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BCG Vaccination amongst Maternal and Child Leprosy in Endemic Area of Tuban, Indonesia

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ABSTRACT

Leprosy remains a significant health burden, especially in the area where the disease remains endemic. In Indonesia, the number of cases reached 19,938 in 2019 and the disease remains endemic in several part of the country. The course of leprosy and its development of the disease are determined by several factors, including immunity. Thus, this paper aims to evaluate and analyze the immunity status amongst child and maternal leprosy. A cross sectional study was conducted in an endemic and non-endemic area of leprosy in Tuban regency, Indonesia. We found significant difference on BCG vaccination status amongst pediatric subject between the group with child leprosy and healthy mother in endemic area compared to the healthy child and mother in nonendemic area. No significant association were observed amongst other groups and other parameters. In conclusion, the difference in BCG vaccination status could be associated with leprosy. However, it is affected by several factors, such as the waning effect of BCG and co-infection amongst leprosy patients.

Keywords: Leprosy; BCG vaccination; Endemic, Non-endemic

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INTRODUCTION

Leprosy is a chronic infection caused by *Mycobacterium leprae*. Previous studies showed that men were predominantly more affected by leprosy than women do. The significant difference could be attributed to underdiagnosis due to the sociocultural factors amongst women, such as illiteracy, limitation of mobility, and having low social status.¹ In addition, the position of women in the household increases the risk of leprosy transmission to their child; and the high incidence of leprosy amongst pediatric population should prompt a warning of an uncontrolled transmission of the disease.¹⁻⁴ In 1991, the World Health Organization (WHO) has proposed the leprosy elimination program that aimed to reduce the global prevalence of leprosy to less than one case per 10,000 population by the year 2000.^{5,6} However, leprosy remains endemic in some country, with relatively high burden in children and an increase in the new cases detection rate.^{7,8} In 2019, 177,175 registered cases and 202,185 new cases of leprosy were observed globally.⁹ Three countries with the highest leprosy cases i.e. India, Brazil, and Indonesia accounted for 80% global leprosy cases.¹⁰ In Indonesia, registered leprosy cases reached 19,938 cases in 2019, in which 17,439 were new cases; leprosy on female add up to 10,741 cases (61.59%) and 2,009 (11.52%) cases were observed amongst children.¹¹ Despite rarely being lethal, leprosy cause numerous morbidity; ranging from skin and peripheral nerves manifestation to tissue damage, deformity, disability, and stigma.^{4,12-15}

The most determining risk factor to contract leprosy is proximity and close contact with person with the disease, especially patient with multibacillary (MB) type.¹⁶⁻¹⁸ In addition, other factors such as age older than 15 years, frequency of changing bed linen, and education status are also determine the development of clinical leprosy.¹⁸⁻²⁰

However, *M. leprae* is known to have low virulence and not everyone who has been exposed to the bacteria would develop the disease.^{21,22} Several factors that affect host immune response are also known as a risk to develop leprosy, such as polymorphism in the gene involved in innate immunity and inflammatory response.^{23,24} Furthermore, viral coinfection, notably hepatitis B virus (HBV) is associated with leprosy and leprosy reactions.²⁵⁻²⁷

Due to the nature of the disease, that highly influenced by environment, and immune response of the host, prophylaxis to boost the immune response or immunoprophylaxis is considered a promising prevention method against leprosy. Preceding study found that the Bacillus Calmette-Guérin (BCG) vaccination offer partial immunity against *M. leprae*. However, the degree of BCG protective effect varies greatly amongst different studies, it confers 60% protection in observational studies but in clinical trials the majority cases did not benefit from BCG vaccination as the protective effect is only 40% in clinical trials.^{28,29,29} In addition, immunization with BCG also poses undesirable result, such as increasing the risk of developing leprosy and leprosy reactions after vaccination especially in person who is already exposed to the mycobacteria.³⁰⁻³²

Previous findings found the importance of immunization in leprosy prevention with BCG, and possibly, with hepatitis B vaccine as stated by hepatitis B virus is associated with leprosy. Nevertheless, the results of the research regarding BCG effect differs dramatically between studies and currently there is no study about the association of non-BCG vaccines with leprosy. Thus, this paper aims to evaluate and analyse the issue regarding immunity status amongst patients with leprosy, especially in maternal and child leprosy, through immunization history of BCG and non-BCG vaccines.

MATERIALS AND METHODS

Study design and data collection

This cross-sectional study was conducted in endemic area and non-endemic area of leprosy in Tuban regency, East Java Province, Indonesia from March until June 2020. Tuban regency is considered a leprosy pocket area with 173 cases in 2018, of which 43.35% cases were maternal leprosy and the leprosy cases amongst children accounted for 5.81% of the total cases.³³

Study population of this study include mother and her child who live in endemic and non-endemic area. The inclusion criteria for subject with leprosy was those with confirmed diagnosis of leprosy and aged between 5-18 years old for children; whilst the excluded were those with any leprosy reaction, poor general condition, and diagnosed with inflammatory or autoimmune disorder, allergy, or infection other than leprosy, and pregnancy. All of the subjects were given informed consent. Leprosy cases were selected from the local primary health centre's registry data. Thereafter, to confirm the diagnosis, the subjects underwent clinical examination done by a dermatologist and then acid-fast staining by trained health and laboratory professional from Dr Soetomo General Hospital and Tropical Disease Centre of Airlangga University.

Subjects were divided into 5 groups as follows (Figure 1), group A was child with leprosy and mother without leprosy in an endemic area; group B was child without leprosy and mother with leprosy in an endemic area; group C were child with leprosy and mother with leprosy in an endemic area; group D was child without leprosy and mother without leprosy in an endemic area; group E was child without leprosy and mother without leprosy in non-endemic area.

Survey was done to examine BCG scar and the history of other vaccinations. Positive history of BCG vaccination was defined with a presence of BCG scar on deltoid region, whilst history of other vaccinations was considered as positive with the completion of immunization according to the subject's age that were written down in the monitoring book or chart or positive recall by the mother. The study protocol has been approved by the Health Research Committee of Dr Soetomo General Hospital, Surabaya (Ref. 1664/KEPK/XI/2019).

Statistical analysis

Data were analysed using SPSS® software (IBM Corp., Armonk, New York, USA). Descriptive statistics were done to present the data. One-way analysis of variance (ANOVA) was used to analyse the inter-group means comparison. A p -value of <0.05 was considered statistically significant.

RESULTS

Data were obtained from 212 subjects, in which 38 were assigned to group A, 48 into group B, 6 into group C, 66 into group D, and 54 into group E. Subjects were a pair that composed of a mother and her child. Table 1 and 2 shows the demographic characteristics of the child aged subjects and the mother, respectively.

Children in the group B (child without leprosy and mother with leprosy in an endemic area) and group E (child without leprosy and mother without leprosy in non-endemic area) tend to have low body mass index, with the average BMI are 17.59 and 16.78, respectively. Whereas for the mother, normal BMI were observed amongst the group with group A in exception, with an average of BMI of 25.30 that considered to be overweight. The highest coverage was BCG in the group E; however, the coverage

was only 56% of the population. Overall, most of the subjects did not undergo vaccination. Furthermore, children and mothers in the group C has no history of BCG immunization. The children in this group also has no history of other vaccinations.

The statistical analysis on anthropometric parameters (Table 3) showed statistically significant difference on almost all group comparison amongst the pediatric subject, except for the comparison between group B (child without leprosy and mother with leprosy in an endemic area) and group E (child without leprosy and mother without leprosy in non-endemic area), and between group D (child without leprosy and mother without leprosy in an endemic area) and group E. It coincides with the trend of group B and group E having low BMI compared to the other groups. No anthropometric parameters showed significant difference amongst the mother groups.

A statistically significant difference ($p= 0.049$) was observed on the difference of child's BCG parameter between group A and E i.e child with leprosy and mother without leprosy in an endemic area; child without leprosy and mother without leprosy in non-endemic area, respectively. However, no significant association was found amongst other vaccination parameters nor groups.

DISCUSSION

The BMI amongst child subjects showed notable difference compared to the control groups ($p= 0.042$, $p= 0.024$, and $p= 0.042$; for group A, B, and intergroups comparison for ABCD: E, respectively). According to the current evidence, BMI is associated with leprosy and lower BMI increase the risk of developing leprosy.^{34,35} Lower BMI reflects low nutritional status that could potentially cause dysregulation of the immune system, as both macronutrient and micronutrient, particularly in children, are needed in the modulation of cell-mediated immune response and immune regulation.^{36,37} The dysregulated immune response, which characterized by T-cell anergy, increased apoptosis, and disbalance between T helper 1 (Th1) and T helper 2 (Th2) response, in turns could lead to impaired innate and adaptive response; thereby potentiate the chance of contracting leprosy.³⁸⁻⁴⁰ Notwithstanding the evidence of low nutritional status and leprosy, our study found that subjects in the group E (control group) have a significantly lower BMI compared to the other groups. This could be associated with the fact that in addition to the multi drugs therapy (MDT), leprosy patients in Indonesia is also given dietary supplement such as vitamins, ferro sulphate, anti-oxidants and neurotropic drugs such as vitamins B1, B6, and B12. In contrast, the subjects without leprosy that live in non-endemic area (group E) did not receive any dietary logistic from the government.⁴¹

In this study, we found statistically significant difference ($p= 0.049$) in BCG vaccination between group A (child with leprosy and mother without leprosy in endemic area) and group E (child without leprosy and mother without leprosy in non-endemic area). This is in accordance with previous studies. Systematic reviews conducted by Setia et al in 2006 showed and Merle et al in 2010 observed that BCG confer partial immunity, although the extent of protective effect of BCG is different in each of the studies.²⁸ The protective effect of BCG against *M. leprae* infection is caused by the interaction between BCG antigen and host immune system. The bacterial arabinogalactan and mycolic acid would elicit immune response via pattern recognition receptors (PRRs) such as TLR2 and TLR4 that

are expressed on the cell surface of dendritic cells and macrophages.⁴²⁻⁴⁴ In addition to inducing memory of the adaptive immune system, the antigen interaction with BCG also stimulated the formation of innate immune memory called trained immunity. Nucleotide-binding oligomerization domain 2 (NOD2) is thought to mediate the development of trained immunity, in which increased production of TNF α and IL-6 by macrophages was observed.⁴⁴⁻⁴⁶ Activation of the NOD2 receptor and the genesis of trained immunity might play a pivotal role against *M. leprae*; previous study found that some genetic variation in the NOD2 gene receptor is markedly associated with leprosy in several populations.^{47,48} Significant difference on BCG parameter is not observed in any other groups. In addition, even previous evidence of BCG protective effect against leprosy showed a dramatic variation; in experimental and observational research, BCG provides 26% and 61% immunity, respectively.⁴⁹ A systematic review carried out by Merle et al in 2010 also observed that BCG confer partial immunity, amounted to 40% in experimental study and 60% in observational study.²⁸ This evidence suggest that the protective effect of BCG against leprosy and thereby its association with the disease remains controversial. On top of that, our research is the first to study the association of BCG with leprosy in Indonesia.

Several factor may explain this insignificant association. First, protective effect of the BCG vaccine against *M. leprae* would wane over time; after 20-25 years, BCG only offers about 25% protection and only 1% efficacy in 25-29 years following vaccination.^{50,51} The decrease in BCG efficacy could explain the not significantly difference in leprosy incidence between subject with prior history of BCG vaccination and those who did not, especially amongst mother who had the vaccination long time ago. Second, soil-transmitted helminth infection could impair immunogenicity effect of BCG, thereby lowering its protective property, including the immunity against *M. leprae*.^{52,53} In chronic helminth infection, transforming growth factor β (TGF- β), interleukin 10 (IL-10), and IL-4 levels are elevated. The cytokines are known to induce the development of Th2 and suppress Th1 subset.^{52,54-56} However, Th1 and its cytokines such as IL-12 and interferon γ (IFN- γ) play a crucial role in *M. leprae* elimination;^{38,40} therefore, helminth coinfection could potentially lower BCG efficacy against *M. leprae*. Furthermore, the insignificant findings in group C compared to group E might be attributed to the few numbers of subjects in the group C.

Our study found no marked difference on other vaccinations, including hepatitis B. However, this could be caused by misclassification bias during the data collection process. We defined positive (non-BCG) vaccination history by performing interview and examining the completion of immunization in the monitoring book or through positive recall by the mother. This means of data collection is not the most objective method and prone to bias.

Currently there is no data from preceding study about the association of non-BCG vaccines with leprosy. Previous study observed significant association between hepatitis B virus (HBV) infection with leprosy, especially the lepromatous form.^{25,57,58} In lepromatous leprosy, the main immune response is the Th2 subset, whilst Th1 response is impaired. In spite of that, Th1 is the primary response in HBV clearance;^{38,40} hence, patient with lepromatous form of the disease is at a higher risk to contract HBV.^{59,60} According to those studies, HBV infection develop

subsequent to leprosy due to the immune dysregulation in leprosy lead to impaired HBV clearance. However, our study evaluates the association between immunization status and leprosy incidence; in other words, protective effect of vaccination and the influence of immune dysregulation resulting from vaccine-preventable infection in leprosy. Furthermore, there is no other study that analyse the association of other non-BCG vaccination with leprosy incidence.

Factors that explain no significant difference in leprosy incidence amongst subjects are the immune response against the pathogen i.e., HBV, Polio virus, *Corynebacterium diphtheriae*, *Bordetella pertussis*, *Clostridium tetani*, *Haemophilus influenza*, *Measles virus*, *Mumps virus*, and *Rubella virus*. Infection caused by those pathogens does not caused typical immune dysregulation that could impair immunity against *M. leprae*. Viral infection cause an elevation of IFN- γ and IL-12 cytokines that lead to the development of CD4+ Th1.^{61,62} In *B. pertussis* infection, there is increased production of IL-6 and TGF- β that cause polarization towards Th17.⁶³⁻⁶⁵ The production of antibody by Th2-induced immunity in *C. tetani* infection is needed in disease resolution against the bacterial exotoxin. However, natural infection does not confer specific immunity against the toxin. To rephrase it, although Th2 response is needed, there is no excessive response of Th2 that could lead to immune dysregulation, and eventually, the development of leprosy. In addition, earlier research observed difference in immune response to diphtheria vaccine between female and male sexes; female has an increased risk to suffer from vaccination failure compared to their male counterpart. Thus, diphtheria vaccination cannot be used as the sole parameter to evaluate the immunity against *C. diphtheriae*.^{66,67} The mentioned mechanism could explain the reason that subjects with prior non-BCG immunization is not specifically protected from *M. leprae* compared to the subjects without history of vaccination.

CONCLUSION

The difference in BCG vaccination status is associated with leprosy amongst child with leprosy and mother without leprosy compared to the control group. It is affected by several factors, such as the duration of BCG protective property and co-infection amongst leprosy patients. However, there is a limitation to this study due to the means of data collection and the study design. Therefore, further prospective cohort study about BCG and other vaccinations are needed to confirm our findings.

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CONCLUSION

All authors discussed the results and contributed to the writing of the manuscript equally

CONFLICT OF INTEREST

None of the authors have any conflict of interest to declare in this review.

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Table 3: Statistical analysis of the inter-group comparison on anthropometric parameters

Anthropometric Parameters	Group Comparison				
	A : E	B : E	C : E	D : E	(A+B+C+D) : E
Pediatric Parameter	1				
BMI	$p= 0.042$	$p= 0.472$	$p= 0.024$	$p= 0.050$	$p= 0.042$
Maternal Parameter	1				
BMI	$p= 0.360$	$p= 0.975$	$p= 0.196$	$p= 0.329$	$p= 0.543$

Table 4: Statistical analysis of the inter-group comparison on vaccination

Vaccination	Group Comparison				
	A : E	B : E	C : E	D : E	(A+B+C+D) : E
BCG (mother)	$p= 0.685$	$p= 0.642$	$p= 0.110$	$p= 0.657$	$p= 0.488$
BCG (child)	$p= 0.049$	$p= 0.615$	$p= 0.068$	$p= 0.586$	$p= 0.370$
Hepatitis B	$p= 0.279$	$p= 0.971$	$p= 0.271$	$p= 0.092$	$p= 0.188$
Polio	$p= 0.279$	$p= 0.971$	$p= 0.271$	$p= 0.092$	$p= 0.188$
DTaP	$p= 0.412$	$p= 0.940$	$p= 0.314$	$p= 0.169$	$p= 0.278$
HIB	$p= 0.588$	$p= 0.904$	$p= 0.361$	$p= 0.296$	$p= 0.401$
MMR	$p= 0.928$	$p= 0.811$	$p= 0.474$	$p= 0.760$	$p= 0.775$
Measles	$p= 0.412$	$p= 0.422$	$p= 0.314$	$p= 0.169$	$p= 0.152$
Hepatitis A	$p= 0.643$	$p= 0.878$	$p= 0.543$	$p= 0.795$	$p= 0.968$

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