Latent tuberculosis infection in family members in household contact with active tuberculosis patients in Semarang City, Central Java, Indonesia

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Abstract

A quarter of the world's population is infected with *Mycobacterium tuberculosis* (M.tb), 10% of cases develop active tuberculosis (TB), and 90% have a latent TB infection. Family members of TB patients have the highest potential for latent TB infection. This study aims to identify latent TB infection and risk factors in family members within the household contacts of active TB patients. This study used a cross-sectional study design with a contact tracing method. The selected subjects were 138 people from 241 total family members of 112 active TB patients. Subjects underwent a tuberculin skin test (TST), using 2 units of tuberculin (TU) purified protein derivative (PPD) 0.1 mL (PT. Bio Farma Persero, Bandung, Indonesia). Data risk factors were collected during home visits. Data were analyzed using the chi-square test and multiple logistic regression. A total of 63.8% (88/138) of family members of active TB patients' household contacts had latent TB infection. The type of occupation of laborers/farmers/fishers is the most dominant risk factor associated with latent TB infection (AOR: 7.04; 95% CI: 1.70–29.02), followed by unqualified bedroom density (<8 m2/2 people) (AOR: 5.33; 95% CI: 2.44–12.71) and contact duration ≥5 hours/day (AOR: 4.70; 95% CI:1.33–16.66). Latent TB infection in family members of active TB patients' household contacts was quite high. Occupation type, contact duration, and bedroom density were simultaneously confirmed as the main risk factors related to latent TB infection. Therefore, it is recommended to identify and prevent latent TB infection in family members in household contact with active TB patients.

Introduction

Tuberculosis (TB) is an infectious disease caused by the bacteria *Mycobacterium tuberculosis* (M.tb). TB is still a global health issue, especially in developing countries such as Indonesia, which ranked second-highest for TB cases after India, followed by China in third place.[1] It is estimated that a quarter of the world's population, around 1.7-2.3 billion people, are infected with M.tb.[1,2] About 10% of cases have developed into active TB,[3] and 90% persist in the form of latent TB or latent TB infection.[4] Latent TB infection can occur upon contact with active TB patients.[5] The risk is potentially increased with the closer exposure intensity. Household members have the biggest risk for latent TB infection,[6] because they share the same air with active TB patients for a longer time.[7] Sharing a bedroom,[7] spending time with active TB patients, smoking habits,[8] gender,[8] overweight status and alcohol consumption are included in the risk factors for latent TB infection.[8] It is estimated that 5-10% of individuals with latent TB infection will have reactivation to active TB.[9] The potential reactivation of latent TB infection to active TB in household contacts is usually higher than in other general cases.[10] Household contacts with active TB patients are considered to have a high priority for contact tracing.[7] However, contact tracing for identifying latent TB infection is not applied in Indonesia. Currently, the contact tracing in family members of the household contact with active TB patients is being used to discover new cases of active TB.[11]

Therefore, tracing the contacts of household members with active TB patients is important to detect and identify cases of latent TB infection, and risk factors for latent TB infection. This will contribute to preventing and suppressing the development of active TB cases in the future. This study aims to identify latent TB infection, and risk factors associated with latent TB infection in family members in household contact with active TB patients.

Materials and Methods

Scientific and ethical considerations

The research protocol and procedure have been reviewed and approved by the Health Research Ethics Commission, Faculty of Public Health, Diponegoro University, Semarang, Indonesia, No.32/EA/KEPK-FKM/2021, February 26, 2021. Informed consent was approved and obtained from each research subject.

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Study design and research subject

The study design was cross-sectional with contact tracing method in family members in household contact with active TB patients. This research is the first part of an intervention study, "Effect of giving vitamin D supplementation to healing response and immune response to latent TB infection". There are 241 family members in household contact with 112 indexed cases of active TB patients registered in the TB-01 form in 2020 and 2021 at the Kedungmundu Health Center, Semarang City, Central Java, Indonesia.

The subjects were required to fulfill the inclusion and exclusion criteria. The inclusion criteria were: the subjects must be the family member that had contact with active TB patients, aged 15 to 70 years, not having the active TB clinical symptoms, had consented to become study subjects, and signed the informed consent. The subjects were excluded based on exclusion criteria: having another infectious disease, pregnant, and breastfeeding. Based on these inclusion and exclusion criteria there were 138 subjects of a total of 241 family members of active TB patients.

Data collecting

Data were collected from the 4th of June to the 13th of August, 2021. Subjects must complete the TST procedure by intradermal injection in lower arm 2 TU PPD RT 23 SSI, with 0.1 mL dosage (PT. Bio Farma Persero, Bandung, Indonesia). The diameter of the transverse induration was measured with a transparent ruler and recorded in millimeters (mm) after 72 hours of TST.[12] The TST result will be confirmed positive if the induration measures ≥10 mm.[12,13] The TST was carried out by a competent, trained, and skilled nurse under a doctor's supervision at the local public health center. Meanwhile, risk factors were collected by interview method and observed using a questionnaire and a checklist during home visit. Data was collected by the skilled and trained enumerator recruited from Health Polytechnic of Semarang Minister of Health and Muhammadiyah Semarang University.

Statistical analysis

The risk factors of latent TB infection were analyzed bivariate with the chi-square test and simultaneously analyzed using multiple logistic regression. The differences were considered statistically significant if $p<0.05$. Data analysis was carried out using SPSS version 21.0 for Windows, licensed from the Faculty of Public Health, Diponegoro University, Semarang.

Results

In this study, the participation level of the subjects was quite good. Among 241 household contact family members of active TB patients, 138 (57.3%) people agreed to participate in the study procedure as subjects, and 88 subjects (63.8%) were confirmed to be infected with latent TB based on the results of the TST test. The latent TB case was confirmed by an induration size of TST ≥10 mm.

Table 1 shows that, of the 10 variables identified as risk factors for latent TB infection, four variables had significant differences related to latent TB infection, namely: i) nutritional status (p=0.022), ii) type of contact (p=0.027), iii) contact duration (p=0.041) and iv) bedroom density (p=0.001).

As for nutritional status, the least proportion of subjects with latent TB infection are obese (25%), compared to overweight (72.2%), normal (67.7%), and underweight (58.3%). FAs for the type of contact, the proportion of latent TB was greater in close contacts (75.4%) than in non-close contacts (55.6%). Close contact between subjects with active TB patients increased latent TB infection by 2.46 times (95% CI:1.17-5.18) compared to non-close contact.

As for contact duration, the proportion of latent TB infection was greater in subjects with a contact duration of ≥5 hours/day (67.2%) compared to a contact duration of <5 hours/day (37.5%). Spending 5 hours or more with active TB patients increased the risk of latent TB infection by 3.42 times (95% CI:1.16 -10.06) compared to less than 5 hours a day.

In the bedroom density variable, the proportion of latent TB infection was greater in subjects with unqualified bedroom density (<8 m^2/2 people) (74.4%), compared to subjects with eligible bedroom density (≥8 m^2/2 people) (43.8%). The density of unqualified bedrooms (<8 m^2/2 people) can increase the risk of latent TB infection by 3.74 times (95% CI: 1.78-7.86) compared to the density of eligible bedrooms (≥8 m^2/2 people).

Based on Table 2, three variables simultaneously were the major risk factors for latent TB infection: i) occupation type (p=0.024), ii) contact duration (p=0.016), and iii) bedroom density (p=0.000).

The type of occupation of laborers/farmers/fishers is the most dominant risk factor associated with latent TB infection (AOR:7.04; 95% CI:1.70–29.02). The occupation of laborer/farmer/fisherman has a risk of latent TB infection 7.04 times greater compared to housewives and unemployed people after having controlled the variables of contact duration and bedroom density.

The contact duration ≥5 hours/day had a risk of latent TB infection 4.70 times greater (95% CI:1.33–16.66) compared to <5 hours/day contact duration after having controlled by the variables of occupation type and bedroom density.

Unqualified bedroom density (<8 m^2/2 people) had a risk of latent TB infection 5.33 times greater (95% CI: 2.24–12.71) compared to qualified bedroom density (≥8 m^2/2 people) after having controlled by the variables of the occupation type and contact duration.

Discussion

This study used TST to detect latent TB infection. In Indonesia, TST is better known as the Mantoux test, which has been used to detect TB infection in children for many years. TST has several limitations, including the need for 2 visits, namely injection and observation after 48-72 hours of injection, reader variability in measuring induration, reduced response caused by immunosuppression, increased retesting, and potential for cross-reaction with non-TB mycobacteria and BCG immunization.[14] However, despite all the limitations, TST remains the top choice due to the availability of resources and support.

According to various studies, there is no ideal test to detect M.tb infection, even TST is a fairly sensitive and specific test to detect TB.[14,15] TST has become the most common test to detect latent TB infection.[16] A study in Sudan reported that TST reactivity with an ≥10 mm induration was as good as the IFN-γ release assay (IGRA) when it comes to diagnosing latent TB infection.[17] The World Health Organization (WHO) has recommended TST to diagnose the latent TB infection for low and middle-income countries.[18]

This study found quite high latent TB infection, as about 63.8% latent TB was detected from 138 subjects. Eighty-eight subjects out of 138 were positive for latent TB infection (induration diameter ≥10 mm). This result is much higher than that of the study in Singapore, which only detected 12.7%.[19] Meanwhile, the study in the US and Canada reported that out of 3040 family members of TB patients, 1390 subjects (48%) were TST positive (≥10 mm), and 62% of them were living in the same household with the TB patients.[20] Another research in Brazil reported that out of 838 family members, 523 subjects (62.4%) had latent TB, confirmed by TST positive (≥10 mm).[21]

Similar previous studies at BKPM (pulmonary health public center) Semarang City in 2011-2012 found as much as 79.4% of family members of TB patients had latent TB infection.[22] This big results difference is likely due to differences in the study population. In the previous study, the research subjects were family members of TB patients that also had a role as PMO (medication supervisor).[22] Meanwhile, in this study, the research subjects were family members of adult active TB patients aged 15 to 70 years. PMO is generally closely related to active TB patients, while not all family members have close contact with active TB patients, and this affects the results of previous and current studies.

Another effect of latent TB infection found in this study which is lower than previous studies is the role of officers, in this case the TB program manager, who pro-

Table 1. Bivariate analysis results of risk factors of latent TB infection (chi-square test).

Variable	Latent TB infection				p	Crude OR (95% CI)
	Positive (n=88)		Negative (n=50)			
	n	%	n	%		
Age (n=138)						
<25 years	26	60.5	17	39.5	0.963	-
26-35 years	22	66.7	11	33.3		
36-45 years	16	66.7	8	33.3		
46-55 years	12	66.7	6	33.3		
>55 years	12	60.0	8	40.0		
Sex (n=138)						
Male	46	73.0	17	27.0	0.056	-
Female	42	56.0	33	44.0		
Occupation type (n=138)						
Laborer/farmer/fisherman	16	80.0	4	20.0	0.069	-
Trader/entrepreneur	19	73.1	7	26.9		
Employee/soldier/officer/civil servants	25	64.1	14	35.9		
Student	15	65.2	8	34.8		
Housewives/unemployee	13	43.3	17	56.7		
Nutritional status (n=138)						
Obesity	3	25.0	9	75.0	0.022	-
Overweight	26	72.2	10	27.8		
Normal	44	67.7	21	32.3		
Underweight	14	58.3	10	41.7		
BCG vaccine (n=138)						
Not get vaccinated	11	64.7	6	35.3	0.610	-
Got vaccinated, having scar	62	66.0	32	34.0		
Got vaccinated, not having scar	15	55.6	12	44.4		
Smoking behavior (n=138)						
Yes	24	72.7	9	27.3	0.308	-
No	64	61.0	41	39.0		
Alcohol consumption (n=138)						
Yes	7	87.5	1	12.5	0.258	-
No	81	62.3	49	37.7		
Type of contact (n=138)						
Close contact	43	75.4	14	24.6	0.027	2.46 (1.17-5.18)
Not close contact	45	55.6	36	44.4		
Contact duration (n=138)						
≥5 hrs/day	82	67.2	40	32.8	0.041	3.42 (1.16-10.06)
<5 hrs/day	6	37.5	10	62.5		
Bedroom density (n=138)						
Unqualified (<8 m^2/2 person)	67	74.4	23	25.6	0.001	3.74 (1.78-7.86)
Qualified (≥8 m^2/2 person)	21	43.8	27	56.2		

BCG = Bacilli Calmette-Guérin, OR=Odds Ratios, CI=Counfident Interval.

Table 2. Multivariate analysis results of risk factors for latent TB infection (multiple logistic regression test).

Variable	p	AOR	95% CI
Occupation type	0.024		
Laborer/farmer/fisherman	0.007	7.04	1.70-29.02
Trader/entrepreneur	0.021	4.29	1.25-14.76
Employee/soldier/officer/civil servants	0.009	4.55	1.46-14.15
Student	0.014	5.27	1.40-19.83
Housewives/unemployee	1 (reference)		
Contact duration	0.016	4.70	1.33-16.66
Bedroom density	0.000	5.33	2.24-12.71

AOR=Adjusted Odds Ratios.

vides detailed education about how to transmit and prevent TB disease in every patient and family member who has household contact with active TB patients. Public health center officers' have conducted socialization to reduce contact with active TB patients, separate eating and drinking utensils between the sick and healthy, and use masks to communicate between patients and family members. These efforts can minimize the possibility of transmission of M.tb. Another consideration, this research was carried out during the COVID-19 pandemic which had lasted more than 1 year. Although there is no supporting data yet, the pandemic itself creates awareness as for keeping a distance and reducing direct contact increasing.

In addition to the main causative factor from M.tb bacteria, latent TB infection can occur due to various supporting factors, both internal and external, which could attach to and affect the host. Several risk factors that influence latent TB infection from various literature are gender, age, close relationship with TB patients, contact duration with the patients, room-sharing with patients, education level, smoking behavior, alcohol use, and HIV serostatus.[23]

The considered high-risk places to spread the TB are schools, densely populated residences, and workplaces. High frequency of social contacts, contact duration, and public transport use can be another possibility in addition to the generally mixed index of TB patients at home and a higher proportion of re-inhaling the exposed air.[24] Also the poor ventilation and overcrowding in these places also significantly support the TB transmission by droplet nuclei from infectious active TB patients.[25]

This study found a significant difference in latent TB infection based on nutritional status (p=0.022), although the proportion was not consistent between nutritional status groups. The proportion of latent TB infection in underweight subjects (58.3%) was lower than in subjects with normal nutritional status (67.7%) and overweight subjects (72.2%), but in underweight subjects it was greater than in obese subjects (25%).

This finding is almost similar to a study report in China in which a Body Mass Index (BMI) below 18.5 kg/m^2 significantly reduced the latent TB infection risk as much as 0.35 times (OR:0.65; 95% CI:0.46-0,92), while overweight increased latent TB infection as much as 0.36 times (OR:1.36; 95% CI:1.17-1.57).[8] Another study in Panama seemingly had the same result, concluding that obesity and overweight had a risk factor for latent TB infection.[26] Many studies reported that individuals with a higher BMI also have a higher risk for developing active TB. However, many statements that BMI affects M.tb infection are not well explained. At least, the study in China that carried out a large sample size could imply that being overweight might contribute to an increased risk of latent TB infection.[8]

Type of contact was also a significant risk factor for latent TB infection (p=0.027; 95% CI:1.17–5.18). The proportion of latent TB infection in the close contact category was higher (75.4%) compared to the non-close contact category (55.6%). These findings are similar to those of the study in China, where close contact with TB patients was significantly associated with latent TB infection (OR:2.38; 95% CI:1.20-4.75).[8] Another study in Thailand reported that being partners of active TB patients also had a significant risk factor for TB infection (OR:24.94; 95% CI:2.36-263.91).[27]

People who are partners or parents of active TB patients spend a lot of time and have many opportunities to interact, both frequency and duration create a very high chance of M.tb transmission compared to non-close contact. Couples or parents have a higher potential to get TB infection than children, nieces, or nephews.[27] These results reflect the role and importance of the degree of proximity to the indexed disease case.[28] Another previous study in Bangkok proved that the risk of TB infection was significantly related to close contact, such as parents who had TB.[29]

The occupation type in the multivariate analysis was significantly confirmed as a risk factor for latent TB infection (p<0.05), but was not significantly confirmed in the bivariate analysis (p=0.069). All groups who work and have outdoor activities have a higher risk of latent TB infection than the group of housewives and unemployed. In fact, the professions of farmer/laborer/fisherman were reported to have the most dominant risk for latent TB infection (p=0.007; AOR:7.04; 95% CI:1.70–29.02).

The results of the study in Sudan reported that the profession of housewife had the highest percentage (8.43%) for latent TB infection compared to all types of work, although the difference was not statistically significant (p=0.10).[28] This study implies that M.tb does not only spread within the household but also outside the household, such as in the workplace or school environment, public transportation, and others. However, this study could not explain the evidence of infection from outdoor contact with active TB patients. Observation of M.tb transmission outside the home is important, because according to one source 32% of diagnoses of latent TB infection occurred outside of household contact.[20] In another source it is stated that 50-80% of all M.tb transmission is estimated to occur outside the household.[30] The duration of contact or duration of exposure needs to be considered and controlled for latent TB infection. This study reported that the variable duration of contact was significantly associated with latent TB infection (p=0.041). The proportion of latent TB infection with contact duration ≥5 hours/day (67.2%) was higher than contact duration <5 hours/day (37.5%). The contact duration in multivariate analysis was included in the three main variables as a risk factor for latent TB infection. Contact duration with active TB patients for ≥5 hours/day can increase the potential of latent TB infection by 3.70 times (AOR: 4.70; 95% CI:1.33–16.66) compared to the <5 hours/day contact with active TB patients.

This result is similar to that of a study in Thailand which reported that close contact with active TB subjects for ≥5 hours/day increased the risk of latent TB infection by 9 times (OR:9.15; 95% CI:1.44-58.05), compared to family members who only spend <5 hours/day in contact with TB patients.[27] Other studies in the US and Canada have shown that the prevalence of latent TB infection increases with the length of contact. This study reported that latent TB increased in prevalence by 8.2% per 250 contact hours (p<0.0001).[20] The length of contact provides an opportunity for M.tb transmission to occur to family members who are in household contact with active TB patients. The longer the contact time, the higher the exposure to M.tb and the greater the risk of latent TB infection, and *viceversa*.

Bedroom density is one of the important environmental risk factors associated with latent TB infection. This study reported that the proportion of latent TB infection was higher in the density of unqualified bedrooms (<8 m^2/2 people), which was 74.4%, much higher than the density of eligible bedrooms (≥8 m^2/2 people) which only has a proportion of 43.8%. This difference was confirmed to be significant in bivariate analysis (p=0.001) and multivariate analysis (p=0.000). The risk of latent TB infection in unqualified bedrooms density (<8 m^2/2 people) was 5.33 times higher (95% CI:2.44–12.71) than in eligible bedrooms density category (≥8 m^2/2 people).

The results of this study are similar to reports from the US and Canada that household contacts who share a bedroom with indexed patients have a higher prevalence of latent TB infection than household contacts who do not share a bedroom or non-home contacts.[20] In contrast, a study in

Thailand found that household density was not a risk factor for latent TB infection.[27] These findings indicate that the site of exposure has a higher influence on the risk of latent TB infection. Indexed patients in household contacts had a higher potential and chance of exposure than in other locations even though they did not share a bedroom within the home.[20]

This study is limited by the population of family members who have active TB relatives, who live in the area with the highest active TB cases in Semarang City, Central Java, Indonesia. This study may not be representative of all other regions in Indonesia.[28-30] The cross-sectional study design was not designed to reveal temporal relationships between risk factors and effects. Therefore, there are limitations in the interpretation of the results of the risk factors for latent TB infection.

Conclusions

Latent TB infection in family members of active TB patients' household contacts was quite high. This study confirmed occupation type, contact duration, and bedroom density were risk factors related to latent TB infection. The results of this study have implications and support the important role of contact tracing to identify and prevent latent TB infection in family members in household contact to suppress the transmission and control active TB in the future.

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