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A MULTI - CENTERED STUDY OF THE INFLUENCE OF HIV INFECTION ON THE TRANSMISSION OF TUBERCULOSIS TO HOUSEHOLD CONTACTS THREE STATES OF MALAYSIA

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Abstract

A multi-centered cross-sectional study was carried out to examine tuberculin (Mantoux) response among household contacts of pulmonary TB (PTB) patients registered in Kota Bharu Hospital, Kelantan; Alor Setar Hospital Kedah and Institute of Respiratory Medicine, Kuala Lumpur from year 2000 through 2004. HIV status of patients based on ELISA results. Information on household contacts was recorded during house visit. Three hundred and twenty household contacts of 165 HIV-negative patients and 84 household contacts of 50 cases of HIV-positive PTB patients were included. Thirty-three percent (28/84) of household contacts of HIV-positive PTB had positive tuberculin response compared with 52% (166/320) to HIV-negative patients. The difference, however, was not significant after performing multiple logistic regression analysis to adjust for variables associated with infectiousness of TB (OR=0.62, 95% CI 0.35-1.10, p = 0.103). Adult contacts aged 25 - 44, having longer duration of stay with index cases and presence of positive sputum smear in the index cases were significantly associated with tuberculin positive among household contacts. It is suggested that HIV-infected PTB patients are not more infectious to their household contacts than HIV-negative patients.

Keywords: multi centered, pulmonary tuberculosis, HIV, household contacts, secondary transmission

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INTRODUCTION

According to the World Health Organization (WHO), one third of the world's population is already infected with *M. tuberculosis* which causing about 3 million deaths each year (Kochi et al., 1995). The Human Immunodeficiency Virus (HIV) pandemic is also increasing rapidly in many communities worldwide; more than 40 million people are currently infected with 3 million reported AIDS by year 2003 (UNAIDS, 2003). Nearly 14 million people are expected to be infected with HIV and TB by the year 2000 (WHO, 1998). In year 2000, the revised estimates of global HIV/TB burden indicated that nine percent out of total 8.3 million new TB cases in adults (15 – 49 years) and 12 percent of the 1.8 million deaths were attributable to HIV infection (Corbett et al, 2003).

TB is an important cause of mortality amongst the infectious diseases in Malaysia. Data from the Ministry of Health showed that the incidence of TB were in the range of 60 to 65 per 100, 000 population annually for the last five years (Ministry of Health Malaysia, 2003). There were about 50,000 reported HIV infected cases in the country until year 2003, and the trend is increasing year by year. All TB patients have been routinely screened for HIV status in Malaysia since 1990, and the trend of HIV/TB continuously increased (Ministry of Health Malaysia, 2003).

Few reports have specifically investigated the rate of TB in the contacts of HIV infected tuberculous index cases. It is interesting to note that the information on the potential for HIV-associated TB cases to transmit *M. tuberculosis* and to produce a secondary increase in TB morbidity in the community is relatively unknown in this region. If alterations in the TB mediated by HIV infection result in more efficient transmission or behavioral factors result in the exposure of more contacts, there would be a potential for an accelerated epidemic. It is of considerable importance of public health concern to establish whether patients with HIV-associated TB are more or less infectious than those without HIV infection. The purpose of this study was to identify the influence of HIV on the epidemiological transmission of TB to the household contacts, and to determine whether necessary changes are required in the management of TB as well as their contacts in light of the HIV epidemic.

MATERIALS AND METHODS

This cross-sectional study was conducted to compare the prevalence of tuberculosis infection between household contacts of HIV-positive and HIV-negative PTB index cases, based on a survey of the tuberculin reactivity in the household contacts. The study population was represented by the TB patients and their household contacts attended Kota Bharu Hospital in Kelantan (eastern region of Malaysia), Alor Star Hospital in Kedah (northern region) and Institute of Respiratory Medicine, a tertiary TB center in Kuala Lumpur between years 2000 and 2004.

Required sample size determined for index cases was 50 for HIV positive TB patients and 100 for HIV negative TB patients. For household contacts, 100 for HIV positive TB patients and 200 for HIV negative TB patient. The sample size managed to achieve was 50 HIV positive TB patients and 165 HIV negative TB patients. For household contacts, 84 HIV positive TB patients and 320 HIV negative TB patients were obtained. All cases of HIV positive TB cases were included in the study as there were very limited cases. For HIV negative TB cases, systematic sampling was applied.

After obtaining informed consent, index cases of pulmonary TB patients (PTB) with known HIV status and their respective adult household contacts aged 12 years and above were selected for the study. The contacts of newly diagnosed PTB index cases were interviewed during home visits using structured questionnaires and records of their tuberculin (Mantoux) testing done under the TB contact managements at the clinics were traced. Those who have not undergone the test were subjected for the intradermal injection of 10 T.U in 0.1 ml tuberculin solution (Tuberculin PPD RT 23 SSI, Denmark®) and the results were read after 72 hours to determine the size of indurations in millimeters by two experienced nurses at the participating chest clinics.

Information on demographic data, clinical and radiological findings of newly diagnosed PTB index cases were obtained from the medical records. HIV status was determined from the enzyme-linked immunosorbent assays (ELISA) test (Abbot Diagnostics, USA®) and by Particle Agglutination (PA) of Serodia of Japan®.

Statistical analysis

SPSS® Version 10.0 was used for data entry and analysis. Descriptive statistics and cross-tabulations were used to explore all data. Univariate analyses including Student's t test were used to compare means of continuous variables while the chi-square test was used to detect the significance of association between categorical variables. For dichotomous variables with small cell sizes, Fisher's exact test was used. The level of significance (p value) was taken at 0.05.

Because *M. tuberculosis* infection tends to aggregate within households, analyses of treat each household contacts as an independent observation would give precise results. The relationship between positive tuberculin responses of household contacts (with induration of $\geq$ 10 mm) and the HIV status of the index cases, and also other variables related to the index patients including household setting were examined by using backword stepwise multiple logistic binomial regressions. Simple logistic regression was applied in univariate analysis to determine potential predictors. Variables found to be statistically significant in univariate analysis ($p < 0.25$) and also proven significant in other studies were included in multivariate modeling. The statistical significance based on likelihood Ratio test statistics, biological plausibility, clinical importance and variables found significant by previous studies were considered in the final model. Results were tabulated with crude and adjusted OR, 95% confidence intervals and p values.

RESULTS

A total of 215 index cases of PTB cases and 404 household contacts from the 3 centers were recruited (Table I). There were 50 index cases of HIV-positive PTB and 165 index cases of HIV-negative PTB together with their 84 and 320 household contacts respectively who were included for the analysis.

Characteristics of index PTB cases

Majority of HIV-positive PTB patients were from the younger age group (78% aged 25 – 44 years) compared to HIV-negative PTB index cases (Table 2). Only one of HIV-positive PTB index cases was female while majority of them were Malays and single. Analysis on the clinical features showed that there were some significant differences in the TB sites and chest X-rays results between HIV-positive and HIV-negative index PTB cases. Higher proportion of HIV-positive PTB cases were found to be either extra-pulmonary or both types, while chest X-rays results showed more of minimal lesions with less cavitation and normal x-ray findings when compared to findings in HIV-negative PTB cases. Meanwhile, there was no significant differences in cough duration and sputum smear positivity between HIV-positive and negative PTB cases. With regards to behavioural risk of HIV infection, majority of HIV-positive PTB index cases seemed to be infected through injecting drug use.

Characteristics of household contacts

The ratio for household contacts per index case was almost similar (1:1.7 and 1:1.9 respectively) for both groups of HIV-positive cases and HIV-negative PTB index cases. There were also no significant difference in gender of the contacts ($p = 0.151$) and the presence of BCG scars among household contacts of the two groups ($p = 0.123$). However, there was a significant difference in crowding of house between the two groups, i.e. household contacts of HIV-negative PTB index cases live in more crowded houses (≥ 2 members per room) compared with those of HIV-positive PTB index cases (43.4% vs 22.6%, $p = 0.719$). Moreover, the study also reported that household contacts of HIV-positive PTB index cases had a shorter duration of stay with the index cases (19.4% vs 50.4%, $p = 0.002$)(Table 3).

Table 2. **Characteristics of Pulmonary TB cases by HIV status according to sociodemographic, clinical, chest X-ray findings and behavioral risk of HIV in Hospital Kota Bharu, Kelantan, Hospital Alor Setar, Kedah and Institute of Respiratory Medicine, Kuala Lumpur, Malaysia**

Characteristics		HIV§ +ve (n = 50)	HIV§-ve (n = 165)	p#
		No. (%)	No. (%)	
1. Age group (years)				
	< 24	5 (10.0)	27 (16.4)	0.001 *
	25 – 34	20 (40.0)	24 (14.5)	
	35 – 44	19 (38.0)	24 (14.5)	
	45 - 54	5 (10.0)	29 (17.6)	
	> 55	1 (2.0)	61 (37.0)	
2. Sex	male	49 (98.0)	122 (73.9)	0.001 *
	female	1 (2.0)	43 (26.1)	
3. Race	Malay	44 (88.8)	130 (78.8)	0.346*
	Chinese	5 (10.0)	23 (13.9)	
	Indian	1 (2.0)	4 (2.4)	
	Others	0	8 (4.8)	
4. Marital status				
	married	20 (40.0)	127 (77.0)	0.001 *
	single	23 (46.0)	35 (21.2)	
	others	7 (14.0)	3 (1.8)	
5.Type of tuberculosis				
	pulmonary	38 (76.0)	152 (92.1)	0.002
	both (extra and pulmonary)	12 (24.0)	13 (7.9)	
6.Cough duration (weeks)				
	< 2	34(68.0)	100 (60.6)	0.639
	2 – 4	4 (8.0)	16 (9.7)	
	> 4	12 (24.0)	49 (29.7)	
7. Initial chest X-ray classification				
	minimal	26 (52.0)	62 (37.6)	0.045
	moderately advanced	8 (16.0)	60 (36.4)	
	far advanced	10 (20.0)	31 (18.8)	
	no lesion	6 (12.0)	12 (7.3)	
8.Chest X-ray findings				
	cavitation/s	4 (8.0)	38 (23.0)	0.008
	infiltrates/opacity	36 (72.0)	118 (71.5)	
	pleural	2 (4.0)	2 (1.2)	
	hilar +/ med.nodes	1 (2.0)	1 (0.6)	

clear	7 (14.0)	6 (3.6)	
9. Sputum smear AFB‖			
positive	28 (19.7)	114 (80.3)	
negative	22 (30.1)	51 (69.9)	0.087
10. Risk factor for HIV infection			
Injecting drugs use (IDU)	43 (86.0)	1 (0.6)	0.000*
homo/heterosexual	6 (12.0)	4 (2.4)	
None/ undetermined	1 (2.0)	160 (97.0)	

§ Human Immunodeficiency Virus
‖ Acid-Fast Bacilli
p value of < 0.05 is significant
* Chi square test

Relationship between HIV status of index casess and Ttuberculin (Mantoux) response in household contacts

The observed prevalence of tuberculin positivity in household contacts of HIV-positive PTB index cases was significantly lower than those in HIV-negative PTB index cases (33.3 % vs 51.9%) (crude OR = 0.46 with 95% CI 0.28 - 0.77, p = 0.003) in univariate analysis.

However, the influences of other potential variables and predictors that may have affected the relationship between HIV status of index cases and tuberculin p ositivity among their household contacts were observed (Table 3). The results showed that after adjusted for other confounding variables, there was no significant association between the status of HIV of index PTB cases and the and tuberculin positivity among household contacts (adjusted OR = 0.62, 95% CI 0.35 – 1.10, p = 0.103). Significant predictors that were found in the final model, after adjustment for other related variables, were the age of household contacts (p = 0.009), d uration of stay w ith the index PTB cases (p = 0.002) and sputum positivitiy of the index cases (p = 0.002). Household contacts who were younger (age less than 15 years had significantly higher odds of having positive tuberculin response. Being a contact to positive sputum smears or exposed for a longer duration to a symptomatic index PTB cases was significantly associated with greater likelihood of having positive tuberculin response. Presence of cavitations in CXR or having longer cough duration in the PTB index cases, although clinically are the potential variables that may influence the infectiousness of tuberculosis were found to be not significant after adjustment for other variables (Table 3).

TABLE 3. Univariate and multivariate analysis showing the relationship between Mantoux positivity* and variables related to household contacts and index cases

Variables	No. (% tve)	Odds ratios (OR) crude	p value	Odds ratios (OR) adjusted (95%CI)	p value#
Household contacts					
Age groups (years)					
< 15	8/20 (40.0)	1.25	0.034	1.22(0.42 – 3.51)	0.009
15 - 24	44/105 (41.9)	0.45		0.37(0.18 – 0.75)	
25 -34	48/74 (64.9)	1.29		1.25(0.58 – 2.68)	
35 - 44	20/51 (39.2)	1.15		1.12(0.63 – 2.27)	
45 - 54	30/66 (45.5)	0.83		0.78(0.40 – 1.52)	
> 55	44/88 (50.0)	1.00		1.00	
Duration of stay					
< 3 months	6/31 (19.4)	1.00	0.001	1.00	0.002
≥ 3 months	188/373 (50.4)	4.23		4.67(1.76 – 12.39)	
BCG scar					
absent	54/98 (55.1)	1.00	0.107	1.00	0.123
present	140/306 (45.8)	0.687		0.61(0.33 – 1.14)	
Crowding of house					
≤ 2 persons/room	113/133 (45.9)	1.00	0.295	1.00	0.719
> 2 persons/room	81/158 (51.3)	1.24		1.09 (0.69 – 1.72)	
Relationship to index cases					
others	31/71 (43.7)	1.00	0.522	1.00	0.167
son/daughter	51/109 (46.4)	0.89		1.12(0.58 – 2.17)	
sibling	23/55 (41.8)	1.08		0.77(0.35 – 1.72)	
parents	41/79 (51.9)	0.72		0.44(0.20 – 0.97)	
spouse	48/89 (53.9)	0.66		0.61(0.29 – 1.25)	
Intimacy to index case					
share a bed	41/80 (51.3)	1.00	0.632	1.00	0.535
share bedroom	13/24 (54.2)	0.88		0.52(0.14 – 1.96)	
share living room	140/300 (46.7)	1.20		0.44(0.10 – 1.89)	
Index PTB cases					
Sputum smear AFB					
negative	51/142 (35.9)	1.00	0.001	1.00	0.002
positive	143/262 (54.6)	2.14		2.01(1.29 – 3.13)	
Cavitation on CXR					
no cavity	148/321 (46.1)	1.00	0.130	1.00	0.432
cavity	46/83 (55.4)	1.45		1.24(0.73 – 2.11)	
Duration of cough					
< 2 weeks	20/38 (52.6)	1.00	0.418	1.00	0.782

2-4 weeks	55/118 (46.6)	1.27		1.32(0.59 – 2.95)	
> 4 weeks	119/248 (48.0)	1.20		1.25(0.59 – 2.64)	
HIV status of cases					
negative	166/320 (51.9)	1.00	0.003	1.00	0.103
positive	28/84 (33.3)	0.46		0.62(0.35 – 1.10)	

* Taken as induration of 10 mm or more
# Based on multivariate logistic regression analysis adjusted for all variables were significant on univariate analysis and were biologically significant on the infectivity of tuberculosis (Likelihood Ratio test applied)

DISCUSSION

This multicentered study has shown that there was a lower prevalence of positive tuberculin (Mantoux) response in household contacts of HIV-positive PTB index case and household contacts of HIV-negative index cases. However, after adjustment for other potential confounding variables, no significant difference was observed.

Available literature showed that HIV-positive PTB index cases may be less or not more infectious to their close contacts. A study on HIV seropositivity among patients diagnosed as suffering from TB in Florida by Pitchenik *et al* (1987) observed no significant difference in the unadjusted tuberculin reactivity rate among 162 home contacts of HIV seropositive and seronegative cases. Espinal *et al.* (2000), in a prospective study on the infectiousness of *M.tuberculosis* in contacts living with HIV-positive and HIV-negative tuberculous cases, showed that there was no statistical difference between the tuberculin responses of two groups (15% vs 22%, p = 0.070). In a cross-sectional study in Kenya, it was found that the HIV-associated PTB was not more infectious than the HIV-negative group to their household contacts, even at different cut-off points of 5 mm and 10 mm for the tuberculin reaction (Nunn *et al.*, 1994). A study by Klausner et al (1993) in Zaire also indicated that HIV-positive PTB was not more infectious than HIV-negative TB.

The similarity in the trend of prevalence for tuberculin response between household contacts of HIV-positive and HIV-negative index cases in this study and those documented in other similar studies suggested that HIV infection may not influence the infectivity of index pulmonary TB patients to their contacts. Such a difference could result either from a difference in infectiousness between HIV-positive and negative cases or from the effect of confounding variables among them.

The differences in infectiousness between HIV-positive and negative PTB index cases may be mostly due to pathophysiologic interactions between HIV and TB. A reduction in cell-mediated immune response may alter the clinical and radiological features of TB, which may result from the interaction between host and pathogen. The clinical presentation of TB in the presence of HIV co-infection may be altered in which there will be less cavities formation and extrapulmonary sites are more often seen in those whose $CD4^{+}$ is markedly depressed. On the other hand, cavitation is common in HIV-negative PTB cases, except in immunocompromised patients (Cohen *et al.*, 1978). HIV-infected TB patients could be less infectious since infectiousness is related to cavity formation, as seen in this study. Pitchenik (1987) noted in a study that cavitary chest X-ray was not present in any of HIV/AIDS patients but was noted in over two-thirds of non-HIV or AIDS groups.

Majority of the HIV-infected PTB patients presented with pulmonary infiltrates while only 8% of them have cavitation in their chest X-rays (Table 2). Moreover, there was higher proportion of pleural disease, hilar and/or mediastinal lymphadenopathy as compared to HIV-negative PTB patients. These findings might indicate that the radiographic features of HIV-infected PTB patients, in this particular study are typically primary TB features, which are less severe form of PTB in terms of the extent of pulmonary lesion and presence of cavitation. Perlman *et al.* (1997) reported that cavitation was more common in those PTB patients with $CD4^{+}$ counts of more than $200/m^{3}$ and in those with less advanced HIV infection i.e when cell-mediated immunity is more intact. Unfortunately, due to limited resources, the level of immunosuppression of HIV-infected PTB patients in this study could not be assessed from $CD4^{+}$ counts results for all patients.

Sputum smear positivity correlates with the severity of TB disease in terms of the presence of cavities visible on chest radiography, and also with the extent of lung involvement. This study showed that the chest X-ray findings in the HIV-positive group, presenting with significantly milder chest lesions and less cavitation, might explain the lower infectiousness of tubercle bacilli to their household contacts. The measurement of sputum smear, either being positive or negative, in this study may not have been sufficiently precise because the positivity representing too wide range of bacillary load. There was a possibility that the bacillary load in the sputum may associate with the stage of immunosuppression in HIV-infected patients (Sepkowitz, 1995; Daley, 1995). This study was able to show that significantly lower sputum posititvity among the HIV-infected index cases of PTB may largely contribute to lower prevalence of tuberculin response among their household contacts.

This particular study, nevertheless, was able to show that some variables that were known to influence the transmission of TB such as crowding of house or have longer duration of stay with the index cases showed higher odds of being tuberculin positive among the contacts. Household contacts of HIV-infected PTB cases seemed to have significantly shorter exposure (less than 3 months) with the index cases. Behavioural factors such as stigma or alienation for HIV/AIDS patients may influence these predictors which highly influence the probability of transmitting the TB infection. Those who shared living rooms with the patient, especially among siblings, had higher risk to be tuberculin positive than those who shared same bed or bedroom, even though these results were mixed in other similar studies (Elliot *et al.*, 1990; Nunn *et al.*, 1994; Espinal *et al.*, 2000). The most probable explanation was that this might have been due to a longer duration and more opportunity of being exposed to tubercle bacilli among them during the symptomatic illness.

Estimation of secondary transmission rates in this cross-sectional study may bias the results and conclusions. Tuberculin reactivity may present lifetime exposure to mycobacteria (*M.tuberculosis* or non-tuberculosis mycobacterium), BCG vaccination as well as exposure to the index cases. As it was assumed that the index pulmonary TB case was the first case presenting in the family, and since all contacts were sputum smear negative and none had history of exposure to TB patients other than the index cases, the assumption of relative infectivity from the index to the contacts were reasonable. Snider (1995) had stated that if BCG scar was administered more than 10 years before PPD skin test, it should not be allowed to influence the interpretation of the skin test results. This study showed that absence of association between BCG scars among the contacts and the tuberculin response (which was also adjusted by statistical analysis) and also presence of tuberculin positivity at higher age groups indicated that BCG vaccination during childhood might not largely influence the outcome of tuberculin reactions, particularly in older age groups.

Due to limited resources from the secondary data of the PTB index patients, the results of $CD4^+$ counts were not available for all patients for further analysis. This parameter was very important in determining the level of immunosuppression and the stages of HIV-infection among the index cases which was useful to assess the severity of the TB disease among them. The data available could not describe the typical or atypical appearances of primary or reactivation TB from the results of chest x-ray films which may be associated with the degree of underlying immunosuppression.

HIV infection, depending on the degree of immunosuppression, might have led to anergy to tuberculin or alter the infectiousness of TB (CDC, 1991). However, interpretation of tuberculin response among them may be difficult because such unresponsiveness may be frequent as the HIV infection progress. Most HIV-infected TB have been noted to have tuberculin positive when the TB was diagnosed two or more years prior to development of AIDS, but this declined to about one-third of patients who had AIDS-defining illness (Rieder, 1989). Therefore, unrecognized HIV status among contacts and absence of stratification of the severity of HIV infection or AIDS, which was not done in this study due to limited resources and ethical constraint, could underestimate the prevalence of TB infection among them.

CONCLUSIONS and RECOMMENDATIONS

The data presented in this study supported the hypotheses that HIV-positive TB cases were not more infectious than HIV-negative cases in transmitting tuberculous infection to their household contacts. The study suggested that the more advanced HIV-associated immunosuppresion among the PTB index cases, the less infectious is the PTB as the extent of pulmonary lesion become less severe. The transmissibility of PTB may depend on the stage of HIV infection i.e patients who were immunosuppressed were less likely to cavitate and most likely to have milder pulmonary lesions with negative sputum AFB, and therefore are less infectious than those patients who were at an early stage of HIV infection.

The current contact management policy of TB in the general population in developing countries may not need to be revised following the rise of HIV epidemic. However, the findings of the study should not make the authority to be complacent. Rapid initiation of contact investigation is crucial especially among immunosuppressed HIV-infected contacts as incubation period as short as 20 days from infection to overt disease has been observed. In fact, some experts recommend that HIV-positive contacts of PTB cases should receive prophylaxis regardless of tuberculin skin test results, although this recommendation is not based on a controlled study (Chaisson, 1996). Qualitative studies to determine sociocultural and behavioral factors that influence transmission of TB in HIV patients and contacts may also need to be highlighted in future research.

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