RISK FACTORS FOR TUBERCULOSIS INFECTION AMONG HOUSEHOLD CONTACTS IN BANGKOK, THAILAND

Songpol Tornee[1], Jaranit Kaewkungwal[1], Wijitr Fungladda[1], Udomsak Silachamroon[1], Pasakorn Akarasewi[2] and Pramuan Sunakorn[2]

[1]Department of Social and Environmental Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok; [2]Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand

Abstract. A cross-sectional study was conducted to determine the prevalence of tuberculosis infection and risk factors for tuberculosis infection among household contacts aged less than 15 years in Bangkok, Thailand, between August 2002 and September 2003. During the study period, 342 index cases with sputum smear positive pulmonary tuberculosis patients were recruited into the study and their 500 household contacts aged under 15 years were identified. The prevalence of tuberculosis infection among household contacts was found to be 47.80% (95%CI = 43.41-52.19). In multivariate analysis, a generalized estimating equation (GEE) was used to determine the risk factors for tuberculosis infection among household contacts. The results indicated that the risk of tuberculosis infection was significantly associated with close contact (adjusted OR = 3.31, 95%CI = 1.46-7.45), exposure to female index case (adjusted OR = 2.75, 95%CI = 1.25-6.08), exposure to mother with tuberculosis (adjusted OR = 3.82, 95%CI = 1.44-10.14), exposure to father with tuberculosis (adjusted OR = 2.55, 95%CI = 1.19-5.46), exposure to index case with cavitation on chest radiograph (adjusted OR = 4.43, 95%CI = 2.43-8.05), exposure to index case with 3+ sputum smear grade (adjusted OR = 3.85, 95%CI = 1.92-7.70), and living in crowded household (adjusted OR = 2.63, 95%CI = 1.18-5.85). The distribution of tuberculosis infection and risk factors among contact cases are significant for health care staff in strengthening and implementing tuberculosis control programs in Thailand.

INTRODUCTION

Tuberculosis remains an important determinant of morbidity and mortality worldwide. It has been estimated that one third of the people on the planet have been infected with *Mycobacterium tuberculosis* (Orme, 2001). The World Health Organization estimated that at least 180 million children aged less than 15 years were infected with *Mycobacterium tuberculosis* worldwide (Dolin *et al*, 1994). Persons living in the household of a tuberculosis patient therefore have a high risk of becoming infected and developing tuberculosis themselves, particularly if their immune defenses are at all impaired (Zellweger, 2002).

Young children with tuberculosis infection represent recent, ongoing transmission in community. They are also at greatest risk for activation of their infections, and of developing disseminated disease (American Thoracic Society and the Center for Disease Control and Prevention, 1994). The detection of latent *Mycobacterium tuberculosis* infection is an important tool for controlling the spread of tuberculosis in the community (Rose, 2000). Since children have an increased risk of developing severe disease within weeks to months of infection, they are high priorities when identified as contacts of infectious tuberculosis patients.

The Centers for Disease Control and Prevention recommended identifying and offering therapy to all close contacts of persons with active tuberculosis (ACET, 1999). The International Union against Tuberculosis and Lung Disease recommends treating children under five who are contacts of infectious cases. Therapy for recently infected persons may not only be beneficial to those treated, but also serve as an effective tuberculosis epidemic control measure (Enarson *et al*, 2001). Newly infected person may be identified by investigation of close contacts of an infectious case. Contact investigation is rarely done in de-

Correspondence: Songpol Tornee, Department of Social and Environmental Medicine, Faculty of Tropical Medicine, 420/6 Rajvithi Road, Bangkok 10400, Thailand.

veloping countries because of other priorities and lack of resources.

Approximately one third of the population of Thailand is infected with tuberculosis. Nearly 100,000 people suffer from active tuberculosis every year, including 37,000 who have infectious disease, and spread the bacteria to the community (WHO, 1999). Nearly 20% of people with tuberculosis live in Bangkok where one sixth of the total population of Thailand live (WHO, 1998). However, there has been no recent confirmed estimate of tuberculosis infection among household contacts in Bangkok. The association between contact infection and epidemiological, as well as environmental factors, has never been explored in Bangkok. This study was thus conducted to determine the prevalence of tuberculosis infection and risk factors for tuberculosis infection among household contacts aged less than 15 years in Bangkok, Thailand.

This study was reviewed and approved by the Ethics Committee of the Ministry of Public Health, and the Ethics Committee of the Bangkok Metropolitan Administration.

MATERIALS AND METHODS

Study population and data collection techniques

The index cases included sputum-smear-positive pulmonary tuberculosis patients aged over 15 years who registered for tuberculosis treatment at Bangkok Chest Clinic, under the Ministry of Public Health and Health Care Centers, under the Bangkok Metropolitan Administration, between August 2002 and September 2003. All of the identified household contacts <15 years old of the index cases were subsequently investigated.

All sputum-smear-positive pulmonary tuberculosis patients during the specified period were asked to enrol in the study. Three hundred and forty-two tuberculosis patients and their 500 household contacts were eligible for the study. All patients were asked to give informed consent for study participation. Household contacts of tuberculosis patients were enrolled after obtaining written informed consent from their parent or guardian.

The medical records of tuberculosis patients were reviewed, including information on patient demographics, sputum smear result, and chest radiograph. All subjects were required to complete a structured questionnaire. A questionnaire regarding children's infection was administered in person to the child's parent or guardian who accompanied the child. Each child was examined for the presence of a Bacillus Calmette-Guerin (BCG) scar. The tuberculosis patients were asked to bring their household contacts <15 years of age to the tuberculosis clinic for a tuberculin skin test. For those children who did not come for evaluation, home visits were done to assess tuberculosis infection.

Tuberculin skin test

Tuberculin skin test was performed by the Mantoux method. The Mantoux skin test was administered by injecting 0.1 ml of 5 tuberculin units (TU) of purified protein derivative (PPD) intradermally into the volar surface of the forearm. The result was read 48-72 hours afterwards (American Thoracic Society, 2000). Participants were instructed to return in 48 hours for their test result. Home visits were done for participants who did not return in 48 hours. The diameter of the induration area was measured across the forearm. The result of the tuberculin skin test was recorded in millimeters of induration. In this study, a test was considered positive if the area of induration was at least 15 mm. Similar to other studies, the cut-off point was selected due to the effects of waning and high coverage of BCG vaccination (Beyer *et al*, 1997; Rathi *et al*, 2002). The study of Lockman *et al* (1999) suggested that the tuberculin skin test is useful for identifying tuberculosis infection in children, despite the high BCG vaccination rate.

In the official statement of the American Thoracic Society, interpretation of the tuberculin skin test result does not depend on BCG vaccination status, but varies according to risk of infection, with three different cut-off levels to define a positive test result. The mean reaction size among persons who have received BCG is often less than 10 mm. In high-prevalence countries, the tuberculin skin test is highly specific and a positive test is highly likely to indicate tuberculosis infection (American Thoracic Society, 2000b).

Moreover, several additional studies have indicated that the presence or absence of a BCG scar was not statistically associated with the degree of tuberculin sensitivity. Prior BCG vaccination at birth had no impact on the interpretation of the tuberculin skin test in household contacts of patients with smear-positive tuberculosis (Johnson *et al*, 1995; Mudido *et al*, 1999).

Questionnaire

The structured questionnaire used in this study was divided into three parts: index case, contact, and environmental factors. Index case information included socio-demographic data, residence, relationship with contact, tuberculosis symptoms, duration of tuberculosis symptoms, delay in treatment, and number of family members. Contact information included gender, age, sleeping in same room with index case, and duration of contact with tuberculosis patient. Environmental information included type of house, number of rooms, and house size.

An index case was defined as a smear-positive pulmonary tuberculosis patient aged >15 years who had at least one household contact aged <15 years. The contact could be a family member or any other person living and sleeping in the same house as the tuberculosis patient for at least three months before the commencement of tuberculosis treatment of the index case. Close contact was defined as a person who slept in the same room with the tuberculosis patient.

Duration of contact was measured as the total number of times per day that the contact was exposed to the index case. The sputum smear grade of acid-fast bacilli was recorded into three categories (1+, 2+, 3+). Cavitation was defined as the presence of cavitarion on a chest radiograph. Tuberculosis patients presenting with cough for as much as two weeks were designated suspects for tuberculosis. Delay in treatment was the duration in months between the onset of tuberculosis symptoms and the start of tuberculosis treatment.

House size was defined as the number of rooms in the house. Household size was determined by the number of family members in the household. Crowding was expressed as the average number of persons per room. It was estimated by dividing the number of people living in the house by the number of rooms. The definition of slum area was an urban residential area characterized by deteriorated unsanitary buildings, poor ventilation, poverty, and social disorganization. In this study, slum area was defined using the criteria set by the Bangkok Metropolitan Administration.

Statistical analysis

The data abstraction and interview form were checked for completeness and then double-entered and validated in Stata Program version 7 (Stata Corp, College Station, TX). Univariate analysis was performed using χ^2 to assess associations between all categorical risk factors and tuberculin skin test positivity. Odds ratios and their 95% confidence intervals were also calculated.

Factors found to be significantly associated with tuberculosis infection in univariate analysis were considered for inclusion in the multivariate model. In multivariate analysis, generalized estimating equation (GEE) was used to determine the risk factors for tuberculosis infection among household contacts of sputum-positive pulmonary tuberculosis patients. The GEE was selected due to outcomes for different contacts being exposed to the same tuberculosis case, thus, tuberculosis infection tends to aggregate within households. In such cases, the outcomes within clusters of contacts were not independent. This was taken into account by the GEE procedure. The GEE corrects for correlation and lack of independence of responses for contacts with an index case in common (clusters within households) using quasi-likelihood methods and robust variance estimators (Liang and Zeger, 1986). Adjusted odds ratios and their 95% confidence intervals were estimated. For all statistical tests, associations were considered significant at p-value ≤ 0.05.

RESULTS

During the study period, 342 eligible index cases and their 500 household contacts were identified. All contacts enrolled in the study had received BCG vaccination at birth. Of the 500 exposed children, the median age was 6 years (range 1-14 years). The prevalence of tuberculosis in-

Table 1
Factors associated with tuberculosis infection among household contacts.

Variables	TST Positive/total	TST (%)	OR	95%CI	p-value
Contact factors					
Gender					0.481
Male	117/253	46.24	1		
Female	122/247	49.39	1.13	0.79-1.61	
Age (year)					0.168
1-5	100/231	43.29	1		
6-10	94/184	51.08	1.36	0.92-2.01	
11-15	45/85	52.94	1.47	0.89-2.42	
Type of contact					0.000
Not close contact	32/177	18.08	1		
Close contact	207/323	64.09	8.08	5.18-12.62	
Duration of contact (Hour/day)					0.000
1-8	41/214	19.16	1		
9-16	188/272	69.12	9.44	6.16-14.46	
17-24	10/14	71.42	10.54	3.15-35.32	
TB case factors					
Gender					0.000
Male	122/306	39.87	1		
Female	117/194	60.31	2.29	1.58-3.31	
Age					0.069
< 21	7/18	38.89	1		
21-40	175/337	51.93	1.69	0.64-4.48	
41-60	49/123	39.84	1.04	0.37-2.87	
> 60	8/22	36.36	0.89	0.24-3.25	
Education					0.149
Primary school	157/307	51.14	1.79	0.68-4.68	
Secondary school	75/174	43.10	1.29	0.48-3.45	
Other	7/19	36.84	1		
Occupation					0.432
Unemployed	56/128	43.75	1		
Officer	14/26	53.85	1.50	0.64-3.49	
Labor	134/283	47.33	1.15	0.76-1.76	
Merchant	35/63	55.56	1.60	0.87-2.95	
Income (Baht, 1 US$ ≃40 Baht)					0.600
< 5,000	63/157	40.13	0.75	0.36-1.55	
5,000-10,000	159/307	51.79	1.20	0.60-2.39	
> 10,000	17/36	47.22	1		
Relationship with contact					0.000
Mother	78/91	85.71	15.60	7.90-30.80	
Father	97/178	54.49	3.11	1.98-4.89	
Grandparent	19/69	27.54	0.99	0.52-1.85	
Other	45/162	27.78	1		
Cavitation on chest radiograph					0.000
Noncavitary	53/234	22.65	1		
Cavitary	186/266	69.92	7.94	5.30-11.88	
Sputum smear grade					0.000
1+	40/162	24.69	1		
2+	49/144	34.03	1.57	0.95-2.58	
3+	150/194	77.32	10.39	6.36-16.97	
Cough > 2 weeks					0.000
Absent	27/99	27.27	1		
Present	212/401	52.87	2.99	1.84-4.85	

Table 1
Factors associated with tuberculosis infection among household contacts (cont).

Variables	TST		OR	95%CI	p-value
	Positive/total	(%)			
Hemoptysis					0.128
Absent	193/417	46.28	1		
Present	46/83	55.42	1.44	0.89-2.31	
Chest pain					0.078
Absent	113/257	43.97	1		
Present	126/243	51.85	1.37	0.96-1.95	
Dyspnea					0.110
Absent	112/253	44.27	1		
Present	127/247	51.42	1.33	0.93-1.89	
Fever					0.389
Absent	80/177	45.20	1		
Present	159/323	49.23	1.17	0.81-1.69	
Weight loss					0.222
Absent	129/284	45.42	1		
Present	110/216	50.92	1.24	0.87-1.77	
Delay in treatment					0.000
< 1 month	27/99	27.27	1		
1 month	82/205	40.00	1.77	1.05-3.00	
2 months	56/90	62.22	4.39	2.37-8.11	
3 months	44/66	66.67	5.33	2.71-10.49	
> 3 months	30/40	75.00	8.00	3.44-18.55	
Environmental factors					
House size (no. of rooms)					0.000
1	176/253	69.56	5.87	3.76-9.17	
2	21/97	21.65	0.71	0.39-1.29	
> 2	42/150	28.00	1		
Type of house					0.000
Slum	164/288	56.94	3.20	2.05-4.99	
Flat/apartment	37/82	45.12	1.99	1.12-3.54	
House	38/130	29.23	1		
Household size (no. of family members)					0.072
1-3	54/106	50.94	1		
4-6	151/302	50.00	0.96	0.61-1.49	
> 6	34/92	36.96	0.56	0.32-1.00	
Crowding (persons/room)					0.000
≤2	42/159	26.41	1		
2.1-3	65/151	43.05	2.10	1.30-3.39	
> 3	132/190	69.47	6.34	3.96-10.13	

fection among household contacts was found to be 47.80% (95%CI = 43.41-52.19). About half (253/500) were male. Of 500 children, 231 were between 1-5 years of age, 323 were close contacts, and 194 were exposed to an index case whose sputum smear 3+ for AFB. The majority of contacts (288/500) lived in slum areas.

The univariate analysis of risk factors for tuberculosis infection in household contacts is summarized in Table 1. Close contacts exposed to index cases were eight times more likely to have tuberculosis infection (OR = 8.08, 95%CI = 5.18-12.62). The risk of positive tuberculin skin test in household contacts was found to increase with duration of contact. Children exposed to an index case for 9-16 hours per day were nine times more likely to have tuberculosis infection (OR = 9.44, 95%CI = 6.16-14.46), and children exposed to an index case for 17-24 hours per day were ten times more likely to have tuberculosis infection

(OR = 10.54, 95%CI = 3.15-35.32). Household contacts exposed to female tuberculosis patients were more likely to have tuberculosis infection (OR = 2.29, 95%CI = 1.58-3.31).

Children with a positive tuberculin skin test were more likely to have been exposed to a father or mother with tuberculosis. Children exposed to a mother with tuberculosis were 15 times more likely to have tuberculosis infection (OR = 15.60, 95%CI = 7.90-30.80), and children exposed to a father with tuberculosis were three times more likely to have tuberculosis infection (OR = 3.11, 95%CI = 1.98-4.89). The risk of positive tuberculin skin test in household contacts was found to increase with the presence of cavitation on the chest radiograph of the index cases (OR = 7.94, 95%CI = 5.30-11.88). The risk of infection increased with increasing intensity of sputum smear grade in the index case. The risk was highest for children exposed to a 3+ smear positive case (OR = 10.39, 95%CI = 6.36-16.97).

The percentage of infected children increased significantly with delay in treatment of the index cases, from 27.27 in those delayed < 1 month to 75.00 in those delayed > 3 months (p = 0.000). The prevalence of a positive tuberculin skin test was inversely associated with house size (p = 0.000). The risk was greatest in household contacts living in a house with 1 room (OR = 5.87, 95%CI = 3.76-9.17). Household contacts living in slum areas were three times more likely to have tuberculosis infection (OR = 3.20, 95%CI = 2.05-4.99). The risk of positive tuberculin skin test in household contacts was found to increase with household crowding. Children living in a household of > 3 persons per room were six times more likely to have tuberculosis infection (OR = 6.34, 95%CI = 3.96-10.13).

The prevalence of a positive tuberculin skin test was not significantly associated with the presence of tuberculosis symptoms in index cases (hemoptysis, dyspnea, chest pain, fever, and weight loss) except cough > 2 weeks (OR = 2.99, 95% CI = 1.84-4.85). The prevalence of a positive tuberculin skin test was not significantly associated with gender of contact, age of contact, age of index case, education of index case, occupation of index case, family income, or household size.

The results of multivariate analysis are summarized in Table 2. Variables that were significant in univariate analysis at a level of p-value ≤ 0.05 were included in the multivariate model. Because of collinearity between house size and household crowding, house size was excluded from the multivariate model. The interactions between all independent variables were explored, but there was no interaction between any of the variables in the model. In the generalized estimating equation (GEE), the risk of tuberculosis infection was still significantly associated with close contact (adjusted OR = 3.31, 95%CI = 1.46-7.45), exposure to a female index case (adjusted OR = 2.75, 95%CI = 1.25-6.08), exposure to mother with tuberculosis (adjusted OR = 3.82, 95%CI = 1.44-10.14), exposure to father with tuberculosis (adjusted OR = 2.55, 95%CI = 1.19-5.46), exposure to index case with cavitation on chest radiograph (adjusted OR = 4.43, 95%CI = 2.43-8.05), exposure to index case with 3+ sputum smear grade (adjusted OR = 3.85, 95%CI = 1.92-7.70), and living in a crowded household (adjusted OR = 2.63, 95%CI = 1.18-5.85).

DISCUSSION

Prevalence of TB infection

A high prevalence of tuberculosis infection (47.80%; 95%CI = 43.41-52.19) was found among household contacts in Bangkok, Thailand. This may be explained, since *Mycobacterium tuberculosis* is virtually always transmitted by a patient with sputum-smear-positive tuberculosis to persons with whom he/she may be in contact. Persons living in the household of a tuberculosis patient are at high risk of becoming infected and developing tuberculosis themselves, particularly if their immune defenses are at all impaired (Zellweger, 2002). Tuberculosis in children is usually due to a recent infection, implying that transmission has occurred due to close contact with an adult with infectious tuberculosis and close contact is generally accepted to occur in the household. Several studies reported that the prevalence of tuberculosis infection among household contacts was around 41-49% (Lutong and Bei, 2000; Marks *et al*, 2000; Kenyon *et al*, 2002; Rathi *et al*, 2002). This leads to the assumption

Table 2
Multivariate analysis of factors associated with tuberculosis infection among household contacts.

Variables	Adjusted OR	95%CI	p-value
Contact factors			
Type of contact			
Not close contact	1		
Close contact	3.31	1.46-7.45	0.004
Duration of contact (Hour/day)			
1-8	1		
9-16	2.07	0.95-4.51	0.065
17-24	1.54	0.27-8.90	0.626
TB case factors			
Gender			
Male	1		
Female	2.75	1.25-6.08	0.012
Relationship with contact			
Mother	3.82	1.44-10.14	0.007
Father	2.55	1.19-5.46	0.016
Grandparent	0.55	0.21-1.43	0.219
Other	1		
Cavitation on chest radiograph			
Noncavitary	1		
Cavitary	4.43	2.43-8.05	0.000
Sputum smear grade			
1+	1		
2+	1.57	0.77-3.18	0.212
3+	3.85	1.92-7.70	0.000
Cough > 2 weeks			
Absent	1		
Present	1.60	0.53-4.76	0.401
Delay in treatment			
< 1 month	1		
1 month	0.90	0.42 - 1.92	0.779
2 months	1.27	0.51-3.15	0.606
3 months	1.60	0.53-4.76	0.401
> 3 months	1.87	0.59-5.96	0.286
Environmental factors			
Type of house			
Slum	1.59	0.74-3.42	0.237
Flat/apartment	1.05	0.44-2.52	0.909
House	1		
Crowding (persons/room)			
≤2	1		
2.1-3	1.31	0.60-2.88	0.497
> 3	2.63	1.18-5.85	0.017

that many of these current cases were actually infected by a member of their own family (Claessens *et al*, 2002).

Risk factors for tuberculosis infection

Close contact. Close contact with tuberculosis patients was associated with tuberculin skin test positivity among household contacts. Transmission of *Mycobacterium tuberculosis* usually follows close and prolonged contact between the infectious patient and a susceptible individual. Factors that influence transmission of tubercle bacilli include the environment into which the organisms are dispersed, the quantity of bacilli expelled by the index patient and the duration of exposure to the infectious patient (Golub *et al*, 2001). Transmission occurs most frequently to contacts who have spent prolonged periods in a close environment with the index case, generally, people who live and sleep in the same household (Menzies *et al*, 1999). The children sleeping in the same room as the index patient are more likely to get infection (Rathi *et al*, 2002).

Gender of index cases and relation with contacts. The results of this study confirmed existing knowledge, that tuberculosis transmission was associated with increased proximity, close female relative, and higher sputum smear grades (Lockman *et al*, 1999). The results of this study also revealed that tuberculin skin test positivity was associated with the relationship of index cases and contacts. The association was greatest if the tuberculosis patient was the mother of the contact. The mother generally spent more time in close proximity to children than other family members. Women have more prolonged and intimate contact than men with young children during child rearing. Earlier studies also reported that exposure to mothers with tuberculosis was associated with tuberculosis transmission to the child (Espinal *et al*, 2000; Kenyon *et al*, 2002).

Cavitation and sputum smear grade. Household contacts exposed to tuberculosis patients with both a positive smear and cavitary on chest radiograph were more likely to have tuberculosis infection. Many studies indicated that the risk of positive tuberculin skin test response in household contact was also found to increase with the presence of a cavitation on the case's chest x-ray and acid-fast bacilli in the case's sputum (Marks *et al*, 2000; Lienhardt *et al*, 2003). Patients with a combination of chest symptoms were significantly more likely to have higher grades of smear positivity (El-Sony *et* *al*, 2002). It is generally accepted that the number of infected contacts depends on the severity of disease in the index cases. The highest infection occurs when the index cases have a cavitation on chest radiograph and produce a large volume of positive sputum. Tuberculosis is spread from person to person through the air by droplet nuclei. Droplet nuclei are produced when persons with pulmonary tuberculosis cough or sneeze (American Thoracic Society, 2000). The presence of cough increases the probability of aerosol generation. In summary, the number of contacts infected by a person with tuberculosis also depends on the severity of disease in the index case, and the number of organisms excreted in the sputum.

Crowding. Overcrowded housing conditions have the potential to increase exposure of susceptible people to those with infectious respiratory disease, and may increase the probability of transmission. The association between housing density and tuberculosis incidence has long been recognized (Hawker *et al*, 1999). The study of Clark *et al* (2002) suggested that tuberculosis incidence was higher in communities with a higher average housing density. It was possible that communities with overcrowded housing also experienced a higher prevalence of latent tuberculosis infection.

In conclusion, the detection of latent *Mycobacterium tuberculosis* infection is an important tool for the controlling the spread of tuberculosis in the community (Rose, 2000). Therefore, current recommendations for the management of tuberculosis limit preventive therapy to children <5 years old, living in the same household as a patient with tuberculosis. Therapy for recently infected persons may not only be beneficial to those treated but also serve as an effective tuberculosis epidemic control measure (Enarson *et al*, 2001). It has been recommended that high-risk contacts should be evaluated within seven days of presentation of the index case and their medical assessment completed within one month (Etkind and Veen, 2000). Although therapy for latent tuberculosis infection is effective in reducing the probability of developing active tuberculosis, providing therapy for such a large fraction of the population is not feasible. An alternative strategy may focus on identifying and treating those at highest risk of developing active tuberculosis.

Household contacts of patients with infectious tuberculosis are at risk of *Mycobacterium tuberculosis* infection and disease. Contact investigation should be conducted for all patients with infectious tuberculosis as a routine part of the tuberculosis control program. Identification and management of childhood contacts should be a part of routine management of smear-positive pulmonary tuberculosis cases. Staff should be trained to perform, read, and record results of tuberculin skin tests. Contacts identified as having been infected with tuberculosis can then be offered preventive therapy to reduce the future risk of moving from the infected to diseased stage. Although the assessment and management of childhood contacts of adult smear-positive pulmonary tuberculosis patients was recommended, this rarely occurs in health care centers in Bangkok, except in the Bangkok Chest Clinic, because of other priorities. However, the lack of active involvement by health care staff could call into question the future sustainability of any contact screening policy. Both new sociobehavioral insights and technological innovations are needed to make this intervention most efficient and effective.

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