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Research Article

RELATION BETWEEN CONTACT HISTORY AND BACILLE CALMETTE-GUÉRIN (BCG) VACCINATION STATUS WITH LEPROSY CASE IN DR. SITANALA HOSPITAL

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ABSTRACT

Banten Province in Indonesia is Leprosy Disease endemic territory. Dr. Sitanala Leprosy Hospital is one of hospital that treat leprosy cases from all over Indonesia. The purpose of this research is to know relations between contact history and BCG (Bacille Calmette-Guérin) vaccination status with leprosy case in Dr. Sitanala Leprosy Hospital. This research uses case-control study method. The research samples are 42 respondents as cases and 42 respondents as controls. The data analysis is conducted by univariate, bivariate using chi square test with degree of meaning 0,05 and calculate the value of Odd Ratio (OR), and also multivariate. From this research found that there is relation between contact history with leprosy patient (value of $p=0,001<0,05$; $OR=4,5$), and there is relation between BCG vaccination status (value of $p=0,000<0,05$; $OR=47,5$). The research summary is there is relation between contact history and BCG vaccination status with leprosy case in Dr. Sitanala Leprosy Hospital.

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INTRODUCTION

Leprosy is a chronic infectious disease and the cause is obligate intracellular *Mycobacterium leprae* (*M. leprae*). The peripheral nerve is the first affinity of *M. leprae*, then the upper skin and mucosa of the respiratory tract can then be transferred to other organs except the central nervous system.¹

Leprosy is a problem that needs more attention because leprosy is a contagious disease that causes complex problems, one of which is disability.² The World Health Organization (WHO) reports the prevalence of leprosy globally at the end of 2015 amounting to 176,176 cases or 0.2 cases per 10,000 population.³

The Ministry of Health's Directorate General of Disease Control and Environmental Health Republic of Indonesia reports that in Indonesia there were 11,755 new cases of leprosy in 2016. This figure places Indonesia third in the world with the most leprosy new cases after India with 134,752 case and Brazil with 33,303 cases.⁴

Mycobacterium leprae is a non cultivable, obligate intracellular, Gram positive, and acid fast bacillus.⁵ Determination of the diagnosis of leprosy can be done by finding two of the cardinal sign signs such as numbness of the skin abnormality, thickening of the peripheral nerve and the

discovery of acid-resistant bacteria (BTA) in scraping the skin tissue.⁶

METHODS

This study use a cross-sectional method with a retrospective case-control study design to determine the risk factors associated with leprosy incidence, namely contact history and BCG vaccination status in Dr. Sitanala Leprosy Hospital. The study was conducted from October to November 2017 with the study location in dermatology and venereology clinic in Dr. Sitanala Leprosy Hospital. The study sample consisted of 42 case respondents and 42 control respondents who fulfill inclusion and exclusion criteria. The inclusion criteria for case samples were patients who were recorded as lepers or who had had leprosy in the medical record of Dr. Sitanala Leprosy Hospital and agree to take part in the study with exclusion criteria disagreed to take part in the study. Control samples were taken from people who came to accompany control patients with inclusion criteria not suffering from leprosy, had never received leprosy treatment, and agreed to take part in the study with exclusion criteria who disagreed to take the study and had a history of leprosy.

This study will assess the relationship between the incidence of leprosy and the duration of contact, contact history and BCG status. Contact history is interpreted as a person who lives in some house with leprosy patient. The sample selection

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technique uses purposive sampling with the consideration of the researcher. Data collected by conducting interviews using a questionnaire form with research samples and clinical examination of BCG scar.

RESULTS

The respondents of this study were 42 cases and 42 control respondents, with the highest characteristics of men were 45 people (53.6%). Based on age, the highest number in age range of 26-45 years were 40 people (47.6%) and the lowest was less than 12 years as many as 1 person (1.2%). Based on the contact history, most of the samples had a history of contact with lepers with 45 people (53.6%). Based on the duration of contact with leprosy sufferers, 44 people (56%) were sampled with contact history more than or equal to 2 years. From the results of the BCG vaccine scar analysis, 43 people (51.2%) never received BCG vaccine.

Table 1 Distribution of Respondents based on Gender, Age, Contact History, Length of Contact and BCG Status

Gender	n	%
Female	39	46,4
Male	45	53,6
Age		
< 12 years	1	1,2
12 – 25 years	15	17,9
26 – 45 years	40	47,6
> 45 years	28	33,3
Contact History		
With history	45	53,6
Without history	39	46,4
Length of contact		
≥ 2 years	44	56
< 2 years	40	44
BCG Status		
Never received BCG	43	51,2
Received BCG	41	48,8

In this study found in the case group 30 respondents (71.4%) had a contact history while in the control group 15 respondents (35.7%) had a contact history. The opposite was seen in the case group that had never had a contact history were 12 respondents (28.6%) while in the control group who never had a contact history were 27 respondents (64.3%). The results from chi square test, the p value is 0.001 so that it can be stated that there is a significant relationship between the contact history with incidence of leprosy.

The OR value of 4,500 with an interval of 1,793-11,293 illustrates that respondents who have a history of contact are more than four times more at risk of leprosy than respondents who do not have a contact history.

Table 2 Test Chi Square between Contact History with Leprosy Events

Contact History	Leprosy Event				P value	OR	CI 95%
	Case		Control				
	Σ	%	Σ	%			
With Contact	30	71,4	15	35,7	0,001	4,500	1,793 – 11,293
Without Contact	12	28,6	27	64,3			
Total	42	100	42	100			

The respondents who have a contact history with leprosy patients more than or equal to 2 years in the case group found 29 respondents (69%), more than the control group 15 respondents (35.7%). In respondents who have a contact history of less than 2 years in the case group as many as 13

respondents (31.0%), fewer than in the control group as many as 27 respondents (64.3%). From these results, p 0.002, so that there can be a significant relationship between lepers and contact history.

The OR value of 4.015 at intervals of 1.618-9.966 illustrates that people who have a contact history of more than 2 years have a risk 4 times more likely to develop leprosy than people who have a contact history of less than 2 years.

Table 3 Chi Square Test between length of contact with leprosy events

Length of Contact	Leprosy Event				P value	OR	CI 95%
	Case		Control				
	Σ	%	Σ	%			
≥ 2 years	29	69,0	15	35,7	0,002	4,015	1,618 – 9,966
< 2 years	13	31,0	27	64,3			
Total	42	100	42	100			

Respondents who did not get the BCG vaccine in the case group were 39 people (90.5%) more than the control group as many as 7 respondents (16.7%). While respondents who received the BCG vaccine in the case group were 4 respondents (9.5%) less than the control group as many as 35 respondents (83.3%). From these results obtained p 0,000 so that it can be stated that there is a significant relationship between the history of BCG vaccine and the incidence of leprosy.

The OR value of 47,500 at intervals of 12,797–176,305 illustrates that respondents who did not get the BCG vaccine were 47 times more likely to develop leprosy compared to respondents who received the BCG vaccine.

Table 4 Chi Square Test between BCG Vaccination Status and Leprosy Occurrence

BCG Vaccination Status	Leprosy Occurrence				P value	OR	CI 95%
	Case		Control				
	Σ	%	Σ	%			
Never Received BCG	38	90,5	7	16,7	0,000	47,500	12,797- 176,305
Received BCG	4	9,5	35	83,3			
Total	42	100	42	100			

From the results of bivariate analysis, the two variables in this study, namely contact history and BCG vaccination status, can be entered into multivariate analysis modeling.

Table 5 Bivariate Results

Variabel	P value	OR (95% CI)
Contact History	0,001	4,500 (1,793-11,293)
BCG vaccine status	0,000	47,500 (12,797-176,305)

The results of multivariate using logistic regression tests (Table 6) showed that all variables have a p value <0.05 and changes in OR > 10% so that this model is the final model that can best describe the incidence of leprosy in Dr. Sitanala Leprosy Hospital which consists of contact history variables and BCG vaccination status. The contact history variable with an OR value of 9,196 shows that respondents who have a history of contact with lepers have a risk of leprosy 9 times greater than respondents who do not have a contact history. In the BCG vaccination status variable, an OR of 74.768 showed that respondents who did not get the BCG vaccine had a risk of leprosy 74 times greater than the respondents who received the BCG vaccine. From these two variables, it can be concluded that the BCG vaccination status is the variable most associated

with the incidence of leprosy, seen from the largest OR value compared to the OR value of other variables.

Table 6 Multivariate Model With Logistic Regression Test

Variabel	P value	OR (95% CI)
Contact History	0,007	9,196 (1,816-46,554)
BCG vaccine status	0,000	74,768 (14,222-393,066)

DISCUSSION

In this study the results obtained that the p value in the contact history variable is 0.001 (p value <0.005), which means there is a relationship between the contact history with the incidence of leprosy. The results of this study are in accordance with Noorden's research in 1978 in South India which found that living with a leper can increase the risk of leprosy by 9.5 times at the most.⁷ This is supported by the existing theory that leprosy is an infectious disease, so transmission in the household and close contact for long periods of time seems to play a role in transmission.⁸ The most possible transmission in leprosy is through the respiratory tract. This is based on: (1) the discovery of leprosy germs in the respiratory tract, (2) evidence that many organisms can be found in the nasal discharge and (3) a high proportion of morphologies that are intact leprosy in nasal secretions.⁹ In addition, according to Ahmad Tarmisi *et al.* In their 2016 study, contact history with previous patients is the main source of transmission and can cause leprosy if close or intimate contact occurs continuously for a long time and people who are susceptible to *M.leprae*.¹⁰ This close contact can be seen from the habits of some families of respondents who indeed often do activities together and have a high level of familiarity. This causes high intensity of contact with each other between the people in the house. In addition, occupancy density in one patient's house can also affect the high intensity of contact between the skin.¹¹

The number of leprosy patients around Dr. Sitanala Leprosy Hospital in Tangerang can allow subclinical leprosy infection to the local community, who do not show clinical symptoms, causing this disease hard to get treated quickly. Whereas according to some studies, this subclinical stage can be an important source of transmission of leprosy because there have been specific antibodies found in the body.¹¹ These theories can prove that there is a contact history or have lived in a house with lepers, can increase the risk of contracting it leprosy.

In this study, the results showed that the p value of the contact length variable was 0.002, which means that there was a significant relationship between the duration of contact with the incidence of leprosy. In this study, the old contact category was categorized more than 2 years or less than 2 years. Respondents who previously answered had never had a contact history, were still categorized as respondents with less than 2 years of contact because they were in the non-risky category. This is based on the time of incubation of leprosy, which is 2-5 years, so that the risk of leprosy is contracted if you have a contact duration of more than or equal to 2 years.⁶ The results of this study are not in accordance with research conducted by PuspitaKartikasari in 2007 who found that the duration of contact with people affected by leprosy is not necessarily a risk factor for leprosy.¹² There are several factors that affect the spread of: (1) the degree of infectious patients who have been infected,

(2) the ease of being affected after contact, (3) proximity, frequency, and the duration of contact with the patient.⁷ In theory, it is explained that leprosy is an infectious disease, but the degree of infection is low.¹³ The incubation time is long, which is for 2-5 years and must have repeated contact with the patient who is infectious or untreated.^{6,13} This can explain that people who have a contact duration of less than 2 years, *M. leprosy* have not been able to fully enter the body and have not been able to cause symptoms of leprosy. Long contact time is needed, which is more than 2 years with patients, to be able to cause leprosy.

In this study it was found that the p value of the BCG vaccination status variable was 0,000 (p value <0.005), which means there is a relationship between BCG vaccination status and the incidence of leprosy. The results of this study are consistent with the research conducted by Bertolli *et al* in Myanmar with OR of 0.34 and Goulart *et al* research in 2008 with OR of 0.27.^{14,15} In addition, Moet in his journal entitled Prevention of The Disease in the year 2007 states that the administration of the BCG vaccine can provide protection between 20-80% of the risk of leprosy events.¹⁶ Yusie LP in 2009 also explained that the BCG vaccine, which is commonly used as tuberculosis protection, can improve the cellular immune response played by the specific immune system, namely especially T lymphocyte cells.¹⁷ The BCG vaccine contains the *Mycobacterium bovis* antigen which has previously passed the process of becoming a weakened antigen and not completely virulent. This antigen can theoretically stimulate the emergence of the cellular immune response but does not cause fatal disease. As a result of this BCG vaccination, scarring will occur at the injection site as a sign that the body's immune response is working and against the incoming antigen. Because of the similarity of the genus and the similarity of the structure of the cell wall, as well as the causes of tuberculosis, namely *Mycobacterium tuberculosis*, the antigen in the BCG vaccine can also provide protection to reduce the risk of leprosy by *Mycobacterium leprae*. In addition, the two antigens also have almost the same properties, namely intracellular parasites, especially in macrophages.

In the administration of the BCG vaccine, germs that are in it have similar cell wall structures that will stimulate cellular immunity that is mediated by APCs, especially macrophages, and TLR complexes through the release of cytokines. Macrophages are host cells that interact a lot with *M. leprae*. Macrophages have 2 main functions, namely as APC through class I and class II MHC molecules presented to CD8 + and CD4 + cells as well as phagocytosis of pathogenic bacteria through nonspecific effector mechanisms. Furthermore there will be differentiation from naïve T cells in the lymph glands. If exposed to an antigen, the naïve T cell will differentiate into effector cells and memory cells. After that, the memory cell will be in the lymphoid organs which then play a role again if there is the same antigen exposure.¹⁷ In lepers who have already been given the BCG vaccine, these cells are ready to fight *M. leprae* naturally. If the body has been exposed to the same antigen before, at least the lymphocyte cells already have a mechanism that has been prepared for a long time and can directly fight the incoming antigen. So that the cellular immune response produced, especially T lymphocyte cells, will work better and can weaken the incoming antigen.

Generally the BCG vaccine is widely used as a protection for tuberculosis. But the research conducted by Ponnighaus JM *et al* in 1992 stated that the BCG vaccine provided more protection against leprosy than tuberculosis.¹⁸ Actually the difference from *M. leprae* and *M. tuberculosis* is its affinity. In *M. leprosy* the main affinity is peripheral cells, especially schwann cells. These cells are classified in "non professional phagocyte", because they cannot express MHC molecules unless they are activated by IFN-activated ones. This situation causes disruption of the process of presenting antigens to T lymphocytes which causes failure to destroy germs. If the schwann cells that are seized are dead and broken, the antigen will come out and be captured by other phagocytes and can spread to other organs.¹⁹ While in *M. tuberculosis*, these germs enter through the airways and nest in the lung tissue to form the primary affection that is followed with inflammation of the lymph nodes.²⁰

CONCLUSION

Contact history has a significant relationship with the incidence of leprosy. It was found that respondents who had a history of contact with people with leprosy were four times more likely to develop leprosy than those without a contact history. There is a significant relationship between the length of contact history with the incidence of leprosy. This study found that respondents who had more than two years of row of contact with leprosy patients were at a risk 4 times more affected by leprosy compared with respondents who had less than two years of contact history with lepers. There is a relationship between BCG vaccination status and the incidence of leprosy. Respondents who did not get the BCG vaccine were 47 times more likely to get leprosy than respondents who received the BCG vaccine.

Potential Conflicts of Interest: The authors declare no conflicts of interests / the following potential conflicts.

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