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Mantoux test results and BCG vaccination status in TB-exposed children

Fadilah Harahap, Ridwan M. Daulay, Muhammad Ali, Wisman Dalimunthe, Rini Savitri Daulay

Abstract

Background Tuberculosis (TB) infection is highly prevalent in Indonesia. The source of transmission of TB to a child is usually via an adult with sputum smear-positive pulmonary tuberculosis. The Mantoux test is a diagnostic tool for tuberculosis infection. The BCG vaccine has been used for the prevention of TB, but its efficacy is still debated.

Objective To assess for an association between Mantoux test results and BCG vaccination in children who had contact with adult pulmonary tuberculosis and to assess for differences in Mantoux test induration with regards to nutritional status, age, type of TB contact, and time duration since BCG vaccination in BCG-vaccinated and BCG-unvaccinated children.

Methods A cross-sectional study was conducted in February-March 2011 on infants and children (aged 3 months to five years), who had household contact with adult pulmonary TB. We performed tuberculin (Mantoux) skin tests to detect TB infection in the children. Subjects were consisted of two groups: BCG-vaccinated and BCG-unvaccinated.

Results Subjects were 100 children (50 BCG-vaccinated and 50 BCG-unvaccinated subjects). Positive Mantoux test results were observed in 9 vaccinated subjects and 33 unvaccinated subjects. The mean diameters of induration in the vaccinated and unvaccinated groups were 7.6 mm and 9.6 mm, respectively (95%CI of difference -4.25 to 0.20; P=0.074). In children who had household contact with sputum smear-positive adult pulmonary TB, BCG vaccination was a protective factor against TB infection, with an odds ratio (OR) of 0.113 (95%CI 0.045 to 0.286; P=0.0001). There were no significant differences in Mantoux test induration associated with nutritional status, age, type of TB contact, and duration since BCG vaccination, between the two groups.

Conclusion BCG vaccination has a protective effect on TB-exposed children, based on Mantoux test results. However, there are no differences in Mantoux test induration associated with nutritional status, age, type of TB contact, or duration since BCG vaccination, between the BCG-vaccinated and BCG-unvaccinated groups. **[Paediatr Indones. 2015;55:7-12.]**

Keywords: *BCG vaccination, Mantoux test, household contact, tuberculosis*

Tuberculosis infection and disease among children are much more prevalent in developing countries.[1-3] The *World Health Organization* (WHO) estimated that worldwide, at least 180 million children under the age of 15 years were infected with *Mycobacterium tuberculosis*.[4,5] According to the WHO 1998 report on the struggle against TB, every 4 seconds, one person becomes infected with TB and every 10 seconds, one person dies.[6] In Indonesia, the TB incidence was reported to be 228 per 100,000 people, and in

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From the Department of Child Health, University of Sumatera Utara Medical School/H. Adam Malik Hospital, Medan.

Reprint requests to: Dr. Fadilah Harahap, Department of Child Health, University of Sumatera Utara Medical School/H. Adam Malik Hospital, Jl. Bunga Lau No. 17, Medan 20136. Tel. +6261 8361721 – 8365663. Fax. +6261 8361721; E-mail: harahap_fadilah@yahoo.co.id.

Medan, TB was suspected to be 264 per 100,000 people, with a positive pulmonary TB proportion of 10.3%, according to Tuberculous Sub-Directorate of Indonesian Ministry of Health (*Subdit TB Depkes RI*) 2000-2010.[7]

In Indonesia, the *Bacille Calmette-Guerin* (BCG) vaccination has been used for TB prevention, but its efficacy is still debated.[3] The protective effect of the BCG vaccine was found to be between 0 and 80%, in clinical and case-control studies carried out in various countries.[8] Persons living in the household of a TB patient have a high risk of becoming infected, so it is important to evaluate children in these homes. The Mantoux test is the standard method to detect TB infection. BCG vaccination can affect Mantoux test results until 5 years after immunization.[3]

The aim of this study was to assess for an association between Mantoux test results and BCG vaccination in children who had contact with adult pulmonary tuberculosis and to assess for differences in Mantoux test indurations associated with nutritional status, age, type of TB contact, and duration since BCG vaccination, in both BCG-vaccinated and BCG-unvaccinated children.

Methods

A cross-sectional study was undertaken on household contacts of adult pulmonary TB patients with positive sputum smears who registered at the pulmonary specialist outpatient center and *Balai Pengobatan Pemberantasan Penyakit Paru paru* (BP4) in Medan. Children aged 3 months to 5 years who lived with adult pulmonary TB patients with positive sputum smears and whose parents approved and were willing to fill out questionnaires were included in the study.

We excluded children with severe malnutrition, measles, mumps, severe tuberculosis, abdominal typhoid, malignancy, those in an immunocompromised state, likely to receive long-term corticosteroid therapy or other immunosuppressive drugs, as well as those with other conditions that affect immune status. In addition, children who received a live vaccine immunization in the 6 weeks prior to the study or a Mantoux test in the 2 weeks prior to the study were excluded from the study. We divided the participants into two groups: BCG-vaccinated and BCG-unvaccinated. Immunization status information was obtained from parents, observation of BCG scars in deltoid area or their *Kartu Menuju Sehat* registration.

The minimum required sample size was calculated using a formula to test the hypothesis of two independent proportions resulting in 50 children per group. Subjects' baseline characteristics and information were obtained from questionnaires completed by parents. Mantoux tests were performed on all subjects using PPD RT 23 2TU at a dose volume of 0.1 mL on the volar left forearm. We read Mantoux test results after 48-72 hours. Measured diameter was based on induration, not hyperemia. Mantoux test results were considered to be positive for induration diameters of ≥10 mm in BCG-unvaccinated children, and ≥15 mm in BCG-vaccinated children.

This study received approval from the Research Ethics Committee of the Faculty of Medicine, University of North Sumatera.

We used SPSS version 15.0 and Microsoft Excel 2007 for data processing. Chi-quadrat test was used to evaluate the relationship between Mantoux test results (nominal scale) and BCG-vaccination status (nominal scale), while ANOVA test was used to assess relationships of Mantoux test induration to age and nutritional status. Independent T-test was used to evaluate the relationship between Mantoux test induration and type of TB contact. Linear regression was used to assess the relationship between Mantoux test induration and time duration since BCG vaccination. Differences were considered to be significant for P values of <0.05 with 95% confidence intervals (CI).

Results

Characteristics and distribution of subjects in both groups are shown in **Table 1.** Mean age, gender, weight, and height were similar in the BCG-vaccinated and BCG-unvaccinated groups. The most common maternal and paternal educational levels were senior high school for both groups.

The mean diameters of Mantoux test induration in the BCG-vaccinated and unvaccinated groups were not significantly different (**Table 2**). However, we found that significantly more BCG-vaccinated subjects had negative Mantoux test results than

unvaccinated subjects with odds ratio (OR) 0.113, indicating that BCG immunization was a protective factor against TB infection (**Table 3**).

Anova test revealed no significant differences in diameters of Mantoux test induration between groups, with regards to age and nutritional status (P>0.05) (**Table 4**).

Table 5 shows there were no significant differences in Mantoux test induration between groups, based on history of TB contact.

Linear regression analysis revealed no significant relationship between duration since BCG vaccination and Mantoux test induration (r=0.03), as shown in **Figure 1**.

Discussion

The aim of our study was to analyze the status of BCG immunization as a protective factor for TB infection,

Table 1. Demographic data of subjects

Characteristics	BCG-vaccinated (n = 50)	BCG-unvaccinated (n = 50)
Mean age, years (SD)	2.7 (1.51)	3.1 (1.44)
Age range, n (%)		
1month – 1 year	4 (8)	4 (8)
>1 - 2 years	15 (30)	7 (14)
>2 - 3 years	10 (20)	10 (20)
>3 - 4 years	4 (8)	11 (22)
>4 - 5 years	17 (34)	18 (36)
Gender, n (%)		
Male	29 (58)	24 (48)
Female	21 (42)	26 (52)
Mean body weight, kg (SD)	13.0 (5.05)	13.3 (4.57)
Mean body height, cm (SD)	89.5 (16.77)	87.2 (15.90)
Paternal educational level, n (%)		
Elementary school	2 (4.0)	5 (10.0)
Junior high school	3 (6.0)	21 (42.0)
Senior high school	41 (82.0)	23 (46.0)
Diploma	4 (8.0)	1 (2.0)
University	0	0
Maternal educational level, n (%)		
Elementary school	2 (4.0)	10 (20.0)
Junior high school	12 (24.0)	17 (34.0)
Senior high school	30 (60.0)	20 (40.0)
Diploma	2 (4.0)	0
University	4 (8.0)	3 (6.0)

Table 2. Mean diameters of Mantoux test induration for both groups

Mantoux test	BCG		95% CI of difference	P value
	Vaccinated	Unvaccinated		
Mean induration diameter (SD), mm	7.6 (5.98)	9.6 (4.89)	-4.25 to 0.20	0.074

Table 3. Association between Mantoux test results and BCG vaccination

	Mantoux test result, n		Total	P value	OR (95% CI)
	Positive	Negative			
BCG, n				0.0001	0.113 (0.045 to 0.286)
Vaccinated	9	41	50		
Unvaccinated	33	17	50		
Total	42	58	100		

Table 4. Differences in diameter of Mantoux test induration between groups, based on age and nutritional status

Characteristics	BCG vaccinated		BCG unvaccinated	
	Mean diameter (SD), mm	P value	Mean diameter (SD), mm	P value
Age				
≤1 year	4.75 (4.27)	0.65	9.00 (6.05)	0.87
1-2 year	7.80 (5.67)		8.43 (4.43)	
2-3 year	6.40 (6.29)		11.0 (3.84)	
3-4 year	10.75 (3.78)		9.27 (4.84)	
4-5 year	8.12 (6.87)		9.72 (5.65)	
Nutritional status				
Obese	7.50 (6.36)	0.72	7.33 (6.43)	0.60
Overweight	5.82 (4.92)		9.79 (2.97)	
Normoweight	8.40 (5.85)		8.81 (5.32)	
Underweight	7.88 (6.94)		10.71 (5.61)	

Table 5. Differences in diameters of Mantoux test induration between groups, based on history of TB contact

Characteristics	BCG-vaccinated			BCG- nvaccinated		
	Mean diameter (SD), mm	95% CI of differences	P value	Mean diameter (SD), mm	95% CI of differences	P value
History of TB contact						
Parent	8.61 (6.06)	-1.59 to 5.25	0.29	10.64 (4.20)	-0.93 to 4.49	0.19
Others	6.78 (5.89)			8.86 (5.31)		

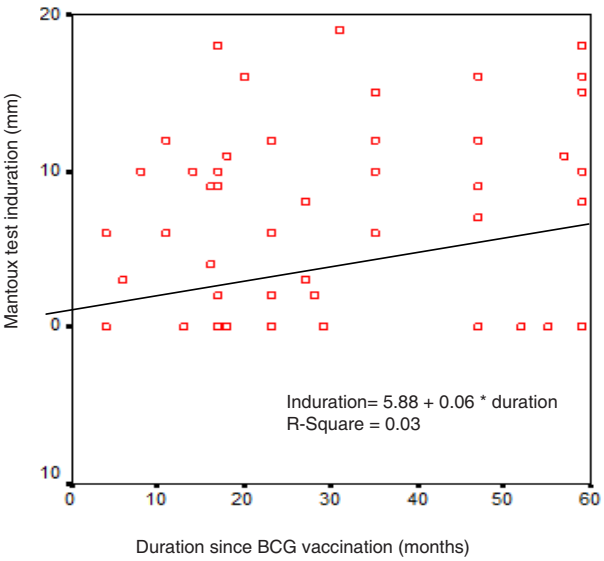

Figure 1. Linear regression analysis of duration since BCG vaccination and Mantoux test induration

where Mantoux test were used to determine the status of TB infection. In this study, all the subjects had been exposed to adults in their household with TB-positive sputum smears. Baseline characteristics of subjects were similar in the two groups.

Tuberculosis remains the most frequently-occurring, infectious disease in the world, and the WHO estimates that the incidence will continue to increase.[9,10] The important risk factors for transmission of infection are young age, an immunocompromised state, and contact with an adult who has TB-positive sputum.[11,12] Additional factors are associated with physical characteristics of the household, e.g, size, crowding, and ventilation.[11,13]

A study in Greenland, Denmark found that low maternal education level was associated with higher risk of TB infection among children, but no relationship with paternal educational level was reported.[14] We did not assess for this association, but we found that maternal educational level was higher in the BCG-vaccinated group than in the BCG-unvaccinated group.

The cellular immune response is responsible for protection against TB infection.[3,15] The tuberculin test is a diagnostic tool with high sensitivity and specificity for detecting TB infection.[16,17] The skin induration resulting from the tuberculin test is triggered by M. *tuberculosis* infection, BCG vaccination, or atypical mycobacterial infection.[18,19] A study in Veracruz, Mexico, reported that Mantoux test results helped

identify children in a BCG-vaccinated population who had recent exposure to persons with pulmonary TB, and were probably infected with *M. tuberculosis*.[20] We considered the Mantoux test to be positive for induration diameters of ≥ 15 mm in BCG-vaccinated subjects. A study in Hamburg, Germany compared a *Mycobacterium tuberculosis*–specific enzyme-linked immunospot (ELISPOT) assay to the tuberculin test. They found that for occasional and BCG-vaccinated contact, the tuberculin skin test cut-off point should be raised from 5 to 10 mm in order to minimize the number of false positive results.[21] A study in Canada showed that Mantoux test induration cut-off point of 15 mm was able to eliminate the false positive BCG effect.[22]

We found no statistically significant difference in mean tuberculin skin test induration in the BCG-vaccinated and BCG-unvaccinated groups. An Istanbul study reported that the tuberculin test induration diameter in BCG-vaccinated subjects was significantly higher than in BCG-unvaccinated subjects.[6] These children stayed in the same house with adult TB pulmonary patients, hence, their daily exposure to *M. tuberculosis* increased their cellular immune response. This cellular immune response was greater than that from BCG vaccination.[6]

We found positive Mantoux test results in 18% of the vaccinated and 66% of the unvaccinated groups, while negative test results were 82% and 34%, respectively (**Table 3**). In an Umerkot, Pakistan study, positive Mantoux test results in the vaccinated and unvaccinated groups were 19% and 81%, respectively, and negative results were 11.7% and 88.3%, respectively.[23] These variations may have been due to different vaccine strains, doses, methods and routes of vaccine administration, subjects' age and nutritional status, virulence of prevealent TB strains, and atypical mycobacterial prevalence.[3] We also used different cut-off points for Mantoux test induration diameters for the BCG- vaccinated and BCG-unvaccinated children. So far, more than 3 million BCG vaccine doses have been used worldwide, but use of the vaccine remains controversial and uncertain.[3] The BCG vaccine can affect Mantoux test results, causing false positive results. This effect declines over time, and should be minimal 5 years after receiving the vaccine.[3,24]

A systematic review performed in Brazil reported that the BCG vaccine has a high protective effect against clinical forms of meningeal and miliary tuberculosis, but its protective effect against pulmonary TB varies widely.[8] These variations have been attributed to different factors, including differences in exposure to mycobacteria in the environment, genetic characteristics of a population, the virulence of the *M. tuberculosis* strains, the strains comprising the BCG vaccines, and nutritional differences in those undergoing vaccinations.[24]

We also found a significant association between negative Mantoux test receiving BCG vaccination (P=0.0001; OR=0.113). Similary, a Turkish study reported that in children exposed to adult TB patients, the ELISpot and Mantoux tests showed that BCG-vaccinated children had an OR of 0.60 for TB infection compared to unvaccinated children.[25] A study in India also found that BCG-unvaccinated children had higher risk for TB infection.[12]

We found no significant differences in Mantoux test indurations between the groups, with regards to age and nutritional status, in contrast to an Indian study.[12] This difference may have been due to the lack of malnutritioned children in our study, although the mean ages were similar.

In our study, we found no association between the duration since BCG vaccination and Mantoux test induration, similar to a Turkish study with no significant differences in Mantoux test induration in the groups of children until 6 years of age.[6] In contrast, a study in Iran showed that Mantoux test induration decreased with age, therefore, it may be necessary to repeat BCG vaccination in children at the age of entering primary school.[26]

The strength of our study was that all subjects had similar characteristics, and the factors that influenced Mantoux test results were comparable between groups. Limitations of this study were that the positive Mantoux test results could not be attributed only to *M. tuberculosis* infection and that the duration after immunization was not the same for all children. Further research is needed to assess the relationship of BCG immunization status with Mantoux test.

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