The Effects of Bacille Calmette-Guerin Immunization and Contact History on the Risk of Leprosy: Meta Analysis of Case Control Study

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ABSTRACT

Background: Leprosy or Hansen’s is an infectious disease caused by Mycobacterium leprosy. The incubation period is 3 to 20 years and affects the skin, peripheral nerves, mucosa of the upper respiratory tract, and eyes. Based on research in leprosy endemic areas, BCG immunization provides protection against the risk of developing disease. Contact with untreated sufferers can lead to leprosy. This study aims to see how much influence BCG immunization and contact history have on the risk of leprosy by meta-analysis.

Subjects and Method: This was a systematic review and meta-analysis. The study was carried out by collecting articles from PubMed, ProQuest, Science Direct, Scopus, Spinger Link, EBSCO, Google Scholar, Embase, LILACS, Embase, Emerald, PLOS, and Perpusnas databases. The key words are "leprosy OR" hansen disease "AND" risk factor "AND" immunization BCG "OR" vaccine BCG "AND" household contacts "AND" odds ratio”. The inclusion criterion was a full text study. Article searches from 1949 to 2020 used English and Indonesian. The study design was case control and the results are reported in Adjusted Odd Ratio (aOR). Articles that meet the requirements are analyzed using the Revman 5.4 application.

Results: Fifteen articles were reviewed in this study with a total of 2,435 case subjects and 4,212 controls. The results of the meta-analysis showed that getting BCG immunization reduced the risk of leprosy by 0.77 times compared to not getting BCG immunization (aOR = 0.77; 95% CI= 0.40 to 1.49; p= 0.43), having a history of contact with lepers increased the risk of leprosy by 3.55 times compared to do not have a history of contact with leprosy patients (aOR = 3.55 95% CI = 1.86 to 6.76; p<0.001).

Conclusion: The risk of leprosy decreases by getting BCG immunization, having a history of contact with lepers increases the risk of leprosy.

Keywords: leprosy, BCG immunization, contact history, meta-analysis

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BACKGROUND

Leprosy is a chronic granulo-matrix infection caused by the obligate intracellular organism Mycobacterium leprosy. Leprosy will first attack the peripheral nervous system, skin, mucosa, respiratory tract, reticuloendothelial system, muscles, eyes, bones and testes. Leprosy is also known as

Leprosy is unique because in the explanation of the characteristics, modes of transmission, prevention and quarantine of lepers, it has also been recorded around 1512 BC by the prophet Moses in the holy book of Leviticus 13: 1-45. After more than 3000 years have passed, the spread of leprosy has not been eliminated (Bible, 2019; Sehgal., Et al 2006).

WHO has been doing treatment since 1981 by providing 3 types of drug therapy or Multi Drug Therapy (MDT), namely dapsone, rifampin, and clofazimine. This therapy is successful for healing but leprosy has not been eliminated from all over the world, especially in developing countries and tropical climates (WHO, 2016, 2019a).

Report of leprosy cases from 152 countries to WHO in 2018 from Africa Region 42, American Region 32, Southeast Asia Region 11, Eastern Mediterranean Region 18, European Region 32 and Western Pacific Region 26. New cases detected were 208,613 and the prevalence of leprosy registered was 184,194 cases. The countries with the highest leprosy burden in 2018 were India with 120,334 cases, Brazil with 28,660 cases, Indonesia with 17,017 cases, Bangladesh 3,729 cases (WHO, 2019b).

Turankar et al., (2016) found that active M. leprosy from environmental soil samples specifically came from public bathing places, washing places used by patients, around the patient’s house, ward or hospital where patients were receiving patients.

A retrospective cohort study for 16 years and a follow-up of 7 years evaluating the presence or absence of BCG immunization scars against leprosy by Gomes et al., (2019) concluded that BCG vaccination at the time provided a protective effect with a risk 0.42 times lower than that didn't receive the vaccine.

A study by Ratanawati (2016) concluded that people who live with leprosy sufferers with unsanitary home sanitation conditions have a risk of contracting 7.85 times than healthy home sanitation. Different research results reported by Aprizal et al. (2017) state that individual characteristic factors, household contact, neighbor contact, home physical environment and occupant density are statistically proven to have no effect on the incidence of leprosy.

The purpose of this study is to draw conclusions by conducting systematic studies and meta-analyzes. By collecting and combining all relevant and pre-existing research results regarding BCG immunization and contact history with leprosy sufferers against the risk of leprosy.

SUBJECTS AND METHOD

1. Study Design
This research is a systematic review and meta-analysis conducted by following the PRISMA flow diagram. The article search databases are presented as follows: PubMed, ProQuest, Science Direct, Scopus, Spinger Link, EBSCO, Google Scholar, Embase, LILACS, Embase, Emerald, PLOS, Perpusnas. The key words are "leprosy OR" hansen desease "OR" leprosy "OR" leprosy", AND" risk factor "AND" immunization BCG "OR" vaccine BCG "AND" household contacts "AND" odds ratio, AND "leprosy and odds ratio ".

2. Inclusion Criteria
The inclusion criteria in this research are full text articles, in English and Indonesian. The articles were published from 1949 to 2020. The study design was an observational with case-control study. The article discusses the history of BCG immunization against leprosy risk and contact history
against leprosy risk. The sample in the case study is an individual diagnosed positive for leprosy, while the control is an individual without symptoms of leprosy with negative results. Study articles were those that were conducted by multivariate analysis and reported results in adjusted odds ratio (aOR).

3. **Exclusion Criteria**
The exclusion criteria in this study were research articles on quasi experimental trials, RCT, study protocol, pilot study, animal studies. Research articles were those that were performed by univariate, bivariate or non-adjusted odds ratio (aOR) analysis.

4. **Operational Definition**
Leprosy sufferers are all people who experience symptoms of leprosy and are diagnosed by health personnel.

BCG Immunization History is all people who have received BCG vaccine immunization with scars or without scars who have been checked for correctness.

Contact History is a track record of an individual in the form of a statement of having had physical contact with a person with leprosy.

5. **Instruments**
The study was conducted by following the PRISMA flow diagram and assessing the quality of research articles, using the Critical Appraisal Check List For Study from the Center for Evidence Based Management, (2014) for a case control study.

6. **Data Analysis**
The data analysis process in this study was carried out using the Review Manager application (RevMan 5.3), to determine the effect size and heterogeneity of the study. The results of meta-analysis data processing are presented in the form of a forest plot and a funnel plot.

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### RESULTS

The process of searching for articles on an electronic data base according to PRISMA flow diagrams can be seen in Figure 1.

Fifteen articles out of 9,878 were reviewed in this study with a total of 2,435 case subjects and 4,212 controls. Five of the articles were research conducted on the South American continent and eleven research articles were conducted in the Asian continent. Next, the researchers conducted an assessment of the quality of the articles (Table 1).

#### 1. The effect of BCG immunization on the risk of leprosy.
Table 2 provides information on 6 articles with a case-control study design as a meta-analysis source of the effect of BCG immunization on leprosy risk.

**a. Forest plot**
Figure 2. Forest plot shows that getting BCG immunization reduces the risk of leprosy by 0.77 times compared to not getting BCG immunization, but this is not statistically significant. The distribution of data is stated to be heterogeneous (random effect model), $I^2 = 91\%$.

**b. Funnel Plot**
Figure 3 funnel plot of the effect of BCG immunization on the risk of leprosy, there is no publication bias, it is shown by the symmetrical plot right and left. The number of left-sided plots is 3 with a graph showing a standard error between 0.4 and 0. The right-sided plot is 3 with the graph showing that the SE is between 0.6 and 0.2.

#### 2. Effect of contact history on leprosy
Table 2 provides information on 12 articles with a case-control study design as a source of meta-analysis of contact history on leprosy risk.

**a. Forest plot**
Figure 4. The forest plot shows that a history of contact with leprosy patients increase the risk of leprosy by 3.55 times.
compared to no contact with leprosy patients and it is statistically significant (p < 0.001).

The heterogeneity value of I² is 91%, meaning that the distribution of data in this study is heterogeneous (random effect model).

b. Funnel Plot

Figure 5. The funnel plot shows publication bias, from the imbalance of the distance between the studies on the left and the right side of the funnel plot.

Asymmetrical shape of the funnel plot with the plot tendency to the right side. The number of plots on the left is 3, the plots in the middle are 2 and 7 plots on the right side. The left side plot on the graph appears to have a standard error between 0.5 and 0 while the right side plot of the graph shows a standard error between 0 and 1. The publication bias in this study also occurs from an imbalance in the distance between the studies on the left and the right side of the funnel plot.
Table 1. Assessment of Research Quality

<table>
<thead>
<tr>
<th>Scoring Item</th>
<th>Publication (Author, Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample adequacy</td>
<td>1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1</td>
</tr>
<tr>
<td>Validity</td>
<td>1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1</td>
</tr>
<tr>
<td>Data search</td>
<td>1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1</td>
</tr>
<tr>
<td>The relevance of the effect size</td>
<td>1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1</td>
</tr>
<tr>
<td>Total</td>
<td>11 12 12 12 12 12 11 12 10 12 10 11 12 10 10 10</td>
</tr>
</tbody>
</table>

Note:
Yes = 1
No = 0
Table 2. Summary of sources of the effect of BCG immunization and contact history on leprosy risk

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Country</th>
<th>Sample size</th>
<th>Intervention (I) and Comparator (C)</th>
<th>Outcome</th>
<th>Effect OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muliyil et al., (1991)</td>
<td>India</td>
<td>397 669</td>
<td>I: BCG, No, contact C: Not BCG, Contact</td>
<td>Leprosy Risk</td>
<td>0.85 (0.59 to 1.10)</td>
</tr>
<tr>
<td>Zodpey et al., (1998)</td>
<td>India</td>
<td>76 172</td>
<td>I: BCG C: No BCG</td>
<td>Leprosy Risk</td>
<td>0.29 (0.21 to 0.41)</td>
</tr>
<tr>
<td>Kerr-Pontes et al., (2006)</td>
<td>Brazil</td>
<td>226 875</td>
<td>I: BCG C: No BCG</td>
<td>Leprosy Risk</td>
<td>0.48 (0.33 to 0.70)</td>
</tr>
<tr>
<td>Jariwala et al., (2013)</td>
<td>India</td>
<td>76 152</td>
<td>I: BCG, No Contact C: No BCG, Contact</td>
<td>Leprosy Risk</td>
<td>0.30 (0.15 to 0.57)</td>
</tr>
<tr>
<td>Efrisal et al., (2016)</td>
<td>Indonesia</td>
<td>56 56</td>
<td>I: BCG C: No BCG</td>
<td>Leprosy Risk</td>
<td>4.13 (1.35 to 12.64)</td>
</tr>
<tr>
<td>Sari et al. (2019)</td>
<td>Indonesia</td>
<td>85 85</td>
<td>I: BCG, No Contact C: No BCG, Contact</td>
<td>Leprosy Risk</td>
<td>2.56 (1.24 to 5.29)</td>
</tr>
<tr>
<td>Harlim et al. (2019)</td>
<td>Indonesia</td>
<td>42 42</td>
<td>I: No Contact C: Contact</td>
<td>Leprosy Risk</td>
<td>9.19 (1.82 to 46.55)</td>
</tr>
<tr>
<td>Lima et al. (2015)</td>
<td>Brazil</td>
<td>185 136</td>
<td>I: No Contact C: Contact</td>
<td>Leprosy Risk</td>
<td>3.86 (2.21 to 6.75)</td>
</tr>
<tr>
<td>Awaluddin (2004)</td>
<td>Indonesia</td>
<td>80 80</td>
<td>I: No Contact C: Contact</td>
<td>Leprosy Risk</td>
<td>30.3 (3.90 to 233.90)</td>
</tr>
<tr>
<td>Feenstra et al. (2013)</td>
<td>Bangladesh</td>
<td>90 199</td>
<td>I: No Contact C: Contact</td>
<td>Leprosy Risk</td>
<td>1.09 (1.00 to 1.19)</td>
</tr>
<tr>
<td>Norlatifah et al. (2010)</td>
<td>Indonesia</td>
<td>31 62</td>
<td>I: No Contact C: Contact</td>
<td>Leprosy Risk</td>
<td>5.45 (1.89 to 15.69)</td>
</tr>
<tr>
<td>Schmitt et al. (2010)</td>
<td>Brazil</td>
<td>121 242</td>
<td>I: No Contact C: Contact</td>
<td>Leprosy Risk</td>
<td>8.33 (4.05 to 17.14)</td>
</tr>
<tr>
<td>Murto et al. (2013)</td>
<td>Brazil</td>
<td>340 340</td>
<td>I: No Contact C: Contact</td>
<td>Leprosy Risk</td>
<td>1.51 (1.0 to 2.28)</td>
</tr>
<tr>
<td>Rodrigues et al. (2019)</td>
<td>Brazil</td>
<td>40 164</td>
<td>I: No Contact C: Contact</td>
<td>Leprosy Risk</td>
<td>8.76 (3.41 to 22.50)</td>
</tr>
<tr>
<td>Masrizal et al. (2020)</td>
<td>Indonesia</td>
<td>32 32</td>
<td>I: No Contact C: Contact</td>
<td>Leprosy Risk</td>
<td>3.90 (0.9 to 16.7)</td>
</tr>
</tbody>
</table>
**Figure 2. Forest plot of the effect of BCG immunization on leprosy risk**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embo et al 2016</td>
<td>1.4103</td>
<td>0.5705</td>
<td>12.5%</td>
<td>4.13 [1.36, 12.63]</td>
<td></td>
</tr>
<tr>
<td>Jokhawa et al 2013</td>
<td>-1.204</td>
<td>0.3537</td>
<td>16.1%</td>
<td>0.30 [0.15, 0.60]</td>
<td></td>
</tr>
<tr>
<td>Keer_Pontes et al 2006</td>
<td>-0.734</td>
<td>0.1812</td>
<td>16.4%</td>
<td>0.48 [0.33, 0.70]</td>
<td></td>
</tr>
<tr>
<td>Muller et al 1991</td>
<td>-0.1625</td>
<td>0.1863</td>
<td>16.5%</td>
<td>0.85 [0.58, 1.22]</td>
<td></td>
</tr>
<tr>
<td>Sart et al 2019</td>
<td>0.3396</td>
<td>0.3709</td>
<td>15.8%</td>
<td>2.56 [1.24, 5.29]</td>
<td></td>
</tr>
<tr>
<td>Zodpey et al 1998</td>
<td>-1.2379</td>
<td>0.1847</td>
<td>18.7%</td>
<td>0.26 [0.21, 0.40]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 100.0% 0.77 [0.40, 1.49]

Heterogeneity: $\tau^2 = 0.58$, $Chi^2 = 53.83$, $df = 5$ ($P < 0.000201$), $I^2 = 91$

Test for overall effect: $Z = 0.70$ ($P = 0.47$)

**Figure 3. Funnel plot of the effect of BCG immunization on leprosy risk**
DISCUSSION

This research is a systematic study and meta-analysis of the risk factors for leprosy. The independent variables in this study were history of BCG immunization and history of contact with patients.

Most of the primary studies only report the results of statistical analysis in the crude odds ratio (cOR), this shows that the results of these studies have not
controlled for confounding factors.

Confounding factor according to Murti (2018) is a mixture of estimated relationships between exposure and the disease under study, by other factors that are related, both to disease and exposure. According to the inclusion criteria, this study uses the results of primary studies that have controlled for confounding factors as shown by multivariate data analysis and the size of the relationship reported is in the form of Adjusted Odds Ratio (aOR).

Estimates of the combined relationship of the association of each risk factor with the incidence of leprosy were processed using the RevMan 5.3 application using the generic inverse-variance method. This method is used to analyze data in the form of: rate, time-to-event, hazard ratio, ordinal scale, adjusted estimate, difference of mean ratio of mean (Anulus, 2019). The results of the systematic review and meta-analysis of this study are presented in the form of a forest plot and a funnel plot.

A forest plot is a diagram that provides an overview of the information from each study examined in the meta-analysis, estimates of the overall results and the heterogeneity between study results. A funnel plot is a diagram in meta-analysis used to demonstrate possible publication bias. The funnel plot also shows the relationship between the Effect Size of the study and the sample size or Standard Error of the Effect Size of the various studies studied (Murti 2018).

1. **The effect of BCG immunization on leprosy.**

The results of the forest plot show that getting BCG immunization can reduce the risk of leprosy, namely 0.77 times compared to not getting BCG immunization, although it is statistically significant.

Sales et al., (2011) concluded that having a BCG scar showed a highly statistically significant protective effect for co-prevalent cases (OR = 0.28; 95% CI: 0.21 to 0.37) and incidence (OR = 0.45; 95% CI: 0.30 to 0.68). Contacts who received the BCG vaccine also showed significant protection against disease (OR = 0.44; 95% CI: 0.29 to 0.64).

According to Murti (2019), when someone pays for immunization, the costs incurred are marginal personal costs. The benefit of immunization is immunity to disease which is a marginal benefit. The positive impact of immunization is that the people around you indirectly benefit even though they do not pay.

BCG immunization does not provide a guarantee that a person can avoid leprosy infection. The results of this meta-analysis study provide evidence that there is an influence between BCG immunization and the risk of leprosy, namely as a protective factor against leprosy. BCG immunization reduces the risk of leprosy. Reducing the risk of leprosy can have an impact on reducing morbidity, disability, social stigma and mortality due to leprosy.

2. **History of Contact with Leprosy**

The effect of contact history with leprosy risk can be seen from the meta-analysis results. Forest plot shows that contact history with leprosy patients can increase the risk of leprosy by 3.55 times compared to not having contact with leprosy patients and it is statistically significant.

Bakker et al., (2004) concluded that household contacts of patients with multi-bacillary leprosy (MB) had an adjusted hazard ratio (aHR) of 4.6 (95% CI: 1.6 to 12.9) and household contacts were positive based on the results of the polymerase chain react-ion (PCR) had an aHR of 9.36 (95% CI: 2.5 to 34.9) compared to no contact.
A history of household contact with a patient with leprosy increased leprosy (aOR= 1.48; 95% CI= 1.17 to 1.88), the risk increased for contacts aged ≥50 years (aOR= 3.11; 95% CI= 2.03 to 4.76) and boys have a higher risk than girls (aOR= 1.70; 95% CI= 1.20 to 2.42) (Teixeira et al., 2020).

Household contacts are the group with the highest risk, because of their closeness to persons affected by leprosy. The risk increases if the patient has a high bacillus content. However, these risk factors are often uncertain, even not well recorded in the leprosy monitoring program. This results in the maintenance of disease transmission chains and delays in diagnosis of leprosy reactions (Bakker et al. 2006; Goulart et al. 2008; Sales et al. 2011b).

According to Murti (2019), one of the reasons that health services for infectious diseases is important is because it has a positive externality of consumption. If cases of infectious diseases increase and are not treated, a large part of the population will become vulnerable to contracting the disease.

The importance of primary health services in controlling leprosy. The difficulty of primary health workers in recognizing community needs is a consequence of the weakness of the integrated health system health surveillance model. Leprosy is associated with information on signs and symptoms, although curable, its impact depends on early diagnosis and prolonged treatment (Figueiredo Vieira et al. 2020; Savassi et al., 2015).

Health education has a positive and statistically significant effect on healthy behavior (b = 0.09; SE = 0.04; p = 0.018) (Nasir et al., 2016). Rahmah et al., (2018) concluded that there is a relationship between personal hygiene and leprosy. The risk of leprosy increased with worse personal hygiene (b= -1.20; 95% CI= -1.92 to -0.49; p= 0.001). Contact with sufferers cannot be avoided, but the risk of leprosy can be reduced through health education about leprosy, evidence-based health care, good personal hygiene and getting BCG immunization.

**AUTHOR CONTRIBUTION**
Priscilla Jessica Pihahey is the principal researcher who chooses topics, collects research data, formulates articles, and processes data. Bhisma Murti formulated the background, research data analysis. Yulia Lanti Retno Dewi helped formulate the framework and document review.

**CONFLICT OF INTEREST**
There is no conflict of interest in this study.

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