



Complications following Bacille Calmette-Guérin Vaccination in Children under the Age of 18 Months: A Multi-center Study

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Abstract

Background: The BCG vaccine, used since 1921 to prevent tuberculosis (TB), considered the world's most widely used vaccine. This study aimed to investigate the frequency and the type of complications associated with Bacillus Calmette-Guérin (BCG) vaccination in Iranian children.

Materials and Methods

This cross-sectional study conducted for 6 months among children aged up to 18 months who presented to primary health care centers in Tehran (under supervision of all three Medical Universities of Tehran) for their routine vaccinations. All children had received BCG vaccination at birth. We investigated the occurrence of BCG complications through history taking from the parents and physical examination by the study physician. Complications categorized into four major groups: local, regional, remote, and generalized and the rate of occurrence compared between the two genders.

Results: Finally, 14,095 children enrolled during the study period; 574 patients (4%) had experienced at least one complication following BCG vaccination. The most common complications were local side effects observed in 304 children (2.1%); followed by lymph node involvement detected in 270 children (1.9%). Lymph node involvement was more common in males ($P < 0.001$) and axillary lymph nodes were the most common site of involvement. There was a significant increase in the frequency of lymph node involvement at age 18 months in comparison to 2 month old infants (odds ratio=7.76, $P < 0.001$).

Conclusion: We found local adverse reactions as the most common complication following BCG vaccination and age was an independent predictor for the time of presentation of post vaccination lymph node involvement. Disseminated BCG and Osteitis not observed among vaccinated children.

Key Words: Bacillus Calmette-Guérin, Children, Complication, Iran, Vaccine.

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1- INTRODUCTION

Bacillus Calmette-Guérin (BCG), the live attenuated *Mycobacterium bovis* vaccination used against tuberculosis produced and utilized as a part of the World Health Organization (WHO) Global Expanded Immunization Program (1). Based on the current national vaccination program of Iran, BCG vaccine recommended at birth for all newborns with no contraindication for this vaccine (2). Although BCG vaccine is safe, its utilization is not eventless as it may lead to several adverse reactions. The most common complications of BCG vaccine include inoculation site abscess and local lymphadenitis, but in children with underlying immunodeficiency, it may cause severe and life-threatening complications with high mortality rates (3). Diagnosis of these complications, particularly BCG lymphadenitis is mostly clinical (4). Large variations in rates of adverse reactions has been reported from different countries and are usually attributed to faulty inoculation techniques, diverse BCG strains, number of vaccine doses administered and diagnostic standards (5). In some instances, various countries have reported outbreaks of BCG lymphadenitis sporadically (6).

Previous studies reported the incidence of disseminated BCG disease is almost one in 100,000 individuals while one in 2,500 vaccinated children present with localized BCG-associated complications (7). Nonetheless, not all countries have provided data regarding the complications of BCG vaccine. The first study on BCG complication dates back to 1962, which was a case-series on post-BCG vaccination adenitis. Since then, various Iranian studies have discussed the complications of BCG vaccination including lymphadenitis, abscess, lymphadenopathy, and fistula formation (5). Despite the presence of complications, even in children with mild immunodeficiency,

most cases respond well to various medications and most complications managed with appropriate therapeutic strategies (8). In the present study, we aimed to identify the frequency of complications following BCG vaccination in children who visited the primary health care centers in Tehran for routine vaccination in accordance with the national immunization program.

2- MATERIALS AND METHODS

2-1. Method

This cross sectional study was performed in 49 primary health care centers in Tehran (capital of Iran), during a six month period from October 2014 to March 2015. Based on cluster random sampling method (9), healthy children up to the age of 18- month who had received BCG vaccine at birth and had come to primary health care centers in Tehran for routine vaccination in accordance with the national immunization program, enrolled. At birth, one of the two different types of BCG vaccines available had vaccinated these children, at that time, one made by the Pasteur Institute in Iran and the other imported from Serum Institute of India. Based on the national vaccination program of Iran, we expected children to come at the ages of 2, 4, 6, 12 and 18 months for follow-up vaccinations (10). We excluded patients with immune deficiency and lack of consent. The Board of Research and Committee of Clinical Ethics at Shahid Beheshti University of Medical Sciences, Tehran, Iran, approved our study protocol.

2-2. Clinical criteria

Upon arrival at the primary health care center, a trained general practitioner obtained a thorough history from the parents or the caregiver of the child about any complications or symptoms appearing following BCG vaccination, performed a meticulous physical examination, and collected all clinical information on a

standardized data collection form. Presence of any of the following signs was recorded: size and number of enlarged lymph nodes, (axillary or other sites), especially lymph nodes ≥ 10 mm in size or lymph node abscess, abscess at the site of inoculation, inability to move the extremity following inoculation, generalized lymphadenopathy, generalized rash, hepatosplenomegaly, prolonged fever or poor feeding. Based on these findings, we categorized signs and symptoms into four major groups:

- Local: Large ulcer, lymph node or any abscess at the site of inoculation
- Regional: Large lymph node, ulcers or any abscess in the region of local drainage of inoculation or signs and symptoms of osteomyelitis on the ipsilateral side.
- Distant: Large lymph node, ulcers or any abscess on the contralateral side, and signs and symptoms of osteomyelitis in remote sites.
- Generalized: Generalized lymphadenopathy, hepatosplenomegaly, prolonged fever, rash, lack of weight gain and poor feeding. In cases with a history of contact with tuberculosis, presence of osteitis or generalized disease, we referred the patient to a specialist.

2-3. Statistical analysis

Numerical variables presented as mean \pm standard deviation; while categorized variables are summarized by absolute frequencies and percentages. Continuous variables compared using the Student t-test, and categorical variables compared using the Chi-square test. A linear regression model used to assess the relationship between adverse reactions and demographic characteristics. All the statistical analyses performed using PASW Statistics 21.0. Substitution of missing data done with SPSS and order "missing value analysis" and algorithm "Expectation

maximization" under "missing at random" assumption. In addition, we reported 95% Confidence Interval (95%CI) of lymphadenitis by Wilson score interval method and Data analysis performed by simple logistic regression. As there was an interaction between age and gender, data analyses performed in each age group separately. We considered P-values less than 0.05 as statistically significant.

2-4. Ethics

This study designed in accordance with the Helsinki Declaration with code of ethic in research 1392-1-91-11711-14329.

3- RESULTS

In the present study, we enrolled 14,095 children under the age of 18-month, but data analysis done on 13,893 patients due to incomplete information for 202 study subjects. Among these patients, 7,221 (52%) were male. The distribution of patients according to gender and age group shown in **Figure.1**; 574 complications (4%) detected following BCG vaccination; 48 children, had both local side effects and lymphadenitis. Local reactions were the most common adverse events observed in 304 children, (2%); 179 (59%) were among males and 125 (41%) among females ($P=0.02$). Lymph node involvement was the second most common side effect as detected in 270 children (2%); 174 males (64%) and 96 females, (36%) ($P<0.001$). Axillary lymph nodes were the most common site of involvement. The size of largest lymph node detected was 3.6 cm. No other BCG complications detected in our population. **Tables 1 and 2** portray details of the general and specific characteristics of the complications. The research group did not follow the children with these complications over time, as it was a cross sectional study. The frequency of local side effects according to age group shown in **Figure.2**. Local side effects were more prevalent at two months of age; odds of

local effects decreased with increasing age. The distribution of Lymph node involvement according to age group shown in **Figure.3**. Lymph node involvement was more common at 12 months and 18 months in comparison to two months-old infants. Unfortunately, the vaccine brand for each vaccine could not be determined, but we detected vaccine brand for those with adverse effects. So the denominators of number of children vaccinated with each vaccine could not presented; Out of

227 children with adverse reactions following the BCG vaccination, 128 (56.3 %) had been inoculated with the vaccine made by the Pasteur Institute in Iran and 59 (26%) infants with the vaccine imported from Serum Institute of India (SII). However, there was no difference between the two types of vaccines (Iranian versus Indian) as regards the occurrence of the local side effects and lymph node involvement.

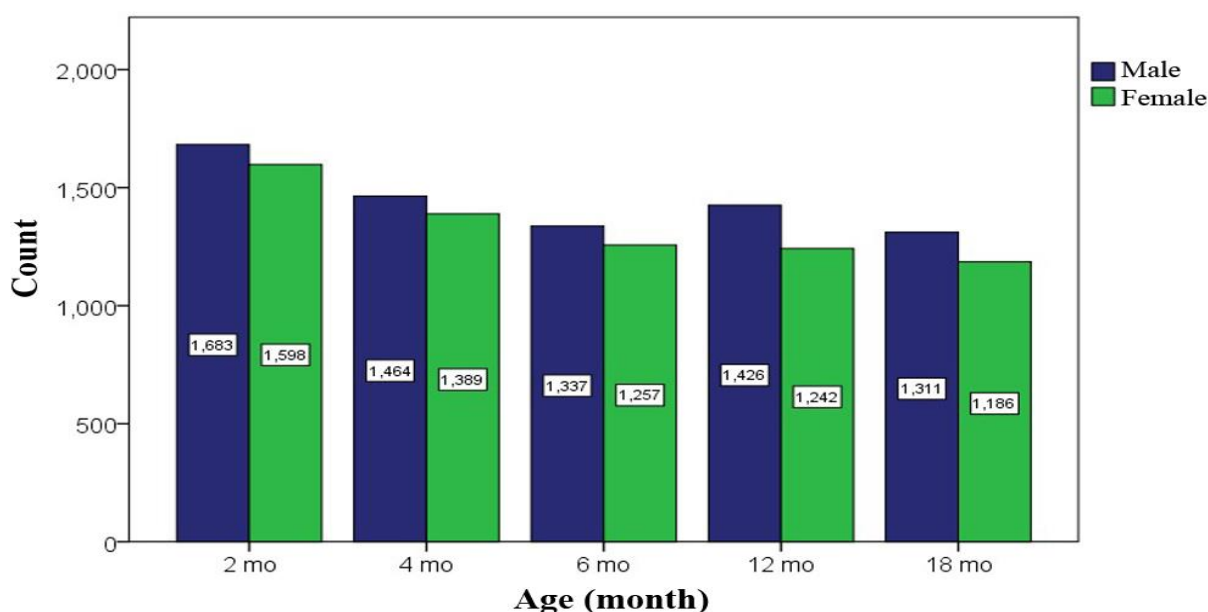


Fig.1: Distribution of patients according to sex and age group.

Table-1: Baseline characteristics of study population according to complications

Characteristics		Percentage according to total number of BCG lymphadenitis, (n=270)	Percentage according to total number of BCG local reactions, (n=304)
Gender	Male	174 (64%)	179 (59%)
	Female	96 (36%)	125 (41%)
Birth weight (gr)	<=1500	4 (1%)	2 (1%)
	1501-2500	15 (6%)	12 (4%)
	>2500	251 (93%)	290 (95%)
Pregnancy length	Term	255 (94%)	292 (96%)
	Pre-term	13 (5%)	10 (3%)
	Post-term	2 (1%)	2 (1%)
Age (month)	2	24 (9%)	151 (50%)
	4	18 (7%)	42 (14%)
	6	10 (4%)	28 (9%)
	12	83 (31%)	36 (12%)
	18	135 (50%)	47 (15%)

Table-2: Specific characteristics of complications in the study population

Characteristics		Percentage according to total number of BCG lymphadenitis (n=270)	Percentage according to total number of BCG local reactions (n=304)
Position of palpable lymph nodes	Axilla	192 (71%)	35 (73%)
	Anterior Cervical	33 (12%)	6 (12%)
	Posterior Cervical	13 (5%)	0 (0%)
	Supraclavicular	7 (3%)	2 (4%)
	Submandibular	7 (3%)	1 (2%)
	Anterior Chest	7 (3%)	1 (2%)
	Others	11(4%)	3(6%)
Type of local adverse effect	Wound with size more than (10 *10 mm)	6 (22%)	38 (16%)
	Nodule	13 (48%)	153 (65%)
	Abscess	6 (22%)	41 (17%)
Palpable lymph nodes at the opposite side of the injection site	Yes	26 (10%)	6 (2%)
Local effect at the injection site	Yes	48 (18%)	304 (100%)
Palpable lymph nodes at the injection site	Yes	270 (100%)	48 (16%)

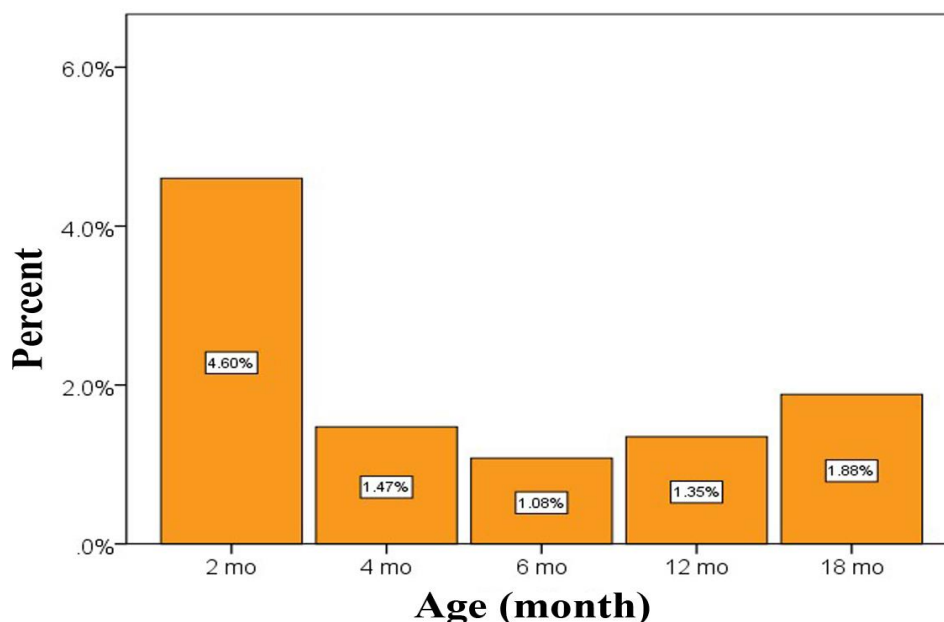


Fig.2: Local side effects as observed by age.

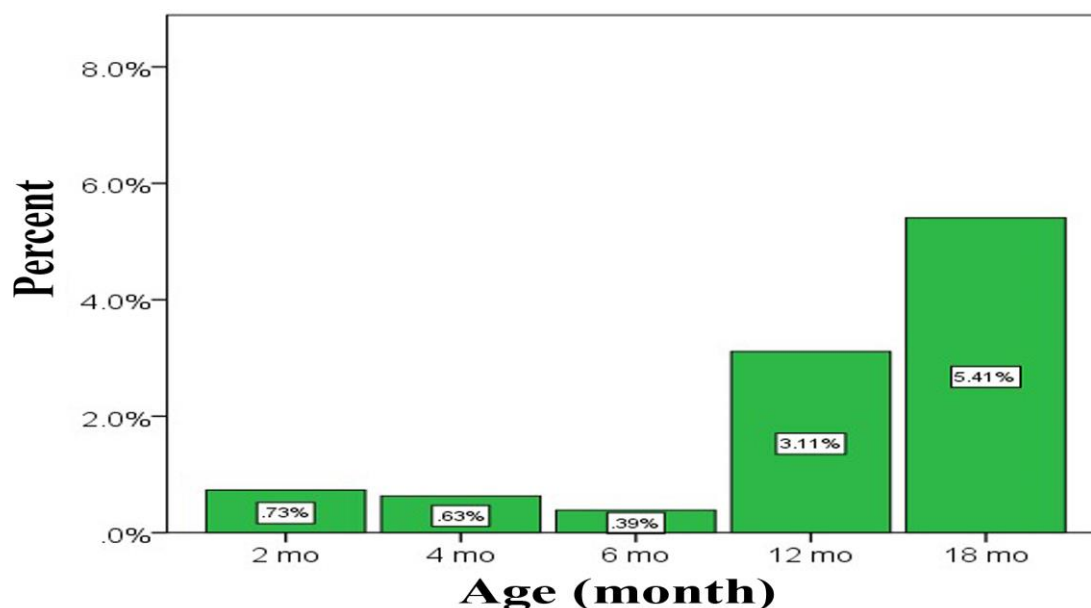


Fig.3: Lymph node involvement as observed by the age.

4- DISCUSSION

In this study, we showed a frequency of 4% for the complications following BCG vaccination. There was a significant increase in the frequency of lymph node involvement at 18- month in comparison to two-month-old infants. We observed no association between gender and development of complications. There are reports of various BCG complications from countries that administer the vaccination. Some of these complications, i.e. mild local reactions considered as a normal outcome following the procedure (11). Injection site reactions and non-supportive lymphadenitis generally respond well to conservative treatment, but some of these reactions are more severe and may require surgical intervention (11, 12). Several predictive factors cause BCG complications, including the patients' age, dosage, BCG strain and the inoculation technique (13-16). Number of received doses may also contribute to the development of adverse reactions; a Brazilian study on 71,341 school children showed that reactions to second doses of

BCG were more common than to the first dose of the vaccine, albeit not statistically significant (17). Disseminated BCG disease is also another complication that is difficult to treat and often is most observe in children with immunodeficiency (18). Although this condition usually seen in infants, cases of older children have been reported (19). However, we did not observe any case of disseminated BCG in our study. Our study was not power to measure disseminated BCG disease, as this is a rare occurrence. The incidence of osteitis following BCG vaccination is not clear in most cases and it is a rare complication. In the Poland surveillance data on Adverse Events Following Immunization, only five patients were diagnosed with osteitis after BCG vaccination during the period from 1994 to 2010 (17). However, it not documented if these children were immunocompromised or not. In a study of children with severe combined immunodeficiency, one out of eight patients had osteitis (20). Although osteitis reported particularly in the Scandinavian countries and Eastern Europe, and linked to changes in the BCG

vaccine strain used during that period, we believe that one should not forget the association of this rare severe complication with any probable underlying condition in the affected patient (21). Due to the varying influences of all of the above-mentioned factors, the incidence of BCG complications has been reported from 0.1% to 17% in different studies (7, 17, 22). A ten-year record-based study of adverse events following immunization in Oman revealed an annual rate of BCG complication of 33.7 per 100,000 populations (23). The most common complications in this study included adenitis and local reactions which were statistically more frequent among male children aged >2 years. Awad studied the rate of BCG complications in the Gaza strip and reported a rate of 14.7 per 1000 infants and 2.5 per 1000 schoolchildren (24). However, a single batch of vaccine considered responsible for the outbreak of these complications. An Irish study reported an overall complication rate of one per 931 vaccines and not suppurative adenopathy as the most common complication (25). The overall rate of BCG complications in British Columbia was 0.01 to 0.24% in infants (26). In another study from Canada, the reported complications following BCG vaccination in the order of frequency included disseminated BCG, osteomyelitis, BCG abscess, lymphadenitis or BCG adenitis and cellulitis (27). In our study, the frequency of complications was higher than these studies and local side effects were most common adverse effects detected.

4-1. Limitations of the study

This study has some limitations: First, we did not consider the exact time of the onset of complications. Although we selected healthy children by history, we did not examine the children for various degrees of immunodeficiency, particularly human immunodeficiency virus infection, as the

frequency of complications tends to be higher and more severe in such patients (16, 20, 28). Finally, we did not include complications related to allergic conditions such as eczema, atopic dermatitis, allergic rhino conjunctivitis, and asthma (29).

5- CONCLUSION

We found local adverse reactions as the most common complication following BCG vaccination in our study on a relatively large population of vaccinated children BCG vaccination would continue to be a useful method of prevention against severe tuberculosis infections. Our survey showed that adverse reactions are not frequent and in most of the cases, accompanied by spontaneous healing. However, it is important to recognize these complications and to provide appropriate treatment.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENTS

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