

# Bacillus Calmette-Guerin lymphadenitis: A 6-year experience in two Saudi hospitals

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## ABSTRACT

**Background:** The World Health Organization (WHO) has recommended Bacillus Calmette-Guerin (BCG) vaccination as a part of the global expanded program for immunization. Although the BCG vaccine is usually a safe vaccine, a number of complications with lymphadenitis being the most common complication, can occur. **Aim:** We evaluated the frequency, the clinical presentation and treatment modalities of lymphadenitis after BCG vaccine in Saudi children. **Results:** A total of 145 patients with BCG lymphadenitis presented between January 2005 and December 2010. In the majority (103) of the cases, the lymphadenitis involved ipsilateral left axillary nodes. Other sites of involvement included the left supraclavicular lymph nodes in 26 (18%) patients, and both the left axillary and supraclavicular lymph nodes were involved in 7 cases (4.8%). A total of 75 patients (65%) were given antituberculous medication. Eight (27%) patients had positive acid-fast bacilli and positive cultures for *Mycobacterium bovis*. **Conclusion:** In light of the findings of this study, it would be advisable to administer the BCG vaccine in Saudi Arabia at a time later than at birth, as the younger children are commonly affected.

**KEY WORDS:** Bacillus Calmette-Guerin, lymphadenitis, tuberculosis

## INTRODUCTION

The Bacillus Calmette-Guerin (BCG), a live attenuated vaccine with a characteristic residual virulence, has been used to prevent tuberculosis since 1921.<sup>[1]</sup>

The World Health Organization (WHO) has recommended BCG vaccination as a part of the global expanded program for immunization (EPI). As Saudi Arabia has an annual tuberculosis (TB) incidence rate of 19 cases/100,000 people, the national immunization program still includes neonatal BCG vaccination.<sup>[2]</sup> Although the BCG vaccine is usually a safe vaccine, a number of complications can occur, such as adverse local reactions, regional lymphadenitis, osteomyelitis and disseminated infection in immunocompromised children, with lymphadenitis being the most common complication.<sup>[3]</sup> In our opinion, it is important to evaluate the frequency, the clinical presentation, and treatment modalities of lymphadenitis after BCG vaccine in Saudi children.

## MATERIALS AND METHODS

We studied the medical records of all cases of BCG lymphadenitis, non-suppurative lymphadenitis, and suppurative lymphadenitis (which is characterized by the appearance of fluctuation with erythema and edema of the overlying skin) presenting to the pediatric infectious disease clinics at King Khalid University Hospital (KKUH) and Security

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Forces Hospital in the Riyadh region. In Saudi Arabia, the BCG vaccine strain was changed in 2005 from French strain to Danish strain till date.

## RESULTS

A total of 145 patients with BCG lymphadenitis presented between January 2005 and December 2010.

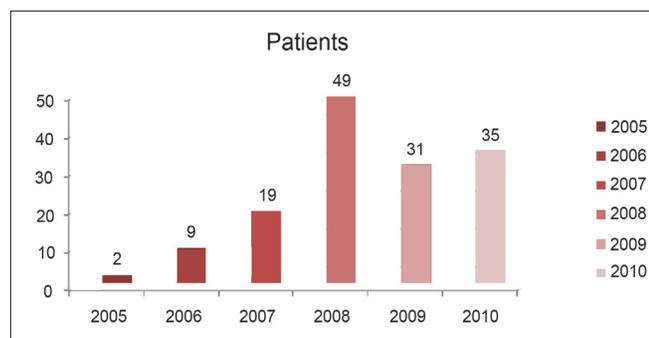
The number of the patients in the year 2005 = 2 (1.37%); in 2006 = 9 (6.2%); in 2007 = 19 (13%); in 2008 = 49 (33.7%); in 2009 = 31 (21%); and in 2010 = 35 (24%) [Figure 1].

All patients ( $n = 145$ ) from the two hospitals were born at full term, and only one had clinical evidence of immune deficiency. The age at which most of the cases presented was three to four months, followed by those of two to three months of age [Table 1]. One patient presented after six months (0.6%).

Among 145 cases of BCG lymphadenitis, 100 (69%) were male and 45 (31%) female. In the majority of cases (103), the

**Table 1: The age distribution of infants with BCG lymphadenitis**

Age (months)	Frequency (%)
>1	8 (5.5)
2-3	60 (41)
3-4	70 (48)
4-5	6 (4)
6	1 (0.6)



**Figure 1: Number of BCG lymphadenitis cases per year from 2005-2010**

lymphadenitis involved ipsilateral left axillary nodes. Other sites of involvement included the left supraclavicular lymph nodes in 26 (18%) patients, and both the left axillary and supraclavicular lymph nodes were involved in 7 cases (4.8%).

The lymph nodes were <1 cm in size in 11 (7.5%) patients, 1-3 cm in 104 (71.7%) cases, 4-6 cm in 29 (20%) cases, and more than 6 cm in only one case.

The first follow-up physical examination of the 145 children with lymphadenitis was done at the age of 2 months, with subsequent examinations at 3, 4, 6, 9, and 12 months. More than 58 (40%) cases had spontaneous resolution, but 87 (60%) progressed and developed suppuration and perforation followed by regression with or without treatment. Thirty (26.1%) cases underwent fine needle aspiration [Table 2].

A total of 75 patients (65%) were given antituberculous medication. Isoniazide was given for six weeks to seven (5.25%) patients and for three months for 29 (22%) patients. Rifampin alone was given for 6 months to two (1.5%) patients. Thirty seven patients were given both isoniazide and rifampin for three months.

Seven patients (4.8%) were given antibiotics, five received augmentin for five days and two received clarithromycin for seven days. Swabs were taken from pus aspirated by fine needle and sent to a microbiology laboratory for acid-fast bacilli and tuberculosis culture for 30 patients. Eight (27%) patients had positive acid-fast bacilli and positive cultures for *Mycobacterium bovis*. Susceptibility tests showed eight isolates, which were susceptible to Rifampin and pyrazinamide. Six of these were also resistant to isoniazide. All patients had complete resolution of the lymphadenitis except two who developed sinus and two who had surgical excisions. Only one case developed into disseminated

**Table 2: Natural course of BCG lymphadenitis during follow-up**

Non-suppurative lymphadenitis that resolved without treatment	58 (40%)
Suppurative lymphadenitis progressed	87 (60%)
Ruptures spontaneously and regresses	12 (10.44%)
Regresses with treatment and fine needle aspiration	30 (26.1%)
Regresses with treatment	45 (39.15%)

BCG infection, and immunological follow-up studies showed this patient to have an interleukin 12 deficiency.

## DISCUSSION

BCG vaccination is recommended routinely for all newborns in the universal immunization program in countries where the incidence of tuberculosis infection is more than 1%.<sup>[1,2]</sup> Normal inoculation site reactions include up to 5 mm of erythematous induration, which progresses to a bluish-red pustule two to three weeks post-vaccination, subsequent ulceration, drainage, exudative crust formation after four to six weeks, and full healing 10-12 weeks post-vaccination, leaving a small residual scar.

Non-suppurative involvement of regional or local lymph nodes is also part of the normal process. In Lotte and colleagues<sup>[2]</sup> review of approximately 10,000 such cases, suppurative adenitis, keloid formation and abscesses comprised the vast majority (84%) of complications reported, with the rate of BCG suppurative adenitis being approximately one per 2800 vaccinations. There is no consensus regarding the management of BCG suppurative complications.<sup>[1-3]</sup>

The incidence of lymphadenitis is influenced by host- and vaccine-related factors. A number of factors such as the age of the child, the technique of vaccination, the BCG strain, the dose, potency, viability and immunogenicity of the vaccine, and prior exposure to mycobacterial antigens are implicated in the pathogenesis of lymphadenitis. In our study, the male gender predominated in 69% of cases. This finding is similar to several previous reports in which the prevalence of lymphadenitis was shown to be higher in males than in females.<sup>[1-4]</sup> BCG lymphadenitis may develop as early as two weeks after vaccination, and most of the reported cases appear within six months.<sup>[1,2,4]</sup>

Most of our cases presented between two to four months of age, and almost 98% presented within six months of age. This result was similar to a study from Iran, where all 26 cases studied (100%) developed lymphadenitis within six months. In another study, lymphadenitis developed within six months in 55 patients (92%), whereas five children developed lymphadenopathy one to five years after the vaccination.<sup>[2-5]</sup>

In the present study, suppurative lymphadenitis was found to be more common than non-suppurative lymphadenitis. Non suppurative lymphadenitis developed in 58 (40%) of the cases, followed a benign course and regressed spontaneously without treatment, while 87 (60%) progressed and developed

suppuration and perforation followed by regression with or without treatment. There was no clinical difference between the children who recover spontaneously and those who received treatment except for the size of the lymph node and the progression of the disease.

Our findings are consistent with the results of studies from Korea (41%) and Zimbabwe (62%).<sup>[6,7]</sup> However, in Iran and India, the incidences were lower, 15.4% and 15%, respectively.<sup>[8]</sup> The localization of the lymphadenopathy varied according to vaccination site. In Saudi hospitals, the site of vaccine injection is the left arm just above the insertion of the deltoid muscle. In our study, the most common region of pathology was the left axillary lymph node, followed by the left supraclavicular lymph nodes, with the less common finding being involvement of both sites (left axillary and left supraclavicular lymph nodes). Nazir *et al.* report a similar result, where most of the cases developed in the left axillary lymph node ( $n = 57$ ) and the remaining cases ( $n = 2$ ) developed in the supraclavicular lymph node.<sup>[9]</sup> In another study, most cases developed in the right axillary area 26 (92.3%) cases because in that country, the site of vaccine injection is the right arm.<sup>[10]</sup> There is no agreed definition as to what contributes to BCG lymphadenopathy, particularly with regards to the degree of lymph node enlargement. In the current study, the lymph node was <1 cm in 11 (7.5%) patients, 1-3 cm in 104 (71.7%) cases, 4-6 cm in 29 (20%) cases, and more than 6 cm in one case only. This distribution was similar to a study from Pakistan, where the size of the enlarged lymph nodes varied from 1.5 cm to 5.0 cm (mean 3.5 cm).<sup>[11]</sup> The optimal treatment to manage BCG lymphadenitis is unclear. Observation alone has been employed in some centers, whereas other approaches have included aspiration, antituberculous chemotherapy alone or in combination with surgical excision, or surgical excision alone.<sup>[12]</sup>

In the absence of evidence-based guidelines,<sup>[12,13]</sup> the decision in the cases we studied to commence antituberculous chemotherapy was based on the potential morbidity of a prolonged chemotherapy course in comparison to spontaneous resolution, given the safety of the drugs used. A total of 75 patients (65%) were given antituberculous medication. All patients (87) improved. However, some of them (26%) had fine needle aspiration performed in addition to antituberculous treatment; in these children, aspiration was not only diagnostic but may also have been therapeutic.

In a study from the UK, eight children out of ten received antituberculous chemotherapy (rifampin and isoniazide). Of the children in that study, four underwent aspiration, and one incision and drainage. All of them had resolved lymphadenitis.<sup>[13]</sup> However, in a different study, Stephen *et al.* reported eight patients who received medical treatment with only antituberculous drugs for six months. These patients had small lymph nodes (~1.5 cm). Five patients showed resolution of lymphadenopathy, but three did not respond, continued to have progressive disease, and underwent surgery.<sup>[14]</sup> It was concluded in that study that 52 children who presented with large (~3 cm)

fluctuant lymph nodes required a surgical procedure to avoid spontaneous rupture and sinus formation. The study concluded that treatment of BCG lymphadenitis with antituberculous drugs is not effective once the lymph node has reached a certain size (>3.0 cm) and has developed fluctuation and inflammation of the overlying skin.<sup>[14]</sup> In the present study, increased susceptibility to the Danish strain of BCG might have contributed to the increased incidence of complications in these children, and hence, caution should be exercised in switching from one vaccine to another in developing countries.

Medical treatment appears to be most effective if used with needle aspiration for enlarged lymph nodes where the inflammatory process has involved or perforated the skin.

In many countries around the world, a BCG vaccine is given at birth or a few months afterward. In Saudi Arabia, the BCG vaccine is given during the first day of life. This is mainly due to a high incidence of tuberculosis (243/100,000 in 1978) and to problems with compliance with the vaccination schedule. The incidence has dropped to 90/100,000 in 1990 and now to 11/100,000 (Ministry of Health statistics). Recent studies have shown that giving the BCG vaccine at birth induces significant mycobacterial immune responses as early as two months of life. When the response was tested at the age of about nine months, it was found to be maintained and comparable to infants who received the vaccine at 2 or 4.5 months of life.

Therefore, in light of the findings of this study, it would be advisable to administer the BCG vaccine in Saudi Arabia at a time later than at birth, as the younger children are commonly affected.

## REFERENCES

- Behjati B, Ayatoollahi J. Post BCG Lymphadenitis in vaccinated infants in Yazd, Iran. *Iran J Pediatr* 2008;18:351-6.
- Available from: [http://www.who.int/gho/mdg/diseases/tuberculosis/situation\\_trends\\_incidence/en/index.html](http://www.who.int/gho/mdg/diseases/tuberculosis/situation_trends_incidence/en/index.html) [Last accessed on 2011 Dec 31].
- Lotte A, Wasz-Höckert O, Poisson N, Dumitrescu N, Verron M, Couvet E. BCG complications. Estimates of risks among vaccinated subjects and statistical analysis of their main characteristics. *Adv Tuberc Res* 1984;21:107-93.
- Nazir Z, Qazi S. Bacillus Calmette-Guerin (BCG) lymphadenitis-changing trends and management. *J Ayub Med Coll Abbottabad* 2005;17:1-2.
- Daoud W. Control of outbreak of BCG complications in Gaza. *Respirology* 2003;8:376-8.
- Dommergues MA, DelaRocque F, Guy C. Local and regional adverse reactions to BCG-SSI vaccination: A 12-month cohort follow-up study. *Vaccine* 2009;27:6967-73.
- Jou R, Huang W. Tokyo-172 BCG vaccination complication. *Taiwan. Emerg Infect Dis* 2009;15:1525-6.
- Kaur S, Faridi MM, Agarwal KN. BCG vaccination reaction in low birth weight infants. *Indian J Med Res* 2002;116:64-9.
- Back HC, Chang JY, Moon SJ, Oh SH. Lymphadenitis following intradermal BCG vaccination. *Korean J Pediatr* 2006;49:46-50.
- Singla A, Singh S, Goraya JS, Radhika S, Sharma M. The Natural course of BCG lymphadenitis. *Pediatr Infect Dis J* 2002;21:446-3.
- Merry C, Fitzgerald RJ. Regional lymphadenitis following BCG

- vaccination. *Pediatr Surg Int* 1996;11:269-71.
12. Teo SS, Smulders N, Shingadia D. BCG vaccine-associated suppurative lymphadenitis. *Vaccine* 2005;23:2676-9.
  13. Praveen KN, Smikle MF, Prabhakar P, Pande D, Johnson B, Ashley D. Out break of Bacillus Calmette-Guerine associated lymphadenitis and abscesses in Jamaican children. *Pediatr Infect Dis J* 1990;9:890-3.
  14. Lotte A, Wasz-Hockert O, Poisson N, Engbaek H, Landmann H, Quast

U, *et al.* Second IUATLD study on complications induced by intradermal BCG-Vaccination. *Bull Int Union Tuberc Lung Dis* 1998;63:47-59.

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