FACTORS ASSOCIATED WITH THE DEVELOPMENT OF TUBERCULOSIS IN BCG IMMUNIZED CHILDREN

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Abstract. In this hospital-based case-control study, children attending Siriraj Hospital and Queen Sirikit National Institute of Child Health from 1 December 2002 to 30 June 2003 were studied to define factors associated with TB in BCG immunized children (n=260). Subjects of the same age and sex were divided into case and control groups by tuberculosis status. Caregivers were interviewed with a structured questionnaire. Data were analyzed by univariate analysis and multivariate analysis for biological factors (birth weight, health status, nutritional status), socioeconomic factors (parental education, education of caregiver, parental occupation, household incomes, and stability of household incomes), and environmental factors (history of contact with a tuberculosis patient, housing ventilation, child's bedroom ventilation, biomass smoke, passive smoking, crowded family and crowded in child's bedroom). Our findings show that children who had contact with TB patients had a very high risk of tuberculosis, even though they were vaccinated at birth. The risks vary according to the closeness level: very close (OR 85.67, 95%CI=11.33-647.79), close (OR 31.11, 95%CI=3.93-246.22) and not close (OR 32.70, 95%CI=4.18-255.94). In order to identify the effect of others variables, the data was reanalyzed only in the group with no history of TB patient contacts (n=192). Living in a crowded family, which was reflected by an average of 5 or more persons per room, also increased the risk (OR 11.18, 95%CI = 2.35-53.20). The other factor that increased the risk for tuberculosis was passive smoking. Children who were exposed to passive smoking had a 9.31 times increased risk of getting tuberculosis (95%CI=3.14-27.58). These findings suggest that the public health department must develop a TB surveillance system in high TB prevalence areas, and in high density communities, and encourage smokers in every family to avoid smoking near children. Latent tuberculosis treatment recommendations for TB control cluster, as set by the Bureau of AIDS/TB and STIs, must be implemented in all health centers and an effective TB control program must be reinforced.

INTRODUCTION

Tuberculosis (TB) in children is more severe than in adults, so the World Health Organization (WHO) suggested that health sections in all endemic areas, such as Thailand, should immunize every child with the BCG vaccine at birth. This vaccine can prevent tuberculosis in children. TB morbidity and mortality in children have been decreasing gradually. However, since 1992 the number of TB cases in Thai children has remained constant. Although the BCG vaccine can reduce the virulence of the TB bacillus, other factors, such as biological, environmental, and socioeconomic factors may play a role in the development of TB in children after infection. Therefore, we conducted a hospital-based case-control study to define factors associated with the development of TB in BCG immunized children under 15 years of age.

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MATERIALS AND METHODS

This hospital-based case-control study was conducted from 1 December 2002 to 30 June 2003 at the Queen Sirikit National Institute of Child Health and Faculty of Medicine at Siriraj Hospital. Two hundred and sixty children, aged less than 15 years, who attended the study hospitals were enrolled in this study. Cases were TB patients who were diagnosed and treated from 2001 to 2003. Controls were children whose ages were similar to the cases (within 2 years) and similar sex, who attended the Orthopedic Department, Queen Sirikit National Institute of

Child Health during the same period of time.

This study was approved by the ethics committees of both study sites and of Mahidol University. Studied factors were divided into three groups: biological, environmental, and socioeconomic factors. Data were collected from medical records and interviews with parents or guardians.

Two hundred and sixty children were enrolled in this study. Their parents and/or guardians were interviewed by the researcher using a structured questionnaire. We conducted analyses for descriptive data and evaluated the association between the three groups for the development of TB using multiple logistic regression. To control the effect of confounding factors, the adjusted odds ratios were calculated by multiple logistic regression.

RESULTS

One hundred and thirty cases and controls were enrolled in this study. The majority of diagnoses were pulmonary TB (50%), TB of the lymph nodes (36.16%), and in the controls were bone fractures (60%), and club foot (16.2%).

Using univariate analysis, the cases and controls seemed to be comparable in terms of socioeconomic factors (Table 1), and biological factors (Table 2). Using univariated analysis, birth weight, general health condition (measured by average frequency of illness per month), underlying diseases and nutritional status, seemed not to be related to tuberculosis. The factors, which were significantly associated with the development of TB (adjusted for age), were: very close contacts with TB patients (OR 85.67, 95% CI=11.33-647.79), close contacts (OR 31.11, 95% CI= 3.93-246.22), and not close contacts (OR 32.70, 95% CI=4.81-255.94). The age was adjusted in the analysis to get rid of its residual confounding effect (Table 3).

Because the history of TB patient contact was the most important indicator of TB in children, the analysis was also performed in the group without a history of TB patient contact in order to see the effect of other factors. Passive smoke exposure was significantly associated with the development of tuberculosis in children

Table 1
Univariate analysis of socioeconomic factors associated with development of tuberculosis in children.

Socioeconomic factors	Case		Control		Odds ratio[a]	95% CI of Odds ratio	p-value[b]
	N	%	N	%			
Father's education	107		121				
Elementary	46	43.0	49	40.5	0.73	0.33 - 2.07	0.683
Secondary	45	42.1	52	43.0	0.75	0.30 - 1.88	0.542
Vocational degree	4	3.7	9	7.4	0.39	0.09 - 1.65	0.201
Bachelor degree or higher	12	11.2	11	9.1	1		
Mother's education	107		121				
Elementary	47	40.9	58	45.3	0.23	0.28 - 1.88	0.513
Secondary	49	42.6	57	44.5	0.74	0.302 - 1.98	0.594
Vocational degree	8	7.0	3	2.3	2.39	0.49 - 11.61	0.282
Bachelor degree or higher	11	9.6	10	7.8	1		
Household income (Baht per month)	130		130				
Less than 5,000 baht	21	16.4	16	12.3	1.08	0.48 - 2.48	0.854
5,001-10,000 baht	35	27.3	51	39.2	0.57	0.29 - 1.09	0.091
10,000-20,000 baht	38	29.7	35	26.9	0.89	0.44 - 1.76	0.728
More than 20,000 baht	34	26.6	28	21.5	1		
Mean (SD) = 18,75 (22,708.57)							
Stability of household income	130		130				
Stable (Every month)	18	13.8	14	10.8	1		
Unstable (Not every month)	112	86.2	116	89.2	1.35	0.64 - 2.85	0.436

[a]Adjusted for age; [b]Chi-square test

Table 2
Univariate analysis of biological factors associated with development of tuberculosis in children.

Biological factors	Case		Control		Odds ratio[a]	95% CI of Odds ratio	p-value[b]
	N	%	N	%			
Birth weight	126		130				
Normal	111	88.1	119	91.5	1		
Low birth weight	15	11.9	11	8.5	1.47	0.65 - 3.33	0.349
Frequency of illness (Per month)	130		130				
Never	91	71.1	100	76.9	1		
1 time	16	12.5	19	14.6	0.91	0.44 - 1.87	0.813
2 times or higher	21	16.4	11	8.5	2.08	0.95 - 4.55	0.069
Underlying diseases	130		130				
No	118	90.8	122	93.8	1		
Measles	4	3.1	5	3.8	0.83	0.28 - 3.15	0.767
Chicken pox	8	6.2	3	2.3	2.76	0.71 - 10.64	0.131
Nutritional status	130		130				
Normal	109	83.6	109	83.6	1		
Malnutrition (Moderate level)	10	7.8	6	4.9	0.73	0.32 - 1.69	0.462
Malnutrition (Severe level)	11	8.6	15	11.5	1.66	0.59 - 4.75	0.334

[a]Adjusted for age; [b]Chi-square test

Table 3
Univariate analysis of environmental factors associated with development of tuberculosis in children.

Environmental factors	Case		Control		Odds ratio[a]	95% CI of Odds ratio	p-value[b]
	N	%	N	%			
History of TB patient contact	130		130				
No	65	50.0	127	97.7	1		
Not close	16	12.3	1	0.8	32.70	4.18 - 255.94	<0.001
Close	13	10.0	1	0.8	31.11	3.93 - 246.22	0.001
Very close	36	27.7	1	0.8	85.67	11.33 - 647.79	<0.001
Passive smoking (1)	130		130				
No	75	57.7	80	61.5	1		
Not close	24	18.5	44	33.8	0.57	0.32 - 1.03	0.064
Close	7	5.4	2	1.5	3.67	0.74 - 18.27	0.112
Very close	24	18.5	4	3.1	6.42	2.13 - 19.39	<0.001
Passive smoking (2)	130		130				
No	75	57.7	80	61.5	1		
Not close	24	18.5	44	33.8	0.57	0.32 - 1.03	0.064
Close (and very close)	31	23.9	6	6.6	5.50	2.17 - 13.95	0.003
Child's bedroom ventilation	130		130				
Good	64	49.2	73	56.2	1		
Poor	66	50.8	57	43.8	1.32	0.81 - 2.16	0.261
Crowded in child's bedroom	130		130				
1 Person	4	3.1	5	3.9	1		
2 Persons	29	22.3	17	13.2	1.80	0.41 - 7.93	0.436
3 Persons	47	36.2	66	51.2	1.03	0.24 - 4.48	0.965
4 Persons or higher	50	38.5	41	31.8	2.55	0.56 - 11.63	0.228
Mean (SD) = 3.2 (1.07)							
Average number of persons per room	130		130				
1 Person or less	19	14.6	5	3.8	1		
1.1 - 2.9 Persons	49	37.7	48	36.9	0.55	0.25 - 1.23	0.146
3 - 4.9 Persons	44	33.8	63	48.5	0.80	0.36 - 1.80	0.591
5 Persons or higher	18	13.8	14	10.8	3.02	0.88 - 10.32	0.078
Mean (SD) = 6.98 (19.43)							

[a]Adjusted for age; [b]Chi-square test

Table 4
Association between significant factors and development of tuberculosis in chidren adjusted by age, average number of persons per room, passive smoking in children without history of TB patient contact.

Factors	Unexposed with TB patient		
	Odds ratio	95 % CI of OR	p-value[a]
Frequency of illness			
Never	1		
1 Time	0.36[b]	0.11 - 1.19	0.087
2 Times or higher	2.59[b]	0.97 - 6.91	0.059
Passive smoking			
No	1		
Not close	0.54[c]	0.25 - 1.16	0.12
Close (and very close)	9.31[c]	3.14 - 27.58	0.0001
Average number of persons per room			
1 Person or less	1		
1.1 - 2.9 Persons	1.04[d]	0.34 - 3.22	0.948
3 - 4.9 Persons	1.44[d]	0.46 - 4.57	0.510
5 Persons or higher	11.18[d]	2.35 - 53.20	0.002

[a]Chi-square test; [b]Adjusted for age, average number of persons per room, and passive smoking; [c]Adjusted for age, average number of persons per room, and frequency of illness; [d]Adjusted for age, frequency of illness, and passive smoking

not exposed to TB patient groups when adjusted for age, average number of persons per room, and frequency of illness (OR=9.31, 95 % CI=3.14-27.58, p=0.0001). This means that children exposed to passive smoke had a higher risk of getting TB than children not exposed to passive smoke, even when they had no direct contact with TB patients. The average number of persons per room, 5 persons or higher, was associated with the development TB in children, (OR= 11.18, 95% CI = 2.35-53.20) in those with no history of being exposed to a TB patient, when adjusted for age, frequency of illness, and passive smoking (p=0.002). This means children who lived in high density families had a higher risk for tuberculosis than children who lived in low density families, even though there were no TB patients in the family.

Frequency of illness (per month) did not show a significant association with the development of TB when adjusted for age, average number of persons per room, and passive smoke exposure in children who had not history of contact with TB patients.

DISCUSSION

According to our results, the risk factors for the development of TB seem to be similar between BCG immunized and non-immunized children, similar to other studies (Romanus, 1982; Lobato, 1995).

One important aspect that should be considered is BCG efficacy. BCG efficacy was not evaluated in this study because non-BCG immunized children are difficult to find in Thailand where BCG vaccination coverage has been almost 100% since 1990. However, many previous studies in Canada, Central Africa Republic and Japan have reported that the protective efficacy against TB is uncertain. The results vary from 0% to 80%, with an average of less than 50% (Colditzn, 1994; 1995; Lanckriet, 1995; Hashimoto, 1997; Brewer, 2000). The BCG vaccine has been reported to decrease the severity and mortality of TB in children (Sirinavin, 1991).

As in many previous studies, this study found a strong association between a history of TB patient contact and the development of TB in children. This study found an unequal association between the closeness of contact and TB in children. The risk increased in children the closer the contact with the TB patient, due to a higher chance of getting the TB bacillus via their respiratory tract (Schaaf *et al*, 1999, 2002;

Luthong and Bei, 2000). This occurs with most air-borne diseases. This result supports the recommendation of the Tuberculosis Control Cluster, which recommends the special care of children who have had close contact with a TB patient. This recommendation is called the latent tuberculosis treatment guideline. All TB close contacts who test tuberculin positive must receive treatment even if they have no signs of TB.

Our results confirm other studies which found TB outbreaks to occur in crowded areas with large family sizes (Scrimshaw *et al*, 1968; Gross *et al,* 1989; Hawker *et al*, 1999; Riv *et al*, 1999).

Passive smoking in the very close contact group showed a significant association with development of TB in children when adjusted for age. This finding agrees with results found in Spain, the United States and China (Molina *et al*, 1980; Houston *et al*, 1990; Altet *et al*, 1994; 1996; Alcaide *et al*,1996). The biological plausibility of smoking being linked to the development of TB is based on the evidence that tobacco smoke adversely affects ciliary action and the movement of the mucus blanket. Children are exposed to tobacco smoke in two ways, mainstream and side stream. Mainstream cigarette smoke is the suspended particles released from the mouth end of a cigarette during a puff. Side stream cigarette smoke is the material released directly into the air from the burning tip of the cigarette. Passive smoking effects children by reducing lung function. The toxic substances in tobacco smoke have an impact on the immune defense mechanism (Molina *et al*, 1980). They interfere with cell mediated lung defense mechanisms (Houston *et al*, 1990) by decreasing the number of macrophages in the lung tissue and the number of T-lymphocytes (T4 and T8), and prevent the activation of T-lymphocytes (Molina *et al*,1980). When exposed to TB, the immune system cannot destroy the organism.

Our study had some limitations. First, it was a hospital-based case-control study. All the cases were diagnosed 1-3 years before the interview, therefore, recall bias may have occurred in this study. Some children may have changed their environment or socioeconomic status. A prospective cohort study is the best in controlling this kind of bias, but a longer follow-up time would be needed. The incidence of TB in children is low. TB in children is difficult to diagnose because this disease has non-specific signs and symptoms in each organ, so the diagnosis must be performed in hospitals, which have adequate equipment (x-ray, laboratory, etc) and skilled personnel (pediatricians, technicians, radiologists, etc). The identification of a small number of cases within a large cohort would consume a large number of resources making the study implausible.

Second, this study was conducted in two government hospitals, Siriraj Hospital and Queen Sirikit National Institute of Child Health, in which their services are commonly known for thier availability and accessibility for all children. The cases from the two hospitals used the same standardized diagnostic criteria. The majority of the samples in the two hospitals came from Bangkok and the central region of Thailand. This can reduce generalizability to the general population of Thailand in terms of socioeconomic conditions. Most of children's parents has stable monthly incomes. There was little diversity in the incomes of the sample groups. This may be the reason why an association between socioeconomic status and TB was not evident. To reduce this limitation, samples might have been collected from several hospitals around Thailand. This could not be done in this study due to limitations of time and budget.

Finally, this study contained no direct observation of behavior or environment. All the information was obtained from the interview. Information bias may have confounded this. To minimize this bias, the interviewer explained to the children's parents or caretakers the significance of this study without telling them the study's hypothesis. The information about ventilation in the house was difficult to assess. The interviewer had to help the parent or guardian recall information regarding this aspect. The ventilation information focused on the child's bedroom and the room the child spent most of the day in. In order to make it easier to recall, the interviewer made a square that represented the room's plan. The child's parent or caretaker pointed to the walls on which doors and windows exist. This was how the ventilation information was obtained. The passive smoking was

an important variable in this study. We asked about smokers in family in two parts: who smoked and where they often smoked.

We found that passive smoking and large family size are factors that influence the development of TB in children. Household contacts were the main risk factor for TB. BCG immunized children who had TB patients in the family or house, and who were always exposed to passive smoking or who lived in large size families were at exceptionally high risk of developing TB.

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