age <60 years	9 (64.3)	17 (60.7)	1.17 (0.31-4.41)	2.07 (0.3-14.26)
BMI ≥18.5	10 (71.4)	16 (57.1)	1.88 (0.47-7.45)	2.78 (0.46-16.95)
Non BCG vaccination	2 (14.3)	8 (28.6)	0.42 (0.08-2.30)	0.37 (0.03-4.1)
Smoking	3 (21.4)	14 (50.0)	0.27 (0.06-1.20)	0.51 (0.08-3.34)
Alcohol consumption	7 (50.0)	16 (57.1)	0.75 (0.21-2.72)	1.22 (0.21-6.96)
Diabetes mellitus	3 (21.4)	7 (25.0)	0.82 (0.18-3.80)	0.97 (0.1-9.02)
Poor or regular appetite	5 (35.7)	14 (50.0)	0.56 (0.15-2.08)	0.85 (0.15-4.81)
Bilateral lesions on CXR	7 (50.0)	9 (32.1)	2.11 (0.57-7.86)	4.07 (0.61-27.3)
Cavitary lesion on CXR	3 (21.4)	12 (42.9)	0.36 (0.08-1.60)	0.35 (0.05-2.64)
TB symptoms ≤14 days	8 (57.1)	7 (25.0)	**4.00 (1.03-15.60)**	2.56 (0.34-19.29)
AFB grading				
Scanty/culture/PCR for TB positive	0 (0)	9 (32.1)	1.00 (Reference)	NA
1+	7 (50.0)	9 (32.1)	**1.78 (1.15-2.74)**	NA
2+	2 (14.3)	5 (17.9)	1.40 (0.88-2.24)	NA
3+	5 (35.7)	5 (17.9)	**2.00 (1.08-3.72)**	NA
Bacillary load				
Low	0 (0)	6 (21.4)	1.00 (Reference)	NA
Moderate	5 (35.7)	13 (46.4)	**1.39 (1.04-1.84)**	NA
High	9 (64.3)	9 (32.1)	**2.00 (1.26-3.17)**	NA

"Transmitted" refers to an infection that occurred in at least one close contact. "Non-transmitted" refers to no infection occurring in any close contacts. The bacillary load was defined by AFB positivity and chest x-ray (CXR) lesions. Poor or regular appetite compared to good or excellent appetite as a reference. NA, not analyzed (result not included in analysis). Bold numbers refer to statistically significant values. Multivariate analysis was performed with adjustment for all factors except AFB positivity and bacillary load due to limited of sample size.

other risk factors were significantly associated with contracting TB on univariate analysis (Table 1).

Multivariate analysis showed being aged ≥20 years (OR=14.02; 95% CI: 1.23-159.45) and being a spouse or parent of an ATB subject (OR=24.94; 95% CI: 2.36-263.91) were risk factors significantly associated with contracting TB. Being

overweight was not associated with contracting TB (OR=4.41; 95% CI: 0.92-21.12). Multivariate analysis revealed CC with exposure to an ATB subject for ≥5 hours/day had a nine-fold (OR=9.15; 95% CI: 1.44-58.05) greater risk of contracting TB than those exposed for <5 hours/day (Table 1).

Occupation and living location of

Table 3
Environmental factors and MTB transmission by pulmonary TB subjects.

Location of residence	Infection among close contacts (*n*, %)		Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
	Transmitted (*n* = 14)	Non-transmitted (*n* = 28)		
Townhouse	3 (21.4)	5 (17.9)	1.26 (0.25-6.22)	1.23 (0.21-7.20)
< 2 bedroom house	2 (14.3)	3 (10.7)	1.39 (0.20-9.45)	1.34 (0.16-10.87)
> 3 members per house	6 (42.9)	15 (53.6)	1.54 (0.42-5.61)	1.60 (0.43-5.92)

Townhouses compared to detached houses as a reference.

the CC were not significantly associated with contracting TB. Twenty-three percent (14/61) of BCG-vaccinated and 11% (1/9) of non-vaccinated CC subjects contracted TB. Having a history of a BCG vaccine was not significantly associated with contracting or not contracting TB.

Factors associated with transmitting TB to CC

The sputum AFB grade category, MTB bacillary load and duration of TB symptoms prior to presentation of ≤14 days were significantly associated with transmission of TB on univariate analysis (Table 2). ATB subjects with sputum smear AFB results of 3+ (crude OR=2; 95% CI: 1.08-3.72), 2+ (crude OR=1.40; 95% CI: 0.88-2.24) and 1+ (crude OR=1.78; 95% CI: 1.15-2.74) were more likely to transmit TB to CC than AFB subjects with scanty AFB or with only a positive TB culture or positive PCR for TB. None of the 17 CC who became infected did so after being exposed to the 9 ATB subjects with scanty AFB or only a positive culture or positive PCR for TB. ATB subjects with a high bacillary load (crude OR=2; 95% CI: 1.26-3.17) or a moderate bacillary load (crude OR=1.39; 95% CI: 1.04-1.84) had a greater probability of transmitting TB than those

with a low bacillary load (Table 2).

The mean age of ATB subjects (48.5±15.3 *vs* 50.7±15.7 years, *p* = 0.67) and the mean duration of TB symptoms (27.1±27.9 *vs* 41.1±43.1 days, *p* = 0.28) were not significantly different between transmitting and non-transmitting ATB subjects. The BMI of TB transmitting ATB subjects was not significantly greater than non-transmitting ATB subjects (21.4±3.4 *vs* 19.4±3.1, *p* = 0.07). Gender, age, BMI, living location, history of BCG vaccination, smoking status, alcohol consumption, chest x-ray findings and occupation were not significantly associated with transmission of TB on univariate or multivariate analyses (Table 2).

Environmental factors and TB transmission

No environmental factors were significantly associated with TB transmission (Table 3). ATB subjects living in a townhouse *vs* a detached house (OR=1.23; 95% CI: 0.21-7.20), living in a house containing <2 *vs* ≥2 bedrooms (OR=1.34; 95% CI: 0.16-10.87), >3 *vs* ≤3 household members (OR=1.60; 95% CI: 0.43-5.92) were not associated with transmission of TB. The mean bedroom number (2.4±1.0 *vs* 2.7±0.9, *p* = 0.39) and the mean number of people per house (3.7±1.5 *vs* 4.4±1.8, *p* = 0.22) in

non-transmitting and transmitting ATB subjects were not statistically different. The ratio of people per bedroom was 1.8 ± 1.0 for transmitting and 1.7± 0.7 for non-transmitting ATB subjects (p = 0.56).

DISCUSSION

Our study showed that older age household contacts were more likely to become infected with TB than younger contacts, similar to a previously report (Mixides et al, 2005). Some studies have reported younger age as a risk for TB infection (Marais et al, 2004; Singh et al, 2005; Nava-Aguilera et al, 2009; Seddon et al, 2013). Household contacts who were students had less exposure to index cases. A spouse or parent was more likely to become infected with TB than a daughter, son, niece or nephew. We also found that exposure to an ATB patient for ≥5 hours per day was a risk factor for TB infection.

Malnutrition (Cegielski and McMurray, 2004) and obesity (de Heredia et al, 2012) can decrease immunity increasing the risk for contracting TB infection. On univariate analysis being overweight was a risk for acquiring LTBI for CC, but on multivariate analysis we did not see this association. Higher concentrations of TB in the sputum increased the risk for CC to acquire LTBI. This is in agreement with a previous study (Espinal et al, 2000). An abnormal chest x-ray combined with a high bacillary loads was associated with a greater risk of transmitting TB than a high AFB grade alone. AFB smear negative ATB subjects who are culture or PCR-positive can transmit MTB to CC (Hernandez-Garduno et al, 2004). However, in our study we found no transmission in these patients. Cavitary lesions have been associated with treatment failure and TB relapse (Palaci et al, 2007). However, in

our study we found no significant difference in transmission between those with cavitary lesions on chest x-ray and those without. A delay in the diagnosis of TB associated with an increased risk of transmission (Golub et al, 2006). In our study, shorter duration of TB symptoms increased the transmissibility of TB, suggesting these patients may have had higher bacillary loads.

In our study there was no gender difference in contracting or transmitting TB, unlike some previous reports (Neyrolles and Quintana-Murci, 2009). Alcohol use, smoking and nutritional state can affect immunity (Ariyothai et al, 2004; Chandra, 2004; Lonnroth et al, 2008; Karavitis and Kovacs, 2011), but in our study these factors were not significantly associated with TB infection. Diabetes millitus has been reported to be associated with increased risk for acquiring TB infection (Dooley and Chaisson, 2009), but in our study we found no such association; but this could be due to the small sample size of our patients with diabetes millitus.

The protective efficacy of the BCG vaccine against MTB infection varies (Colditz et al, 1994; 1995). In our study BCG vaccination was not protective for CC and did not prevent ATB subjects from transmitting TB. The Beijing genotype of MTB, which has been found to not be covered by the BCG vaccine and has high infectivity (van Soolingen et al, 1995) is common in Thailand (Rienthong et al, 2005).

Environmental factors, such as ventilation in the living place, may affect transmission and contraction of TB. Previous studies have found living in a crowded house is a risk factor for MTB infection (Lienhardt, 2001; Tornee et al, 2005). The type of dwelling, number of bedrooms,

number of people per house, and ratio of people per bedroom were not associated with TB transmission in our study. This could be explained by the characteristics of the houses in Thailand, which are generally detached houses containing few but large rooms and good ventilation. Being a spouse sleeping in the same bedroom, was a risk for MTB infection. Therefore, factors regarding both the ATB patient and their CC played a major role in TB transmission in our study population.

A limitation of our study was the limited sample size due to only recruiting for one year. The inability to determine whether a MTB infection in a CC was acquired from the household index case or some other source in the community is also unclear. The virulence of the MTB strains, which is also relevant to infectability, was not addressed in this study. Strength of our study was the use of both the TST and IGRA to confirm an infection. The analysis of the transmission factors among the ATB patients, their CC and the inclusion of the environment is informative and can inform TB control programs.

In summary, in our study the risk factors for MTB infection in the household were being aged ≥20 years, having a relationship with the ATB patient, such as being a spouse or parent and being exposed the ATB patient for many hours per day. The significant transmission factors among ATB patients were the bacillary load as defined by AFB grade and the chest x-ray findings. The living place was not found to be associated with TB transmission.

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