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ORIGINAL ARTICLE

BCG Vaccination and Spinal Tuberculosis in Non-Malnourished and/or Non-HIV Infected Children at Dr. Soetomo General Academic Hospital, Surabaya

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ABSTRACT

Introduction: Spinal tuberculosis (TB) is an extrapulmonary form of TB that affects the spine. The Bacillus Calmette-Guérin (BCG) vaccination program, which has been implemented to prevent TB, should have prevented this type of TB. However, cases of this disease in children can still be found. This study aimed to determine whether there was a relationship between BCG vaccination and the occurrence of spinal TB in children.

Methods: This case-control analytic observational study was performed based on medical record data. The study subjects of each group, both case and control, were taken from pediatric TB patients at Dr. Soetomo General Academic Hospital, Surabaya, from 2017 to 2021. Patients with malnutrition and/or human immunodeficiency virus (HIV) infection were excluded. Statistical analyses were performed using Fisher's exact test.

Results: There were 9 patients in total within each group. Most were 12-17 years old, and the ratio of male by female was 1.25:1. There were 4 out of 9 (44%) spinal TB patients and 9 of 9 (100%) patients with no spinal TB who all received BCG vaccination. The statistical test indicated a significant (p=0.029) and moderate (C=0.527) relationship between BCG vaccination and the occurrence of spinal TB in children.

Conclusion: The Bacillus Calmette-Guérin vaccination should be able to prevent the new occurrence of spinal TB in children.

Highlights:
1. The Bacillus Calmette-Guérin (BCG) vaccination has been widely implemented in Indonesia, but cases of spinal tuberculosis (TB) in children can still be found.
2. There are significant and moderate relationships between BCG vaccination and the occurrence of spinal TB in children.

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Introduction

Spinal tuberculosis (TB), or Pott's disease, is one of the many manifestations of TB disease. This extrapulmonary form of TB attacks explicitly the spine, which can affect one or more vertebrae at the cervical, thoracic, lumbar, or sacral area.[1] The infection will most likely reach the spine from other infection sites, such as pulmonary TB, through the bloodstream or lymphatic fluid.[2] This disease can affect children of all ages, from under five years old to over ten years old.[3] Children who experience this disease will be prone to gaining body posture changes due to kyphosis due to their immature and flexible spine.[4] Additionally, even paraplegic neurological deficits can manifest both during the clinical phase of the disease due to direct compression by abscesses, granulation tissue, and necrotic tissue and during the healing process due to compression by scar tissue and gibbus.[5]

All disturbances that arise due to spinal TB will undoubtedly be detrimental to children, potentially decreasing their quality of life and disrupting their growth and development process. Preventive measures must be taken to prevent these adverse effects from happening to children. One preventive measure for TB is administering the Bacillus Calmette–Guérin (BCG) vaccine.[6] Albert Calmette and Camille Guerin developed this vaccine, which has been widely promoted by the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) since 1948.[7] The BCG vaccine can provide protection (immunity) to a person both against *Mycobacterium tuberculosis* (MTB) infection and its development into active diseases, especially miliary TB and meningitis TB.[8]

The Bacillus Calmette–Guérin vaccination has been widely implemented through a basic immunization program in Indonesia. The vaccine is especially administered to children during the infant age period.[9] Based on its purpose, spinal TB should be prevented in children who have received BCG vaccination. However, cases of spinal TB in children can still happen, as studied by Wardoyo, *et al*. (2012) and Sukamto, *et al*. (2019).[10,11] These findings raise doubts about the usefulness of BCG vaccination, such as whether the protection provided is only limited to certain types of TB, excluding spinal TB. Therefore, this study aimed to examine the relationship between BCG vaccination and the occurrence of spinal TB in children.

Methods

A case-control study is a retrospective analytical observational study that does not require intervention towards the research subjects.[12] This type of study determines the relationship between a cause (independent variable) and an incident that has occurred because of it (dependent variable). The focus of the study lies in the comparison between the case group and the control group. It involves determining whether the cause is present in each member of the groups and observing if any incidents occur in the case group as a result of the cause.[12]

The advantage of this study method is that it is more suitable for rare cases and easier to obtain research ethics permission than experimental studies involving interventions towards research subjects.[13] Such a study design is ideal for this study since its purpose was to determine the relationship between two variables: BCG vaccination as a cause and spinal TB in children. Spinal TB is quite rare, and the resources that can be used for this study are limited. Thus, this study was conducted using a case-control study model.

This study identified two sample groups to analyze the relationship between BCG vaccination and spinal TB in children. The first group, the case group, consisted of spinal TB patients, whilst the second group, the control group, consisted of patients with other forms of TB. All samples from each group were taken from the pediatric TB patient population, both outpatient and inpatient, at Dr. Soetomo General Academic Hospital, Surabaya, from 2017 to 2021.

The number of samples taken from the population for each group was determined using a minimum sample size calculation. The type I error value (α) used was 5%, and the power value (1-β) used was 80%. Spinal TB patient that received BCG vaccination was estimated to be around 48%, while such exposure in TB patients other than spinal TB was estimated at around 1%.[14,15] Thus, based on the calculations using Epi Info version 7.2.5.0, the minimum sample size required for each group was 16, and 32 samples were needed for this study (1:1 ratio).[16]

The sample for the case group was obtained through total sampling, while the sample for the control group was obtained through matched sampling based on age and sex. Samples were selected even though the patients had more than one type of TB. Each sample must have their BCG vaccination record. Patients with malnutrition and/or human immunodeficiency virus (HIV) infection before or around the time of diagnosis were excluded. Malnutrition can disrupt T cells from triggering an adequate immune response during infection. Human immunodeficiency virus infection can cause damage to CD4 lymphocytes, which produce IFN gamma, which is crucial in the primary defence against TB.[17–19] Thus, this exclusion aimed to see as clearly as possible the effect given by BCG vaccination as an independent variable without other interfering factors, such as malnutrition and HIV infection, that may affect the dependent variable within this study.

Children are defined as individuals below 18 years old, including those still within the womb and those who have just been born (0 years old).[20] An individual's age is determined by calculating the interval between the date of birth and when the TB diagnosis was first made. The recorded data was numerical. The sex of each patient was classified into male or female based on what was found during the diagnosis. The BCG vaccination status was determined based on whether there were related anamnesis results or BCG scar examination results. The recorded data was on a nominal scale (have received or have not received). Nutritional status was determined based on an assessment using the anthropometric table, weight/height for 0-5 years old patients and body mass index (BMI)/age for 5-18 years old patients.[21] The recorded

data was on a nominal scale (have malnutrition or do not have malnutrition). Lastly, HIV infection status was determined based on whether there was such a diagnosis. The recorded data was on a nominal scale (infected with HIV or not infected with HIV).

The data required was entirely taken from medical records filled out by the doctors in charge of the pediatric TB patients at Dr. Soetomo General Academic Hospital, Surabaya. Medical records were collected and selected based on the ICD-10 diagnosis code for TB. During the data collection process, all data obtained were recorded using Microsoft Excel version 2019.[22] During this process, no additional contact, intervention, or history-taking was made with the related patient. Each measurement result on the nominal scale of each variable (BCG vaccination and occurrence of spinal TB in children) was given a numerical notation (0 or 1). The coded data was then inputted to the International Business Machines Corporation (IBM) Statistical Package for Social Sciences (SPSS) version 23 for statistical testing using Fisher's exact test and contingency coefficient calculation.[23]

Results

The results of sample recruitment can be seen in Figure 1. Medical record data from 335 pediatric TB patients, represented by the top box, were accessed during the data collection process. Of the 335 patients, 43 were all pediatric spinal TB patients admitted to Dr. Soetomo General Academic Hospital, Surabaya, from 2017 to 2021, represented by the arrow pointing from the top box to the box below on the left. However, not all patients were included within the case group, as 37 patients were excluded, as indicated by all curved arrows pointing to the left. This exclusion was due to an unknown history of BCG vaccination (28 patients), unknown nutritional status (1 patient) and malnutrition at or before the time of diagnosis (5 patients). As a result, only 9 patients met the criteria. They were selected as the case group sample, represented by the arrow pointing from the "spinal tuberculosis cases" box to the "eligible as case group sample" box. Unfortunately, the number of samples did not meet the minimum required based on previous calculations.

Afterwards, pediatric non-spinal TB patients were selected based on the medical records of all TB patients. The search was limited to the same gender and age close to the selected patient as the case group, and 292 patients were found, represented by the arrow pointing from the top box to the box below on the right. Therefore, 335 patients had their medical records accessed to determine whether they met the inclusion and exclusion criteria, enabling their use as sample groups for both the case and control groups.

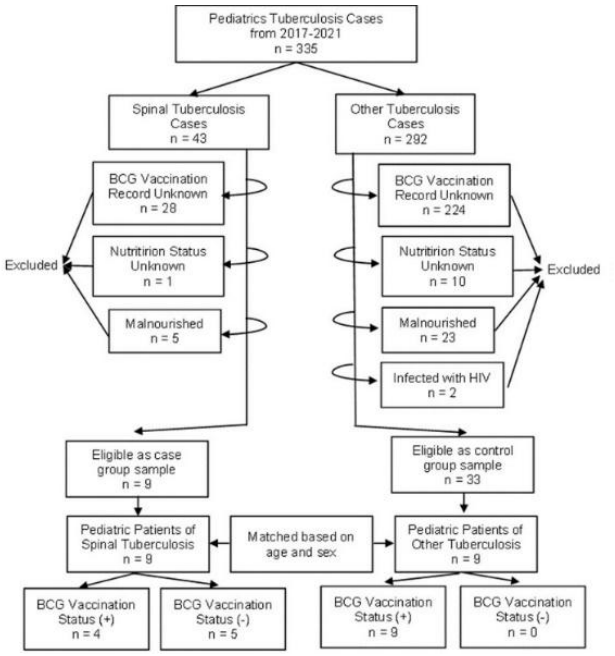

Figure 1. Sample selection result

There were 259 patients of these patients who were excluded from the control group due to an unknown history of BCG vaccination, unknown nutritional status, malnutrition at or before the time of diagnosis, and positive HIV infection status, indicated by all the curved arrows pointing to the right. Only 9 out of 33 patients were eligible as the control group sample after being matched with the case group regarding age and sex. This is represented by the arrow pointing from the "eligible as control group sample" box to the "pediatric patients of other tuberculosis" box.

Table 1. Spinal tuberculosis patients' characteristics

Spinal Tuberculosis Patient	n	%
Sex		
Male	21	49
Female	22	51
Total	43	100
Age		
0-5 years old	13	30
6-11 years old	11	26
12-17 years old	19	44
Total	43	100

Source: Research data, processed

It has been mentioned that 43 pediatric spinal TB patients were admitted to Dr. Soetomo General Academic Hospital, Surabaya, from 2017 to 2021. Most of these patients were females, with a very slight difference between genders. Of the 43 patients, 21 (49%) were males and 22 (51%) were females. The ratio between the total of male and female patients was 1:1.05. Based on what was found, spinal TB could occur in all age ranges of children, ranging

from 0-5 years old (13 patients), 6-11 years old (11 patients), and 12-17 years old (19 patients). However, the patients were mostly 12-17 years old, both male and female. In conclusion, the mean age of spinal TB patients in children was 9.5 years old. These characteristics are summarized in Table 1.

Table 2. Case and control group sample characteristics

Characteristic	Case Group	Control Group	%
Sex			
Male	5	5	56
Female	4	4	44
Total	9	9	100
Age			
0-5 years old	3	3	33
6-11 years old	1	1	11
12-17 years old	5	5	56
Total	9	9	100

Source: Research data, processed

The sample characteristics of the case group can be seen in Table 2. The ratio of male by female patients was 1.25:1. Most patients were between 12 and 17 years old (56%), followed by those aged 0 to 5 years old (33%). The fewest patients were in the 6 to 11 years old range (11%). The mean ages of the patients were 10.2 years old. Sample characteristics of the control group can also be seen in Table 2. The ratio of male to female patients was 1.25:1. Most patients were between 12 and 17 years old (56%), followed by 0 to 5 years old (33%). The fewest patients were in the 6 to 11-year-old range (11%). The mean ages of the patients were 10.2 years old. The characteristics of the case and control groups were the same because of matched sampling.

Table 3. Contingency table

BCG Vaccination	Spinal Tuberculosis		p-value	C
	Yes	No		
Yes	4 44%	9 100%	0.029	0.527
No	5 56%	0 0%		
Total	9 100%	9 100%		

Source: Research data, processed

Table 3 summarizes each group's BCG vaccination status. It shows that the proportion of those not vaccinated with BCG was more significant in the case group than in the control group. Fisher's exact test was conducted to determine whether there was a relationship between BCG vaccination and spinal TB in children. The Chi-square test was not used because its assumptions were not met.

The test produced a p-value of 0.029 ($p<0.05$). A p-value of less than 0.05 serves as the basis for rejecting the null hypothesis and accepting the alternative hypothesis, indicating a relationship between BCG vaccination and the occurrence of spinal TB in children. The relationship was moderately related since the result of the contingency coefficient calculation was $C=0.527$ ($0.4 \leq C < 0.6$). Unfortunately, the effect of the BCG vaccine on the occurrence of spinal TB in children, providing protection or not, could not be inferred because the odds ratio (OR) could not be calculated. The OR could not be calculated since one of the cells in the table contained a value of 0.

Discussion

The mean age of pediatric spinal TB patients found in this study was 9.5 years old, while in studies conducted by Irianto (2018) and Wang, *et al*. (2020), it was 8.9 years old and 8.4 years old, respectively.[24,25] Generally, the risk of developing TB in children is highest for those under 5 years old, decreases until 10 years old, increases slightly until 14 years old, and rises again for those above 15 years old.[26] A similar trend was found in a study conducted by Firnadi, *et al*. (2022), where TB mainly occurred in children under 5 years old, but the incidence did not increase and continued to decline beyond 15 years old.[27] Extrapulmonary TB has similar risks, but the risks do not slightly increase after 10 years old.[28] Additionally, a study conducted by Tidja, *et al*. (2020) concluded that bone TB in children mainly occurred before 10 years old.[29] The underlying cause may be the incomplete development and/or reduced efficacy of the main immunological factors during those years.[28]

This study found that pediatric spinal TB occurred fewer in males than females, with a ratio of 1:1.05. An inverse proportion was found in other studies conducted by Irianto (2018) and Wang, *et al*. (2020), namely 1.33:1 and 1.67:1, respectively.[24,25] Generally, there is no significant difference between males and females in the occurrence of TB. However, the differences become more apparent and more consistent after puberty and over 25 years old, where the disease becomes more likely to occur in males. The reason behind this might be the sex hormones produced after puberty. Different sex hormones may affect the immune system differently, which works against TB infection.[30]

The results of this study regarding the relationship between BCG vaccination and spinal TB in children are in line with several other studies. This study found a relationship between BCG vaccination and spinal TB, which indicated the effect of the BCG vaccination against spinal TB in children. A systematic review and meta-analysis study found that the BCG vaccine was protective against TB disease, including spinal TB as a form of the disease.[8,31] A study by Utami, *et al*. (2021) found a relationship between BCG vaccination and extrapulmonary TB, which included spinal TB.[32]

The results of this study are also in line with how the BCG vaccine works in stimulating the immune system and the nature of the body's immune system. Changes in the immune system, both innate and adaptive, occur following an immune response to the BCG injection and persist for a long time, resulting in a more effective immune response to future infections. These changes include the emergence of "trained cells" in the white blood cell group of myeloid strains due to epigenetic and transcriptional changes and specific TB lymphocyte cells.[33] These immune cells can reach any part of the body, even though they are initially stimulated only at the vaccine injection site.[34] The spine as

part of the body is no exception in this case and can also receive protection from the stimulated immune system.

Some studies found different results, with no relationship between the BCG vaccination and the occurrence of TB in children.[35,36] The epidemiological triangle concept explains that a person's infectious disease results from influences exerted by contagious agents, hosts, and environmental factors. Prevention can be implemented by intervening in any of those three factors.[37] Transmission control measures, such as contact investigation and preventive therapy, have successfully prevented TB in children.[38] Thus, other factors may have a more substantial effect and may cause the effect of BCG vaccination to appear insignificant in statistical analyses of different studies.

In this study, it was found that not all children who had been vaccinated with BCG were protected from spinal TB. Generally, the failure to achieve the goal of BCG vaccination may be caused by several factors. Certain climatic conditions, the location of an area at a certain latitude, certain genetic traits of a person, and certain BCG strains can weaken the efficacy of the BCG vaccine. A person living in an area with *mycobacteria* in the surrounding environment may have been exposed to these bacteria and developed pre-existing immunity against TB. Administering the BCG vaccine to such a person later will only slightly increase their immunity. It turns out that the slightly enhanced immunity eventually fails to provide adequate protection against TB. In addition, the existing immunity might inhibit the replication of the bacteria in the BCG vaccine, which is necessary to trigger an optimal immune response. An immune response that is not optimal can decrease the efficacy of the BCG vaccine.[39]

Strength and Limitations

This study examined the relationship between the history of BCG vaccination and the occurrence of spinal TB. Similar studies in Indonesia generally address TB in general, unlike this study, which specifically focused on one type of TB, spinal TB. This study used a case-control method with a higher evidence level than the cross-sectional method commonly used in similar studies in Indonesia. However, this study relied entirely on medical records, had a small sample size that did not meet the calculated sample size based on previous studies and did not account for potential close TB contacts, and a critical risk factor in TB infection, particularly in children. Hopefully, future research will involve more comprehensive data sources, a larger sample size, and more comprehensive variables. Therefore, how beneficial BCG vaccination is in preventing TB, specifically spinal TB, can be understood in more detail and with greater significance statistically.

Conclusion

There was a significant and moderate relationship between BCG vaccination and the occurrence of spinal TB in children. Therefore, BCG vaccination should be able to prevent the new occurrence of spinal TB in children.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Ethical Clearance

This study was ethically approved by the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, based on Letter of Exemption Ref. No. 0790/LOE/301.4.2/II/2022 on 11-02-2022.

Authors' Contributions

Designed the study: MARA, MF, AE, and RAS. Collected and processed the research data, and wrote the manuscript: MARA. Provided guidance and input throughout the research process and manuscript preparation: MF, AE, and RAS. All authors reviewed and approved the final version of the manuscript.

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