

FAILURE OF SEROCONVERSION (SCAR FORMATION) IN BCG VACCINATED CHILDREN

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Abstract

Objective: The purpose of the research is to find out failure of seroconversion (scar formation) in BCG vaccinated children

Study Design: Descriptive Cross-Sectional study

Study Duration: 06 months from August 24-January 25

Study Place: Department of Pediatrics, CMH Lahore

Methods: A total of 110 BCG-vaccinated children aged 3–48 months were enrolled using non-probability consecutive sampling. Demographic and clinical data were recorded, and BCG scar presence was assessed by physical examination. Absence of a visible scar was considered failure of seroconversion, and associations were analyzed using SPSS version 26. P-value <0.05 was considered significant

Results: This study was done in tertiary care hospital and included 110 BCG-vaccinated children with a mean age of 18.6 ± 9.4 months; 56.4% were males. A visible BCG scar was present in 73.6%, while 26.4% revealed seroconversion failure. Scar absence was significantly associated with low birth weight, prematurity, malnutrition, and delayed vaccination beyond the neonatal period ($p < 0.05$). No significant association was found with age, gender, or place of vaccination.

Conclusion: The lack of scarring of the BCG is also frequent in vaccinated children and indicates a potential failure of seroconversion. It is closely linked with low birth weight, preterm birth, malnutrition and late vaccination. BCG scar assessment is a relatively easy method of determining children, who might need a more detailed follow-up in tuberculosis-prone areas.

INTRODUCTION

Tuberculosis (TB) has been one of the most significant global public health issues especially in low-income and middle-income countries where children are often exposed to this disease. World

Health Organization (WHO) records that children constitute a high percentage of the overall TB burden in the world, and they have increased risks of severe and disseminated

illnesses than adults. The Bacillus Calmette Guerin (BCG) vaccine is almost 100 years old and is the only approved vaccine against the prevention of TB, particularly severe disease, including the miliary TB and tuberculous meningitis among children.¹

In most countries with TB, BCG vaccination is done at birth. The formation of a typical scar at the inoculation site is considered one of the widely agreed measures of a successful immune response to BCG vaccination. Scar formation is discussed as a surrogate epitome of seroconversion and cell-mediated immune response that represents local replication of the attenuated *Mycobacterium bovis* strain and consequential immunological activation. Nonetheless, the absence of scar formation otherwise known as failure of seroconversion has been observed among a significant percentage of vaccinated children.^{2,3}

The prevalence of absent BCG scar, as reported, is variable, that is, 5 to 30 per cent among various populations. The failure of scar formation has been associated with a number of factors, which include; inappropriate technique of vaccine administration, difference in BCG strains, vaccine storage conditions, host factors including malnutrition, prematurity, immunodeficiency and genetic variability that affects immune response. There is also the possibility of influence of environmental mycobacterial exposure and maternal factor on vaccine take and immune responsiveness.⁴

There is a debate on the clinical and immunological implications of missing BCG scarring. Although studies have indicated that absence of scar formation can be associated with diminished protection against TB, other studies have also indicated that this does not mean that there is no protection but this could be through subclinical immune activation. However, a number of epidemiological studies have found a correlation between the presence of BCG scars and lowered risk of TB, leprosy and even all-cause child mortality, and the possibility of scar formation being an indicator of vaccine effectiveness.⁵

Seroconversion failure in TB-endemic conditions is diagnostic and epidemiological of concern. Children who do not have a BCG scar can be mistaken to be unvaccinated and hence unnecessary revaccination or falsified clinical decisions can occur. Moreover, the lack of proper BCG induced immunity in high-TB exposure populations can lead to the vulnerability to the severe TB disease, which further emphasizes the importance of the early diagnosis and proper follow-up.⁶

The prevalence and determinants of failure of seroconversion after BCG vaccination are also important to improve the use of immunization to optimize the situation and enhance child health outcomes. Assessment of risk factors related to it can be used to detect vulnerable populations and support specific response, including revaccination policy, nutrition intervention, or increased surveillance. Thus, the proposed research will examine the rate of failure of seroconversion, which is the absence of the development of BCG scars, in children immunized against the disease and also investigate the factors that may be linked to this effect.

Methodology:

The research was done as a descriptive cross-sectional study in the vaccination center and pediatric outpatient department of tertiary care hospital Lahore. The controlling time frame was a 06-month period (06 months from August 24-January 25). These immunization centers were based on the national Expanded Programme on Immunization (EPI) guidelines whereby vaccination against BCG is done at birth or during the early infancy. The research sample included the group of children who received the BCG vaccination and included in the routine immunization program. Participants who were eligible were enrolled in the study when they were taken through regular check-ups or when they were taken to get immunization services. They approached parents or legal guardians and informed written consent was obtained before enrollment. The 110 sample size was determined by making the assumption that the absence of BCG scar formation was expected at a specific

prevalence rate of with a confidence level of 95 percent and a margin of error of 5 percent. Sample calculation was done using WHO sample size calculator. An eligibility sampling was a non-probability consecutive sampling method, which was used to recruit eligible children until the desired sample size was reached. In the research, consent of institutional ethical review board was taken.

Inclusion Criteria

1. Infants between 03 months and 48 months.
2. History of BCG vaccination documented either by immunization card or record of vaccination center.
3. BCG vaccination during the first year of life or at birth.
4. Access to physical examination of the vaccination site of the BCG.
5. Informed consent which was written and signed by parents or guardians.

Exclusion Criteria

1. Lack of a history showing BCG vaccination.
2. BCG history of revaccination.
3. Precise or presumed primary or secondary immunodeficiency disorders.
4. Past or current history of tuberculosis or anti-tuberculous therapy.
5. Having severe dermatological conditions, burns, or scars in the normal site of BCG vaccination that hampered the evaluation of scar.
6. Children who are on long term immunosuppressive therapy, either systemic corticosteroids or chemotherapy.
7. Parents or guardians who refused to agree.

The demographic and clinical data, such as age, sex, birth weight (where available), nutritional status, gestational age at birth, place of delivery, age at vaccination against BCG, and the center of vaccination were documented with the help of a structured data collection proforma. Available maternal and perinatal history was also recorded where relevant. Evaluation of BCG scar

formation was conducted using the physical examination of the vaccination center or the outpatient clinic by a qualified healthcare worker. The test was specifically in the left upper arm above the deltoid region which is the usual place of vaccination of BCG as recommended by country guidelines.

Inspection of the vaccination site was done under sufficient lighting conditions and the child in a comfortable position. Scar formation was determined as an observable well-defined scar, papule or induration in accordance with a healed lesion of BCG. Scars were assumed to be present in the event that any permanent mark of any size was detected at the place of the vaccination. The lack of any visible or palpable site at the standard site was considered as failure of seroconversion (no BCG scar). The evaluation was categorical (yes or no). In situations in which a parent was found to have a history of local reaction after vaccination, yet there was no scar at the time of the examination, the scar was still deemed to be absent. To ensure a low observer bias, a standardized method of examination was followed and a second examiner was asked to check on the doubtful cases. The main outcome measure was the incidence of failure of seroconversion, which was the failure of BCG scar formation in children that were vaccinated. Secondary outcomes comprised the relationships between the lack of scar and the chosen demographic or clinical factors.

Statistical Package for the Social Sciences (SPSS) version 26 was used in entering and analyzing the data. The demographic and clinical characteristics were summarized using descriptive statistics. Categorical variables were presented as frequencies and percentage whereas the continuous variables were presented as mean +standard deviation. The dichotomous variables between the associations of the absence of the BCG scar and the corresponding variables were evaluated with chi-square test or Fisher exact test, where applicable. The value of p below 0.05 was taken to be statistically significant.

Results:

The study was conducted on 110 children who had a documented history of BCG vaccination. The age of the respondents mean was 18.6 ± 9.4 months and with age range of 3 to 48 months. The ratio of males to females was 1.3:1 with 62 (56.4%) males and 48 (43.6%) females constituting the study population.

Eighty-four children (76.4%) participated in vaccination at birth and 26 children (23.6%) at a later age after birth and during the first year of life. Most of the vaccinations (92; 83.6%) had been at government vaccination centers with 18 (16.4%) having been vaccinated at the private healthcare centers.

When a standard BCG vaccination site on the left side of the deltoid region was examined, 81 children (73.6%), however, had a visible BCG scar, whereas 29 children (26.4%), were found to have no visible BCG scar on examination, suggesting seroconversion failure. In children who had no observable scar, parents of 17 (58.6%) stated that they had a local reaction, which could either be redness or swelling following the vaccination, and parents of 12 (41.4%) did not notice any post-vaccination reaction.

Seroconversion failure was more common in children under 12 months old (15/45; 33.3%) than it was in children at 12 months of age and above (14/65; 21.5%); the difference however was not significant ($p = 0.16$).

The distribution of absence of BCG scar was a little higher in male children (18/62; 29.0%) than in female children (11/48; 22.9%) but the

correlation between gender and scar absence was not statistically significant ($p = 0.47$).

The weight of 31 children (28.2%) was lower than 2.5 kg. Those 14 children (45.2%) were found to have no visible BCG scar, as opposed to 15 children (19.2%) in those who were born with normal weight and this relationship was found to be statistically significant ($p = 0.006$).

The number of children who developed preterm birth was 24 (21.8%), and 11 (45.8%) were found to be unable to seroconvert as opposed to those who were born at term (18), ($p = 0.01$).

In 27 children (24.5%), malnutrition was diagnosed. BCG scar was largely absent among malnourished children (13/27; 48.1%) than well-nourished children (16/83; 19.3%) ($p = 0.004$).

Children who received vaccination following the neonatal period had a greater rate of no scar development (11/26; 42.3%) than those who received vaccination in the neonatal period (18/84; 21.4%), and the difference was statistically significant ($p = 0.03$). The place of vaccination (government vs private centers) and BCG scar formation did not show any statistically significant association ($p > 0.05$).

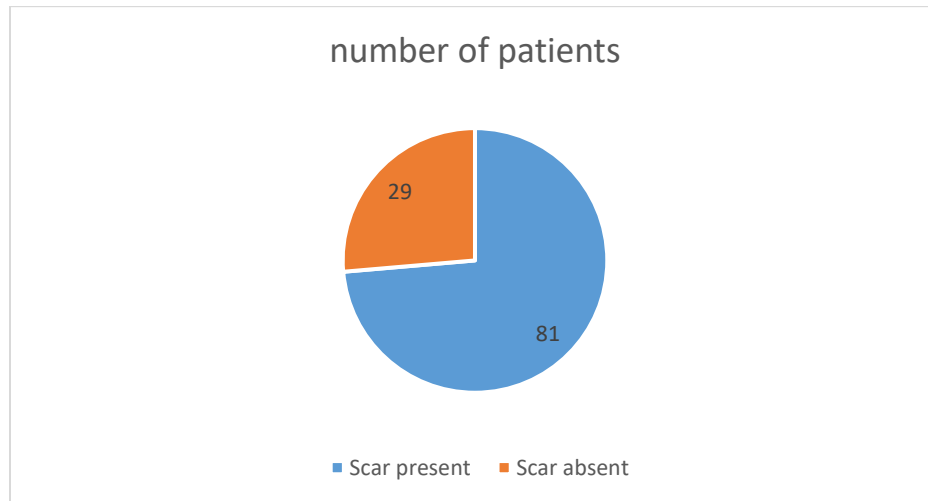
Summary of Key Findings

Overall, 26.4% of BCG-vaccinated children in the study failed to develop a visible BCG scar. Failure of seroconversion was significantly associated with low birth weight, prematurity, malnutrition, and delayed vaccination, while age and gender did not show a statistically significant relationship with scar formation.

Table 1.1: Demography and vaccination record of study population

Variable	Frequency (n)	Percentage (%)
Gender		
Male	62	56.4
Femlae	48	43.6
Age group (months)	18.6 ± 9.4	
< 12 months	45	40.9
≥ 12 months	65	59.1
Age at BCG vaccination		
At birth	84	76.4
After neonatal period	26	23.6

Place of vaccination		
Govt center	92	83.6
Private setup	18	16.4



Pie Chart 1.2: presence and absence of BCG Scar

Table 1.3: BCG scar absence association with demography

Variable	Total (n)	Scar Absent n (%)
Gender		
Male	62	18 (29.0)
Female	48	11 (22.9)
Age group		
< 12 months	45	15 (33.3)
≥ 12 months	65	14 (21.5)

Table 1.4: BCG scar association with nutritional status

Variable	Total (n)	Scar Absent n (%)
Birth weight		
< 2.5 kg	31	14 (45.2)
≥ 2.5 kg	79	15 (19.2)
Gestational age		
Preterm	24	11 (45.8)
Term	86	18 (20.9)
Nutritional status		
Malnourished	27	13 (48.1)
Well-nourished	83	16 (19.3)

Table 1.5: Association of BCG Scar Absence with Vaccination-Related Factors

Variable	Total (n)	Scar Absent n (%)
Timing of vaccination		
At birth	84	18 (21.4)
After neonatal period	26	11 (42.3)

Place of vaccination		
Government center	92	24 (26.1)
Private facility	18	5 (27.8)

Discussion:

The current research assessed the occurrence of unsuccessful seroconversion as shown by the lack of BCG scars development in vaccinated children and discussed the possible demographic, perinatal, nutritional, and vaccination-related variables. The lack of a visible scar of the BCG in this group of 110 children was noted to be observed in 26.4% of children in the group, which indicates that a considerable number of children vaccinated against the BCG do not experience the classical local response after immunization. This observation agrees with prior results in TB-endemic countries, with absent BCG scar prevalence of between 10 and 30, depending on both population attributes and research design.⁷

The prevalence of absent BCG scar observed in this study is consistent with the prevalence of the failure to immunize as shown by Roth et al., who found that a significant percent of immunized children had no visible scar despite her having immunization records. The same findings have been observed in South Asian and African environments indicating that not all immunization programs that involve routine immunization are devoid of failure of scar development. Differences in BCG strain, handling of vaccines, intradermal injection procedure and host immune response have been cited as causative factors.⁸

The present study did not find statistically significant gender and age association with BCG scar formation. Even though male children expressed a slightly greater proportion of scar absence in opposition to their female counterparts, the disparity was not noteworthy, and thus conformed to preceding statements that gender does not contribute significantly to BCG seroconversion. Similarly, the younger age had a tendency of increased scar absence that was not statistically significant, possibly because the scar was still developing to its full level as time went

on or a selection bias in the recall of subsequent reactions to the vaccination.⁹

Perinatal influences became essential factors of the scar formation of BCG. Young children born with low birth weight and those born preterm had considerably more absent BCG scar. These results are biologically plausible, because low birth weight and prematurity are related to immature immune handling, diminished cell-mediated immunity, and impaired inflammatory reactions which could cause poor take of vaccines. Karalliedde and Katugaha also showed similar relationships and revealed that they had weaker tuberculin reactions after BCG vaccination in the babies with impaired perinatal health.^{9,10}

The other factor that contributed to the formation of BCG scar was nutritional status. Failure of seroconversion was also significantly greater in malnourished children in this study than in well-nourished children. Malnutrition has also been known to affect both innate and adaptive immune responses especially the T-cell mediated immunity that is inevitable in the development of a BCG induced immune response. Past research has always shown lower effectiveness of vaccines and defective delayed-type hypersensitivity reactions in malnourished children, which confirms the study results.¹¹

The factors related to vaccinations were also a major cause of scar. Avoidance of BCG scar was much higher in children who were vaccinated post-neonatally than those who were vaccinated at birth. This observation highlights the significance of the timely vaccination and could potentially indicate the difference in the immune response, injection method, or vaccine effectiveness at various ages. According to the description by Brandt et al., delayed vaccination can make the exposure of the environment to mycobacteria more likely, which has been demonstrated to disrupt the process of BCG replication and immune priming.¹²

The fact that the difference between the place of vaccination and scar formation is not statistically significant may indicate that the government and the private centers had similar practices of vaccination. Nevertheless, even slight variations of training, supervision, and cold chain maintenance can have an impact and be subject to further research.

Clinical relevance of lack of scars of BCG is controversial. Protective immunity can still be present in the absence of scar formation even though Scar formation has been widely used as a surrogate marker of successful immunization, there are several studies that have confirmed that protective immunity can still be present without the appearance of a scar. However, with regard to epidemiological evidence, the existence of a BCG scar is attributed to low risk of tuberculosis, leprosy and general childhood mortality. Thus, the lack of scarring in the case might be a sign of poor-quality vaccine-induced immunity in at least a part of children.¹³

The other factor that should be taken into account in the description of the findings of this study is the reliability of BCG scar formation as a surrogate variable of protective immunity. Despite the widespread use of the scar presence in clinical and epidemiological practice as the means of verifying the successful vaccination, immunological protection is not directly measured. There are a number of studies that have shown that scar formation is discordant with tuberculin skin test (TST) or interferon-gamma responses, indicating that children who do not have scars can still develop sufficient cell-mediated immunity. However, in resource constrained conditions where immunological testing is not a standard practice, BCG scar assessment is a useful and cost effective method to measure vaccine take.¹⁴

The rather high percentage of children who lack a distinct scar on the BCG after vaccination in this paper draws an alarm in the regularity and quality of the vaccination procedure. BCG has to be administered intradermally, a technique that demands expertise and mis-injection of a particular depth may cause subcutaneous instead of intradermal injection, which causes a poor

local response and no scarring. Research comparing the efficacy of different types of vaccination have demonstrated that lack of adequate training and excessive workload in the immunization center can reduce the quality of the injection. Frequent refresher training and supervision of vaccinators may thus be a very important activity in enhancing seroconversion rates.¹⁵

Variation in scar formation may also be caused by environmental factors. Tuberculosis non-tuberculosis environmental mycobacteria are widespread in tropical and subtropical areas and have been demonstrated to regulate BCG immune reactions. Previous pre-exposure to environmental mycobacteria can block at the site of inoculation the replication of BCG, which leads to a weaker localized response and scarless. This has been suggested as one of the reasons of geographical variation in efficacy of BCG and should be investigated further in endemic areas.¹⁶

Publicly, a lack of BCG scar may make clinical decision making problematic. Children who do not have a visible scar are commonly assumed to be unvaccinated and this fact can result in unnecessary revaccination or misinterpretation of the TST results in screening tuberculosis. Misclassification can be minimized by clear documentation of vaccination status and standardised scar assessment protocols that would enhance clinical management. Moreover, providing counseling to the parents on the anticipated local response in the case of BCG vaccination can enhance the parental awareness and reporting of abnormal responses in early cases.¹⁷

The results of the studied work also emphasize the significance of incorporation of nutritional and perinatal health programs into immunization programs. The management of low birth weight, prematurity and children malnutrition could result in better response to vaccination and child health outcomes. Indirectly, by maximising neonatal immune competence at the dose of vaccination, strengthening antenatal care, encouraging institutional deliveries and making sure that postnatal follow-up is done early could help to increase the rate of BCG seroconversion.

The next step in research should be longitudinal follow-up of children who do not have any BCG scars in order to define their true risk of acquiring tuberculosis and other mycobacterial diseases. The use of immunological tests like TST, interferon-gamma release tests or cytokine profiling would give a better picture of the immunity induced by the vaccine. Also, comparative research comparing various strains of BCG and revaccination policies in children with missing scars can improve the immunization policy.¹⁸

To summary, although the absence of BCG scars is not necessarily the same as lack of protection, its strong correlation with adverse perinatal and nutritional outcomes supports the multifactoriality of vaccine response. To achieve the most favorable outcomes, it is necessary to address biological and programmatic determinants to improve the efficacy of BCG vaccination in the high-burden environment.

Limitations of study:

There are some limitations of this study. The cross-sectional design does not allow causal inference and immunological tests like the tuberculin skin test or interferon-gamma release test was not done to objectively determine immune response. Also, the assessment of scar was dichotomous and did not consider the size of scar, which could be a prognostic element. In spite of these, the study does shed some light on the occurrence and the determinant of failure of seroconversion in a real-life immunization scenario.

Conclusion:

This research demonstrates that absence of seroconversion which is manifested by the absence of scarring on the BCG is a relatively frequent observation in children who are vaccinated against BCG. Even though the formation of scars is not a conclusive parameter of protective immunity, its lack contributes to significant clinical and social health concerns in the context of tuberculosis-infested conditions. The results prove that the failure of BCG scar formation is strongly related to the negative perinatal and nutritional variables, such as low birth weight, premature delivery, and

malnutrition and delayed vaccination after the neonatal stage. Finally, although the fact that a person has no scar of the BCG does not always mean that he or she does not have immunity, this is a convenient and easy to measure marker of potential suboptimal response to vaccines. Periodic surveillance of the development of BCG scar during vaccination and follow-up appointments could be used to recognize children at risk to receive additional attention and specific measures, which would ultimately lead to a more effective approach to preventing tuberculosis in the high-incidence areas.

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