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The Influence of *Bacillus Calmette-Guerin Scar* on Infant and Child Mortality: an Evidence-Based Case Review

Influence of BCG Scar on Child Mortality – EBCR

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Background
Indonesia is ranked second with the highest number of tuberculosis cases. Bacillus Calmette-Guerin (BCG) immunization as prevention to tuberculosis infection, typically forms a BCG-scar within two to five months. Several studies indicate that formed BCG-scar provides protection from non-specific infections and improve mortality rate.
Method
Taken from three large databases: Google Scholar, PubMed, and Science Direct using keywords ("BCG-scar") AND ("Mortality") AND ("Children" OR "Infants"). These articles which meet the inclusion and exclusion criteria, evaluated using Joanna Briggs Institute (JBI) critical appraisal tools.
Result
Four relevant cohort studies were found and critically reviewed. Three studies showed an association between BCG-scar and mortality to children under one year and one study to children under five years.
Conclusion
BCG-scar serves as a positive indicator of better survival and health. Emphasizes the importance of effective vaccination practices and follow-up in infant health care.
Keywords
BCG-scar, Mortality, Infant, Children

INTRODUCTION

Bacillus Calmette-Guerin (BCG) immunization is strategy to prevent severe tuberculosis (TB) in children, result in vary individual immune responses. It is especially important in Indonesia, which ranks second in global TB cases. BCG immunization also may cause formed-scars, which depends on technique and strain used. Studies proved that formed BCG-scar tend to have stronger immune systems and lower mortality rates from TB and other infections. This report presents a pediatric non formed BCG-scar cases and child mortality, analyzed through an evidence-based approach, highlighting the need for post-exposure evaluation and consideration of revaccination in the future. [1–9]

CASE 1

An 11-month-old boy experiences seizures with eyes looking to the right and stiff hands and feet from three days before admission to the emergency unit. The mother explained the patient had fever from three weeks ago followed by diarrhea, stomatitis and cough about one month ago. His father has been receiving tuberculosis treatment for the past five months. BCG immunization was done when the child was one month old in health center and no BCG-scar was found during hospitalization. There was no history of tuberculosis prophylaxis given to the child while his father was suffering from pulmonary tuberculosis. History of spontaneous childbirth with a weight of 3.2 kilograms and a body length of 50 centimeters according to the mother's explanation. On physical examination, his Glasgow Coma Scale (GCS) was E1V2M1 with a heart rate of 121 times/minute, respiratory rate of 28 times/minute, temperature of 37.6ºC and oxygen saturation of 99% with O2 nasal cannula. The child's weight was 6.8 kilograms and body length 66 centimeters. Based on anthropometric status, it was found that the child is underweight, severely stunted and wasted. the weight age was less than the height age, with a weight age of three to four months, and a height age of five months. On physical examination, a prominent fontanel was found, positive meningeal sign, opisthotonus, chorea, and rhonchi in both lungs. Laboratory tests showed leukocytosis and thrombocytosis with non-reactive HIV. Chest X-ray showed miliary tuberculosis. The tuberculosis score in this child was six with chest X-ray showing miliary tuberculosis, so the diagnosis of tuberculosis was established with suspicion of tuberculous meningoencephalitis although Rapid Molecular Test (RMT) or Acid-Fast Bacilli (AFB) sputum examination could not be performed. Rectal diazepam was given as initial management of seizures in children, intravenous corticosteroids and other supportive drugs were given. The patient passed away on the ninth day of treatment while waiting for referral to a more adequate facility.

CASE 2

A two year eight-month girl came with complaints of shortness of breath, fever and cough for two to three weeks ago. Based on her mother explanation, the child has lost two kilograms of weights in the last three weeks. When she was one-year-old, she had contact with a neighbor who suffered from pulmonary TB. She has been given cough and fever medication and antibiotics but no improvement. She had a history of spontaneous vaginal delivery with the help of a midwife, but her birth weight was not recorded and her mother also forgot. Triple elimination was not recorded. She already got immunization of BCG and MR on time at health center but BCG-scar was not developed in this patient. Diphtheria, Pertussis, Tetanus, Hepatitis B, and *Haemophilus influenzae* type-b (DPT-Hb-Hib) and polio vaccines were missed. Anthropometric examination showed that the child's current weight is nine kilograms with a height of 80 centimeters. The anthropometric status of the child is severely underweight, severely stunted, with good nutrition status. Her weight age was less than her height age. Her growth development chart was not filled. Based on her weight age being less than her height age, her short stature was determined not to be stunting. X-ray examination was suggestive of miliary tuberculosis. Rapid Molecular Test (RMT) sputum examination and TST was performed with negative results. On tuberculosis scoring, a score of five was obtained. The diagnosis of miliary tuberculosis was still established based on the doctor's clinical considerations. Laboratory examination found leukocytosis, microcytic hypochromic

anemia, lymphocytopenia. Serological examination of anti-HIV (Human Immunodeficiency Virus) was performed because the child had intertriginous candidiasis and oral thrush, but the results were negative. Anti-tuberculosis medication was given for tuberculosis, nutritional intervention for stunting and other supportive drugs were given. On the 14th day of treatment, the patient passed away due to respiratory failure.

Clinical Problem

The clinical question for the case: Is the formation of BCG immunization scar related to infant mortality?

Methods

Clinical question (PICO)

Patient (P) : Infant and child
Intervention (I) : Formation of BCG-scar
Comparison (C) : No formation of BCG-scar
Outcome (O) : Infant and child mortality

Search Strategy

Google scholar, PubMed, Science Direct were used to search for articles

Selection Criteria

The keywords were “Children” OR “Infants” AND “BCG-scar” AND “Mortality”. The search results found four journals that correspond to the four cohort journals. The literature search flow can be seen in Figure 1.

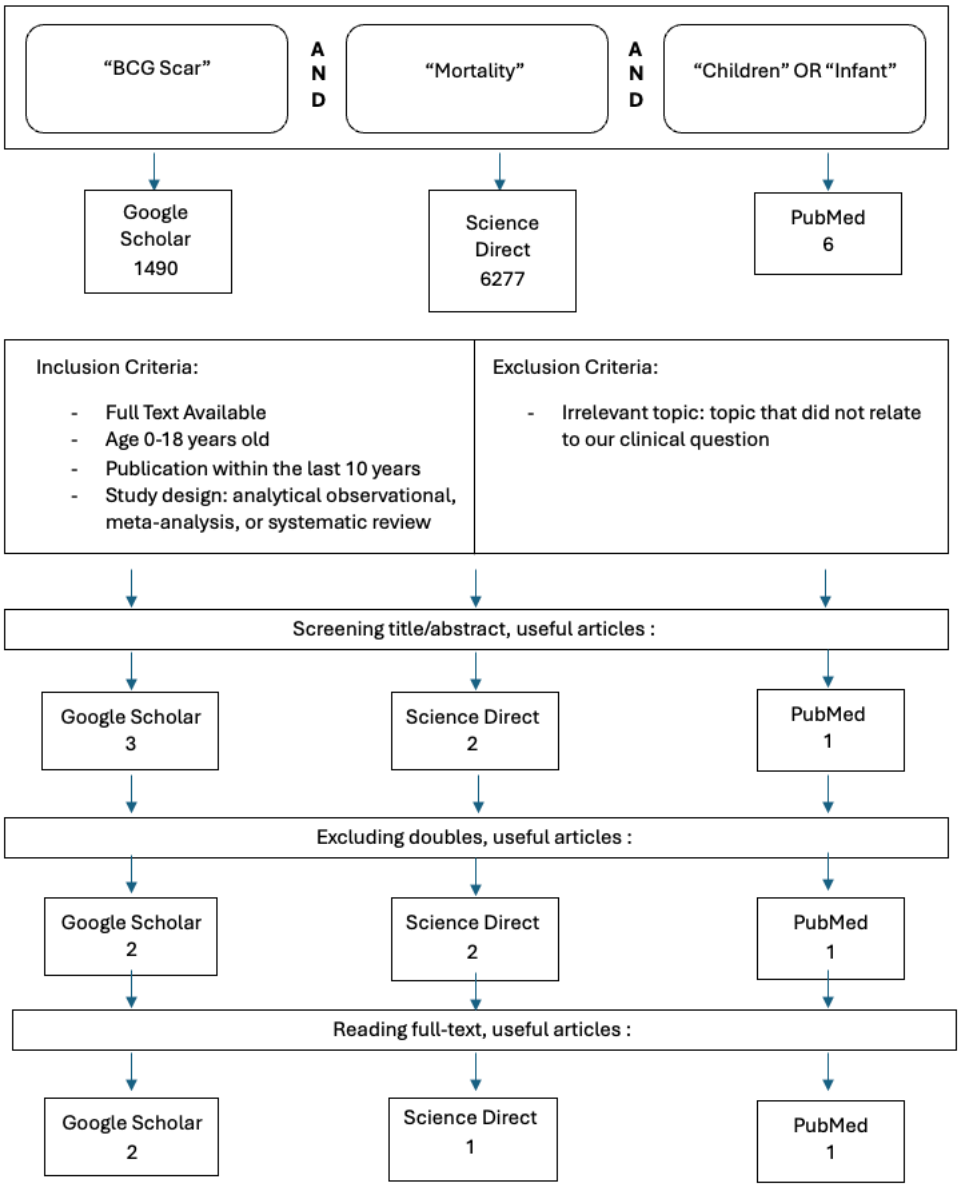

Figure 1. Literature search flow

Critical Review

Critical review of four selected cohort journals using Joanne Briggs Institute (JBI) for cohort studies. The critical appraisal checklists can be seen in Table 1. Risk of Bias (RoB) was assessed and considered high RoB if the question answered "Yes" was 49%, moderate if 50-69% and low if more than 70%. [10,11]

Table 1. Critical review checklists

No.	Critical Appraisal Checklists
1.	Were the two groups similar and recruited from the same population?
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3.	Was the exposure measured in a valid and reliable way?
4.	Were confounding factors identified?
5.	Were strategies to deal with confounding factors stated?
6.	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7.	Were the outcomes measured in a valid and reliable way?
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
10.	Were strategies to address incomplete follow up utilized?
11.	Was appropriate statistical analysis used?

RESULT

There are 4 cohort studies after our literature search. The Schaltz-Buchholzer et al. study examined BCG vaccination in neonates with Tuberculin Skin Test (TST) reactions at two until six months of age and mortality rates at one year of age. This study was designed as an observational cohort in three different periods. The division of these three periods was due to follow the ongoing three Randomized Control Trial (RCT) studies regarding BCG-Denmark, BCG-Russia and BCG-Japan immunization when the cohort study data was collected. Resulted in 4,633 immunized infants, data collection of TST and BCG-scar formation was carried out in three periods to prevent loss to follow up. With total sample of 2105 neonates in RCT I and II, reactive TST showed in lower mortality rate. BCG-*scar* was found more in infants with reactive TST. An Relative Risk (RR) of 4.56 (1.51-13.8) was obtained in infants who did not respond to TST on negative BCG-scar. After six months follow-up, BCG immunization involving RCT I-III studies, showed same result with reactive TST correlated with lower mortality rate. However after we critically reviewed, we found a limitation about exposure between group. There's differences in immunization strain between RCTs. Therefore, this study meet ten criteria out of eleven (90%). We concluded that this study has low Risk of Bias (RoB). [12]

Storgaard *et al*. observational cohort study aimed to measure the risk of mortality in children with BCG-scar. Conducted in Guinea-Bissau and used data from the Bandim Health Project's Health and Demographic Surveillance System (HDSS) with inclusion criteria of under 5 years old age children who received BCG immunization from the local government and present at the time of the BCG-scar examination. Exclusion criteria were immunized children in less than 31 days at the time of the BCG-scar

examination. Mortality analysis used Cox proportional hazard. During six months follow-up, children deaths were found less in formed BCG-scar children. There was a positive association between BCG-scar and respiratory diseases underlying the cause of death. However, in this study, we didn't find any cofounding factors that were identified or discussed. Another inevitable potential bias was the difference of ethnicity, place of birth, and season between groups. BCG reading was conducted with different people within 30 days, which is normally formed between 2-5 months. Also, this study has no data about loss to follow up participants. These might introduce potential bias. Since four out of 11 questions, therefore we concluded that this study had high potential Risk of Bias (RoB). [13]

Timmermann *et al*., a study in Denmark examined the relationship between BCG-scar, TST and mortality in children aged 12 months. The design of the observational analytic cohort study used cox regression for statistical tests on 2709 normal birth weight infants (NBW) and 1102 low birth weight (LBW) infants. Examinations were performed at two and six-months of age and mortality rates at 12 months of age. Formed BCG-scar found more in children with history of LBW infants. Among them, non-formed BCG-scar had two folds mortality rate and children who formed BCG-scar and TST had a lower mortality rate. A 20% reduction in mortality in TST and positive BCG-scar for NBW children. [14] BCG-scar reading was conducted with different field worker and no described number of loss to follow up participants. This study had 72% score (eight out of ten). Therefore, we assumed that this study had low RoB.

Stougaard *et al*. used real data to calculate the coverage of BCG immunization and BCG-scar associated with neonatal mortality. This study was conducted as a cohort study with a multiple visits for every three months from the time of BCG immunization until the age of three years. The children were used the Bandim Health Project (BHP) register data from 2013-2021. Mortality data measurement until the child is one year old. BCG-scar was obtained at the age of two months with a mortality rate lower in formed BCG-scar. [15] However, BCG-scar reading was done by different field workers and numbers of loss to follow up were not mentioned. Six out of eleven question were answered "Yes". Therefore, This study had moderate RoB (54%).

DISCUSSION

Our cases involve infants and children who, unfortunately, passed away while battling the most prevalent cases in Indonesia. Both showed no BCG scar formation despite having received on-time immunization. Neither patient exhibited stunting, but their nutritional status was compromised, rendering them more susceptible to tuberculosis infection. We could not ascertain whether the malnutrition occurred prior to the tuberculosis infection or was a result of it. [16] However, a study by Schaltz-Buchholzer et al. showed that a formed BCG scar is not associated with nutritional status, as BCG scar formation is influenced by several factors, such as immunization technique and the BCG strain used.

A Tuberculin Skin Test (TST) was performed in second case which yielded as non-reactive result. Three studies from Schaltz-Buchholzer et al, Timmerman et al. and Stougaard et al. implied that non-reactive TST indicated a poor immune response during BCG immunization and when TST was performed. Toll-like receptor (TLR) and CD4+ T cells are responsible in this reaction.[8,17–19] Although both BCG immunization were done in health center, there is a study that support the place of birth might affect the BCG-scar status. Storgaard *et al*., despite their high risk of bias because of BCG-scar reading was done in

30 days (meanwhile in Indonesia 2-5 months), showed that BCG immunization done in health center affects the BCG-scar outcome [2,10–15,20]

This EBCR has several strengths, including the use of a systematic EBCR methodology and critical appraisal using the JBI checklist to ensure high-quality evidence selection. However, limitations exist. The included studies had a high risk of bias in certain domains, particularly regarding incomplete follow-up and variations in scar assessment techniques. Additionally, none of the studies were conducted in Indonesia, potentially limiting applicability to local populations. [12–15]

Although no comprehensive systematic review exists focusing specifically on BCG-scar and mortality, this EBCR highlights an important and underexplored area. The findings support that the BCG scar may serve as a marker for better non-specific immune system. Immunological mechanisms such as increased IFN-γ production, CD4+ T-cell activation, and Toll-like receptor stimulation may underlie these effects. The implications for clinical practice include the potential need to monitor BCG-scar formation and reconsider revaccination strategies in children without visible scars. Given Indonesia's lack of national guidelines on BCG revaccination, this evidence may inform future policy decisions. [18,19]

However, BCG-scar formation is not only affected by immune response, it is also influenced by several factors, such as the immunization technique and the BCG strain used. Several researchers stated that BCG-scar affects the survival rate of infants and children where the presence of BCG-scar is associated with the immune response. In contrast, other previous studies that not meet the criteria in this literature search state that there is no relationship between these two variables. [6,13]

Hence, Future research should aim to explore the underlying immunological mechanisms behind BCG-scar formation, its relation to non-specific immune protection, and evaluate the potential benefit and safety of BCG revaccination in children without visible scars through randomized controlled trials, especially in high-TB-burden settings.

Conclusion

Based on the two cases presented with evidenced based approach, it can be seen formed BCG-scar supports infants and children immunity that affects mortality rates. The evidence suggests that a formed BCG-scar supports infant and children immunity that positively affects mortality rates. It's necessary to increase awareness about the risk of infection in children, especially infants, who doesn't develop a BCG scar. Afterward, the consideration of BCG revaccination for infants or children without a BCG scar remains under discussion.

- BCG scar associated with lower infant and children mortality, reflecting a stronger immune response
- Post-vaccination evaluation and consideration of follow up care are needed in children without BCG scar
- Two fatal cases without BCG-scar support evidence from cohort studies linking scar absence with poorer outcome
- Though revaccination is not currently recommended in Indonesia, further research and policy discussion are needed to optimize child survival in high TB-burden settings.

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