

Outbreak of Bacille Calmette-Guérin-related lymphadenitis in Saudi children at a university hospital after a change in the strain of vaccine

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BACKGROUND AND OBJECTIVES: Bacille Calmette-Guérin (BCG) vaccination is part of the expanded program of vaccination in Saudi Arabia. Lymphadenitis is the most common complication of the BCG vaccine. We observed an increase in the rate of BCG lymphadenitis that coincided with the introduction of a new strain of BCG vaccine. The aim of this study was to determine the incidence and the possible causes of BCG lymphadenitis at a university hospital in Riyadh, Saudi Arabia.

DESIGN AND SETTING: Retrospective chart review and prospective follow up of infants who received BCG vaccine.

METHODS: We studied all infants presenting with suppurative or nonsuppurative adenopathy with nodes ≥ 2 cm seen at the infectious diseases clinic at KKUH. The study duration was divided into two periods. The first period reviewed infants who received different BCG vaccine strains between January 2002 and December 2007. The second study period was conducted after close evaluation of the BCG administration technique of the vaccinating staff and reviewed infants who received the BCG SSI Danish strain 1331 between January 2008 and December 2010.

RESULTS: During the study period from January 2002 to December 2007, 19402 infants received four different BCG vaccine strains. Eight infants developed BCG lymphadenitis, and all were associated with the BCG SSI vaccine. The incidence rate in 2007 was 1.96 per 1000. In the second period, 66 of 9921 infants who received the BCG SSI vaccine developed BCG lymphadenitis between January 2008 and December 2010. The incidence rate was 10.14 per 1000 in 2010.

CONCLUSION: We conclude that receipt of the BCG SSI vaccine might have contributed to the increased incidence of lymphadenitis in these children. Hence, caution should be exercised in switching from one vaccine to another, as is often done in developing countries.

BCG (Bacille Calmette-Guérin) vaccines are the oldest vaccines in use today. They were incorporated into the World Health Organization's Expanded Program on Immunization in 1974.¹ BCG vaccines were derived in 1906 by *in vitro* attenuation and were first used as oral vaccines in 1921.² BCG vaccines available worldwide differ in their characteristics when grown in culture and in their ability to induce an immune response to tuberculin. These variations may be caused by differences in production techniques and by genetic changes that have occurred in the bacterial strain

during passaging for attenuation.^{2,3} Although there are controversies regarding the efficacy of BCG vaccines, it is generally agreed that the vaccines are effective against disseminated tuberculosis and meningitis caused by childhood tuberculosis.⁴ Complications with BCG vaccines were reported in 0.01% to 3.8% of cases, even with the earlier strain, and almost all were BCG lymphadenitis.⁵ There is no agreed-on definition as to what constitutes BCG lymphadenitis, particularly with regards to the size of lymph node enlargement and its onset after vaccination. It has been recommended that the term

BCG lymphadenitis be used to refer to cases where the lymph nodes have become large enough to be easily palpable and a cause of concern for the parents.⁶ The aim of the present study was to determine the incidence and the possible causes of BCG lymphadenitis at the major university hospital in Riyadh, Saudi Arabia.

PATIENTS AND METHODS

The study was conducted at King Khalid University Hospital (KKUH), which is the major teaching hospital in Riyadh, Saudi Arabia, with a capacity of 960 beds and an annual newborn delivery rate of 3300. We identified and reviewed the medical records of children with BCG lymphadenitis who were born and vaccinated at birth at KKUH between January 2002 and December 2010. The study was divided into two periods. The first period included January 2002 to December 2007. We determined the time period over which the patients were born and the strain of BCG vaccine that they received. Then we determined the total number of children born per year. The annual incidence rates were calculated by relating the number of defined cases of BCG lymphadenitis to the number of infants vaccinated during that year. Data management and calculations were performed using Microsoft Excel software. Trends over time were explored with the chi-square test for trend using the StatCalc calculator in EpiInfo 6. Trends were considered statistically significant if the *P* value was less than .05. The second study period was done as a prospective follow-up of all newborns delivered between January 2008 and December 2010 up to one year of age. An evaluation of all nurses who were assigned to give the

birth vaccine to the newborns was conducted by a pediatric infectious diseases consultant to ensure that proper techniques were being used for BCG administration in January 2008. Complications related to the BCG vaccine were defined as any infant born and receiving the BCG vaccine at KKUH who presented in first year of life with left axillary and/or left supraclavicular suppurative or nonsuppurative adenopathy with nodes ≥ 2 cm and who was seen at the infectious diseases clinic at KKUH. All infants with immunodeficiencies and those who were born and vaccinated with BCG outside KKUH were excluded from the study. The BCG vaccine strain type and the lot numbers for the period from January 2002 to December 2010 were obtained from the medical storage department at KKUH.

RESULTS

A total of 19402 infants were vaccinated, and 18765 (96.7%) were followed regularly in the Well Baby Clinic for at least one year. Among them, eight were diagnosed with BCG lymphadenitis between January 2002 and December 2007. During this period, four different strains of the BCG vaccine had been given: Pasteur Merieux France (strain 1077) from February 2002 to December 2002, Aventis Pasteur France from January 2003 to January 2004, Eisai Japan BCG from February 2004 to October 2005, and BCG SSI vaccine (Danish strain 1331) from November 2005 to December 2007. All cases of BCG lymphadenitis were associated with the BCG SSI vaccine. The time of diagnosis and the incidence rate per year are summarized in **Table 1**. The mean age of presentation was 4 months (range, 2-6

Table 1. BCG lymphadenitis cases per year at KKUH, 2002-2007.

Year received BCG vaccine	Number of infants who received BCG	Number of infants who received BCG and were followed for one year	Type of BCG vaccine strain	Number of infants with BCG lymphadenitis	Incidence rate per 1000
2002	4688	4570	Pasteur Merieux France	0	0
2003	3516	3398	Aventis Pasteur France	0	0
2004	2810	2711	Eisai Japan BCG	0	0
2005	2685	2604	Eisai japan BCG	0	0
2006	2640	2561	SSI	2	0.76
2007	3063	2921	SSI	6	1.96
Total 2002-2007	19402	18765		8	

Chi-square test for linear trend=16.16, *P*=.00006

Table 2. BCG lymphadenitis cases per year at KKUH, 2008-2010.

Year received BCG vaccine	Number of vaccinated infants	Number of infants who received BCG and were followed for one year	Type of BCG vaccine	Number of infants who developed BCG lymphadenitis	Incidence rate per 1000
2008	3264	3196	SSI	14	4.3
2009	3208	3121	SSI	17	5.3
2010	3449	3356	SSI	35	10.1
Total	9921	9673		66	

Chi-square test for linear trend=8.93, P=.003

Table 3. Lymph node character, treatment model and their effect on the resolution time.

Character of lymph node	No. of patients (%)	Resolution time (months)	P Value
Non-suppurative	24	7.21+1.44	.003
Suppurative	42	6.02+1.57	
Treatment			
Observation	46 (69.7)	7.02 (1.42)	.001
Aspiration	6 (9.1)	6.16 (0.75)	
Isoniazid (3 months)	7 (10.6)	3.71 (0.75%)	
Isoniazid (6 months)	2 (3.03)	6	
Rifampicin (6 months)	3 (4.55)	6	
Rifampicin + isoniazid (6 months) and aspiration	2 (3.03)	5	

Resolution time is mean (standard deviation)

Table 4. Relationship between size of the lymph node and duration of resolution.

Size (cm)	Number of patients	Resolution time (months)	P value
2.00	5	5.60 (0.55)	.368
3.00	11	6.45 (1.57)	
4.00	17	6.59 (1.87)	
5.00	28	6.71 (1.67)	
≥6.00	5	5.40 (0.55)	

Resolution time is mean (standard deviation)

months). All lymphadenitis patients developed suppurative left axillary lymph node swelling with a mean size of 3 cm (range, 2-4 months) with no other systemic manifestations. The male to female ratio was 6:2. A 3-month course of isoniazid was prescribed for all of them.

In the second study period, a total of 9921 infants

were vaccinated with the BCG SSI vaccine. Of these infants, 9673 were followed regularly for one year between January 2008 and December 2010. BCG lymphadenitis occurred in 66 infants. The time of diagnosis and the incidence rate per year are shown in **Table 2**. The mean age of presentation was 4 months (range, 2-8 months), The mean size of the lymph node was 5 cm (range, 2-7 cm). The most common site of BCG lymphadenitis was the left axillary lymph node, in 52 (78.8%) cases. The left axillary and left supraclavicular lymph nodes were involved in nine (13.6%) cases, and the left supraclavicular lymph nodes were affected in five (7.6%) cases. Suppurative lymphadenitis accounted for 63.6% (42) of cases. The ratio of males to females was 1.87. Antituberculosis treatment was prescribed for 14 (21.2%) patients. The treatment course, character and size of lymph node and their effect on the resolution time are summarized in **Tables 3 and 4**. A total of 29 infants with BCG lymphadenitis were excluded from the study: 28 who were born and vaccinated outside KKUH, the majority who presented in 2010, and one infant born and vaccinated at KKUH but diagnosed with interleukin 12 deficiency.

DISCUSSION

The BCG vaccines that are currently in use are produced at several countries throughout the world.⁸ These vaccines are not identical. To what extent they differ in efficacy and safety in humans is not clear at present. Some differences in molecular and genetic characteristics are known. What is not known is if the BCG vaccine from one manufacturer is "better" than one produced at another site.^{8,9} Each BCG is now known by the location where it is produced. In Saudi Arabia, BCG vaccines were introduced 1968 and had an estimated coverage of 33% and 98% in 1980 and 2009, respectively.⁸ The WHO estimates of the TB disease burden in Saudi Arabia are 50:100 000, 40:100 000 and 18:100 000 in 1990, 2004 and 2009, respectively.^{9,10} The TB infection rate is still considerable in

comparison with other countries.¹⁰ The Canadian Immunization guide has recommended BCG vaccination in countries where the incidence of tuberculosis infection is more than 1%. BCG vaccination is recommended routinely for all newborns in the universal immunization programs in these countries.¹¹

The BCG complication rate is very low, about 3 per 1000 (0.3%).¹² In recent studies, complication rates of 0.7 per 1000 vaccinations and 0.2 per 1000 vaccinations have been reported.¹³ BCG lymphadenitis is characterized by regional lymph node enlargement, ipsilateral to the site of administration, with no other identifiable cause for lymphadenopathy. Absence of fever, tenderness, and other systemic symptoms differentiate it from pyrogenic adenitis. Lymphadenitis is the most common complication of BCG vaccination and accounts for about 98% of complications; the remaining 2% consist of abscesses, ulceration, and arthritis.¹⁴ Possible factors causing BCG complications include the vaccine strain, BCG overdose, faulty intradermal technique, vaccination during the neonatal period and disturbance of cellular immunity.¹⁵ In this study, we observed a clear increase in the incidence rate of BCG lymphadenitis starting in 2006 and increasing progressively. This observation can be explained by the introduction of the SSI Danish strain 1331 of the BCG vaccine in November 2005. Our estimation of the incidence of BCG lymphadenitis may in fact be an underestimate, as we may not be aware of all cases with BCG lymphadenitis born and vaccinated at KKHU who were treated in primary care centers or at other hospitals. Our observation was also supported by the progressive increment of BCG lymphadenitis cases (not included in the study) that were born and vaccinated outside the KKHU and evaluated and treated at the KKHU.

Mande et al¹⁶ suggested that introduction of a new BCG vaccine may result in an increased rate of BCG-associated complications. Helmick et al¹⁷ reported an outbreak of BCG adenitis in St. Lucia in 1982 when a Connaught BCG vaccine was used instead of Glaxo vaccines. Since the reintroduction of the Glaxo vaccine, there have been no reported cases of BCG lymphadenitis in St. Lucia. In Malaysia, an outbreak of BCG lymphadenitis in 1990 was related to a change from the Japanese to the Pasteur strain of BCG, and despite a dose reduction, the incidence remained high (15 per 1000 vaccinations), but declined when the Japanese strain was reintroduced in 1992.¹⁸ In Austria, the use of BCG-Pasteur was stopped in 1990, as it was implicated in the increased incidence of regional lymphadenitis, from 0.3% to 7.5%.¹⁹ Teo SS et al²⁰ reported an incidence of 31:10 000 of BCG suppurative lymphadenitis

after the introduction of the BCG SSI vaccine in 2002, compared to no reports of similar cases when they previously used the Evans BCG Copenhagen strain 1077.

Lotte et al²¹ stressed the importance of improper vaccination skills of the staff as the main reason for complications. An outbreak in Gaza in 2001 was mostly related to faulty technique in BCG administration.²² In the present study, all the vaccination staff (6) were senior nurses who had been vaccinating newborns with BCG vaccine for 8-13 years. They were evaluated regarding the BCG vaccination technique in January 2008 and adhered to the manufacturer's instructions with no major concern. They have been evaluated periodically since then. Thus, it is unlikely that the vaccine administration technique was the cause of this outbreak.

In several studies, the incidence of BCG complications was lowered after a 50% reduction in the dose of vaccine. In Moscow, administering the BCG vaccine at a lowered dose (0.025 mg) resulted in a reduction in the regional lymphadenitis complication rate, from 0.08% to 0.01%.²³ Another study in France showed that a 0.025 mg dose of intradermal BCG generates an immunoreponse as satisfactory as that generated by a 0.05 mg dose, while the lymphadenitis complication rate is significantly reduced in infants who receive the 0.025 mg dose.²⁴

The optimal treatment of 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.²⁵

In the absence of evidence-based guidelines, 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 46 (69.7%) patients were treated by observation only. Aspiration of lymph node was performed in 6 (9.1%) patients. Antituberculous medications were given to 14 (21.2%) patients. The study revealed that patients managed by observation only took a longer time to resolution with a mean (standard deviation) duration of 7.02 (1.43) months (compared with those who received isoniazid for 3 months who had a mean duration of illness 3.71 (0.75) months. There was a significant association between the mode of treatment, character of lymph nodes and the time to resolution ($P < .05$) while there was no significant association for the size of lymph node and the time needed for complete resolution ($P > .05$). However, one needs to interpret the results of therapy with caution since this was not a randomized trial and

there were only few patients in each treatment category. This may simply reflect the fact that patients who had a complicated course used medications for a longer duration. There have been several randomized controlled trials that have examined the outcomes of treatment of BCG lymphadenitis.²⁶ However, these have differed in therapeutic interventions, methodology and outcome measures to the extent that no firm conclusion can be drawn.⁷

In conclusion, adverse reactions to vaccines may jeopardize public acceptance of immunization programs. Thus, surveillance of vaccine reactions is a key component of these programs. The progressive increase in the incidence rate of BCG lymphadenitis was suspected to be related to the virulence and viability of the BCG SSI vaccine, and therefore we recommend a dose reduction in the current BCG vaccine or a change to another vaccine strain.

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