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OBSERVATIONAL STUDY OF CLINICAL MANAGEMENT OF AND OUTCOME OF BACILLE CALMETTE-GUÉRIN VACCINE ADVERSE REACTIONS: BAGHDAD/ALRASAFA RESPIRATORY CENTER

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ABSTRACT

Aim of the study: This study aims to describe the outcome of management of patients with localized BCG adverse events which include hypersensitivity reactions, abscesses at the injection site, and localized lymphadenopathy without intervention in Alrasafa Respiratory Center Baghdad, Iraq. **Introduction:** Although the Bacille Calmette-Guerin (BCG) vaccine is usually safe, a number of complications at the injection site and regional lymphadenitis can occur. Most of these complications are normal reactions. However, some unexpected complications may occur such as osteomyelitis and disseminated infection especially in immunocompromised children. Clinical features, treatment modalities and outcomes of these complications have not been clearly defined in literature. We aimed to determine the complications after BCG vaccine and outcomes of management in our Centre. **Methods**: observational study conducted over 4 years between January 2015 and January 2019, included healthy children aged 1-6 months, without underlying disease or drug use history, who were referred to our centre after BCG vaccine. At the first visit, the families were informed about the normal reaction following a BCG vaccination. Children who were seen in the clinic with a BCG adverse event (mostly due to parental anxiety) after reassurance each child was carefully clinically examined. They were followed-up between 1 to 6 months. Families were encouraged to contact the expert in our centre by telephone or interviews during the period of follow-up and in case of unexpected reactions. **Results:** local abscess, site reaction, suppurative lymphadenitis, and non suppurative lymphadenitis were observed. All children were treated conservatively without sequelae or complications. Only two infants who had systemic adverse event were given Anti TB. The first one got full recovery while the second one died. **Conclusions:** the Majority of BCG related lymphadenitis and local site reactions are a benign condition. All children were treated conservatively (watch and wait), and got full recovery. However, the minority of BCG vaccine complications is serious and a treatment is needed. In our study one child died due to disseminated complication and the other had full course of Anti TB and completely recovered.

KEYWORDS: BCG vaccine, Lymphadenitis, Complications, Treatment Outcome, Adverse reactions, Children.

INTRODUCTION

The attenuated Mycobacterium bovis BCG strain was developed in 1921 at the Pasteur Institute from a cow with tubercular mastitis. BCG vaccine strains that are used worldwide differ in terms of their genetic and phenotypic properties.[1] The original BCG vaccine strain was formerly distributed by the Pasteur Institute of Paris and sub-cultured in different countries using different culture conditions that were not standardized. Over the years, more than 14 sub-strains of BCG have evolved and have been used as BCG vaccine in different parts of the world currently.

Five main strains account for more than 90% of the vaccines in use worldwide with each strain possessing different characteristics: the Pasteur 1173 P2, the Danish 1331, the Glaxo 1077, the Tokyo 172-1, the Russian BCG-I, and the Moreau RDJ strains.[3] The concentration of live particles in the vaccines ranges from 50,000 to 3 million per dose, according to the strains. Each strain has a different reactogenicity profile. The Pasteur 1173 P2 and Danish 1331 strains are known to induce more adverse reactions than the others.[4] Globally BCG vaccine is used extensively with approximately 100 million newborns being vaccinated each year. Since 1974, it has been included in the WHO Expanded Programme on Immunization.[1] BCG vaccination was first introduced in Iraq in 1952 and now it is part of the recommended primary immunization schedule in the country.[29]

Overall, BCG vaccine reduces the risk of pulmonary and extra-pulmonary tuberculosis (TB) by approximately 50%[5], but it has 64% efficacy against TB meningitis and 78% against disseminated TB disease. Despite this extensive use, few severe adverse events have been reported. These complications can cause severe anxiety in children parents. Adverse reactions to BCG vaccine are reported in 1–10% of vaccinees, but are likely to be substantially underreported. Adverse reactions are usually seen within the first 6 months of vaccination but can present beyond 12 months.[6] Mild BCG reactions are commonly seen among vaccinees.

The cause of BCG related complications is unclear. It is likely that introduction of a more reactogenic strain coupled with the difficulties of intradermal vaccine administration to newborns may have contributed to this increase. May be there was the potential for dosage errors. The standard dose of BCG vaccine is 0.05 mL of the reconstituted vaccine given intradermally for children aged below one year, and 0.10 mL for recipients aged one year or more. Only one dose of vaccine should be administered.[1] Unfortunately, it is almost impossible to determine with absolute certainty the exact cause of the outbreak. However, more BCG adverse events when the Danish 1331 strain was used in Iraq.

The number of public health centers staff administering the vaccine in Baghdad/Alrasafa is very high. Therefore, assessment of the injection technique of the staff would have been extremely difficult to perform and analyze. In any case, there was no predominance of patients who had been vaccinated at one health Centre compared with other centers, indicating that it is unlikely that poor vaccination techniques alone could account for the BCG complications. It is important that hospitals and referral centers must play a big role in identification and management of complications. The respiratory center in Alrasafa highlights the importance of having a well-functioning and responsive system of adverse events reporting. This is particularly important in relation to nationally recommended vaccine use. Any loss in confidence in a vaccine could potentially damage the remainder of the primary immunization schedule in Iraq. These events also raise a serious question as to the suitability of this vaccine strain for use in a national immunization programme in a country where the prevalence of tuberculosis disease is 42/100 000.[28]

BCG adverse events

Almost all vaccine recipients experience an injection site reaction characterized by a red indurated area at the injection site, which may subsequently ulcerate, then forms a crust, which falls off and healing occur after 2-5 months leaving a small superficial scar. Axillary lymphadenopathy (<1 cm) is also a normal response to BCG vaccination (Tab. 1).

If BCG is administered in the recommended site (deltoid) the ipsilateral axillary nodes are most likely to be affected but supra-clavicular or cervical nodes may also be involved.[7,8] Also, local adverse reactions include regional suppurative and non-suppurative lymphadenitis, injection site abscesses, persistent injection site reactions, ulceration and uncommonly keloid reactions.[17,18] Mild local reactions may occur despite correct intradermal administration. No treatment is required for mild injection site reactions with or without lymphadenitis. The onset of suppuration may be variable with cases presenting from one week to several months following vaccination.[9]

It is important to note that multiple cutaneous lesions may signal disseminated BCG disease usually in an immunocompromised host. Local and regional adverse reactions occur most frequently and the majority is self-limiting.[10] However, many clinicians advocate treatment, including use of antimicrobials, needle aspiration and/or surgery[11] and practice is likely to vary substantially across sites. Systemic reaction is an uncommon but devastating complication of vaccination that should be considered in the appropriate clinical setting, however these types of reactions are rare and Immunocompromised infants and patients with late-stage AIDS are at greatest risk and respond poorly to standard therapies.[14,15,19] (Tab. 1).

Table (1): Summary of mild, sever local and systemic adverse events.[20]

Nature of Adverse event	Description	Rate/doses
Mild local	Injection site papule (onset 2-4 weeks) Mild ulceration (1-2 months) Scar (2-5 months)	Almost all vaccinees
Sever Local	Local abscess Keloid Lymphadenitis Suppuration (onset 2-6 months)	1 per 1,000-10,000
Systemic (1-12 months onset time)	Cutaneous skin lesions	Case reports only 1 per 3,333 - 108
	Osteitis	
	Disseminated BCG Immune Reconstitution Syndrome	1 per 230,000 - 640,000 1 per 640,000

Why these complications may happen?

It is believed that BCG adverse events may happen due to the following factors[20]:

1. Injection technique: Intradermal inoculation of BCG vaccine is a difficult field technique and incorrect administration may lead to local reactions including injection site reactions and lymphadenitis.
2. Change in vaccine strain: The Pasteur and Copenhagen strains have generally been found to be more reactogenic than the Tokyo, Glaxo or Brazilian (Moreau) strains. The cases have decreased in Baghdad after replacing the Danish by the Tokyo 172-1.
3. Effect of age at the time of administration: Infants have a higher risk of lymphadenitis and for this reason a reduced dose of the vaccine is recommended.

Methods and recording of adverse events

Here we describe our experience of BCG vaccine-associated adverse reactions in children referred to Alrasafa Respiratory Centre. We included all children vaccinated with BCG and presenting with vaccine adverse events from January 2015 to January 2019. In Iraq BCG vaccination is usually given in the primary Health Center, once the baby is discharged home after birth. Families reported the BCG complications to the primary health centers, hospitals, private clinics, TB clinics or other. Sometimes they are reported directly to our center. All children with BCG complications who need specialist review were referred to Respiratory Center. Our study reviewed those children in our center. Firstly, parents were interviewed with to reassure them. Secondly, all infants had full clinical examinations and investigations. Thirdly, events were categorized into four categories:

(1) Local reactions including abscess at the injection site and prolonged pustule healing (Fig. 4).
(2) Non suppurative lymphadenitis (Fig. 6).
(3) Suppurative lymphadenitis (Fig. 5).
(4) Systemic reactions.

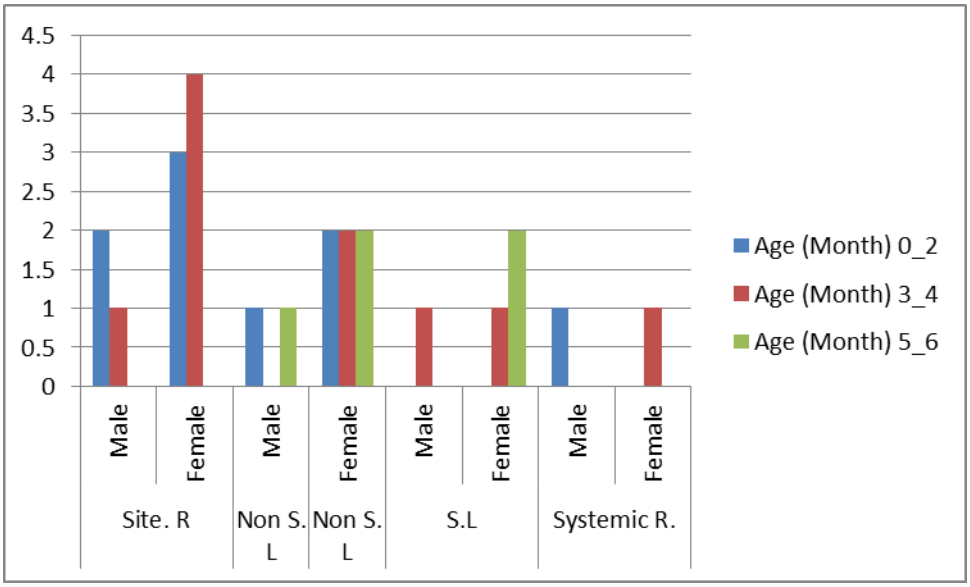
The distinction between regional lymphadenitis and suppurative lymphadenitis was based on the clinical finding of fluctuant swelling and/or secretion from a fistula (Fig. 7, 8). Most cases of suppurative lymphadenitis were confirmed by clinical examination.[21] The complications were classified as a normal reaction after BCG vaccine will leave scar after six weeks A typical reaction following BCG vaccination is a red indurated area at the injection site, which may subsequently ulcerate, then form a crust, which falls off after about 6 weeks leaving a small scar. Axillary lymphadenopathy (<1 cm) is also a normal response to BCG vaccination.[22,21] Distinction of an adverse reaction from a normal reaction according to size of a local abscess or lymphadenitis >1 cm, namely regional lymphadenitis, suppurative lymphadenitis. After recording all these information plus the address and their telephone number. We started contacting their parents daily or every other day in the first two weeks. We asked them about the infant's temperature at night, their appetite, and the size of the lymph node or the local abscess. All infants who had inoculation site abscesses (Fig. 4), suppurative lymphadenitis (Fig.3, 5), or non-suppurative lymphadenitis (Fig. 6) with nodes ≤1 or ⩾2 cm were included.

RESULTS

Twenty four children (16 female and 8 male) presented with adverse reactions (Fig. 2). 10 children presented with BCG site reaction without lymphadenitis (41.6%) (7 female and 3 male), 8 children (33.3%) (6 female and 2 male) presented with both injection site reaction and BCG non supporative lymphadenitis, 4 children (16.6%) (3 female and 1 male) presented with supporative lymphadenitis. Only two children (8.3%) presented with systemic adverse reaction without BCG site reaction, one female had general lymphadenitis and the other had axillary and supraclavicular lymphadenitis together with pneumonia (Tab. 2 and Fig. 1). Twenty two children with Local complication were managed conservatively, no antibiotic or anti TB were given. Overall, 100% showed complete resolution within 2- 6 months. Two children who had Systemic complication had anti-tuberculous therapy. The first one who was male, completely recovered after full course of anti TB and the second one, who was female died two weeks after admission to the hospital because of lymphadenitis and severe pneumonia.

Table 2: The distribution of gender and age factors among the studied cases.

Complication	Gender	Age (Month)			Total
		0-2	3-4	5-6	
Site Reaction	Male	2	1	0	3
	Female	3	4	0	7
Site Reaction Non Supporative	Male	1	0	1	2
	Female	2	2	2	6
Supporative Lymphadenitis	Male	0	1	0	1
	Female	0	1	2	3
Systemic Reaction	Male	1	0	0	1
	Female	0	1	0	1
Total		9	10	5	24



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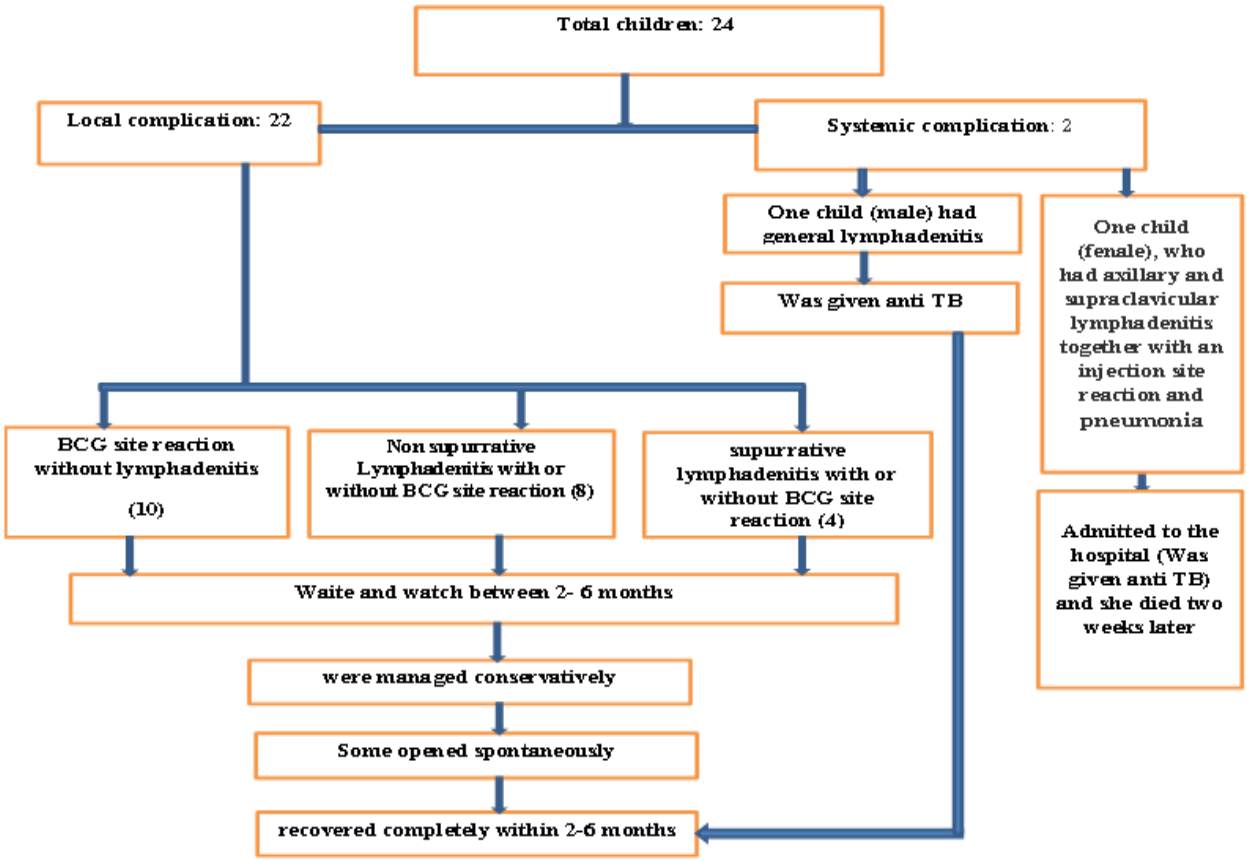

Figure 2: A study flow diagram of BCG complications in Alrasafa center.

Figure 3: Suppurative lymphadenitis post-BCG vaccination.

Figure 4: Inoculation site abscess post-BCG vaccination.

Figure 5: Suppurative lymphadenopathy.

Figure 6: Axillary non-supporative lymphadenitis.

Figure 7: Axillary supurative L, Scar after spontaneous discharge.

Figure 8: Axillary local abscess.

Figure 9: Full recovery after non supporative lymphadenopathy.

DISCUSSION

Bacille Calmette-Guérin (BCG) vaccine is one of the most widely used vaccines globally, Complications of BCG vaccination are well recognized in all regions that routinely administer the vaccine, such that a certain level of mild adverse reactions is considered part of the normal process. The incidence of side effects can be affected by a number of factors, including dosage,[1] age of recipient, the strain of BCG and from faulty technique, including in use the accidental intracutaneous injection of the stronger percutaneous vaccine, or poor selection of subjects for vaccination. An increase in the rates of complication after introduction of a new vaccine strain has often been noted, and at times attributed to the use of more reactogenic vaccine strains, especially if poor inoculation techniques are used.[1] In Baghdad the number of BCG adverse events had increased when the primary health centers used Danish vaccine. Then the health authority changed the vaccine to Japanese type as a result of that, the number of BCG adverse events decreased. The role of our center is to highlight the importance of having a well-functioning and responsive system of reporting BCG adverse events. These events raise a serious question whether we should use anti TB for BCG adverse events or not in a country where the prevalence of tuberculous disease is 42/100 000.

Worldwide, the World Health Organization reports that as many as 100 million children are given the vaccination each year.[1] Normal inoculation site reactions include up to 5 mm of erythematous induration, progressing to a bluish-red pustule 2–3 weeks post-vaccination, subsequent ulceration, drainage, exudative crust formation after 4–6 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 (Fig. 6). Management of local BCG complications (injection site reactions and suppurative or non-suppurative lymphadenitis) varies between clinicians, and the optimal approach remains uncertain. The majority of BCG adverse events are normal reaction and they are self-limiting. There is no convincing evidence that medical interventions, including use of anti-tuberculosis agents, hasten recovery.[27] Similarly, optimum surgical management of suppurative adenitis has not been defined. Repeated needle aspiration has been advocated by some as a way of avoiding suppuration and prolonged drainage[22,23] whereas others recommend complete surgical excision once nodes are tense and fluctuant.[28]

However, in the four year period, we identified: 10 infants presented with BCG site reaction without lymphadenitis, 8 with Non suppurative Lymphadenitis with or without BCG site reaction and 4 had supurrative lymphadenitis with or without BCG site reaction, all those infants did not receive any medicine and recovered [Fig.9]. However those 2 infants who presented with Systemic complications were given anti-TB therapy (rifampicin, isoniazid and Ethambutol) (Fig. 2). The first one who had general lymphadenitis recovered after 6 months full course of anti TB. The second child who had axillary and supraclavicular lymphadenitis together with an injection site reaction two weeks later had pneumonia. She was admitted to the hospital and died two weeks later.

Data supporting the use of isoniazid and erythromycin for the resolution of abscess formation remain inconclusive. Two studies, one comparing isoniazid with erythromycin[23] and the other a controlled placebo study[24], showed no clear benefit from the use of either of these 2 agents for the treatment of suppurative lymphadenopathy and no difference in the resolution of local abscess formation in 18 infants, of whom 9 were given isoniazid therapy and 9 were given erythromycin therapy.[25] There are no significant differences in suppuration and spontaneous drainage in infants. In this study, the researchers noted that rapid development of lymphadenopathy within 2 months of immunization was associated with a higher incidence of suppuration and spontaneous drainage, irrespective of medical therapy. The parents and family physician should be reassured about the usual benign course of such reactions. In many cases, such reassurance will be adequate. In our experience, there is often pressure from parents to do something and in that instance; we gave short course of paracetol. We didn't prescribe isoniazid or anti TB. In our experience, most reactions responded to our conservative approach, and no definitive therapy is required for BCG complication.

CONCLUSIONS

Adverse reactions to BCG vaccine are usually self-limiting. Reassurance is usually adequate for their management unless they are severe. Injection site reactions, suppurative and non-suppurative lymphadenitis were generally managed conservatively, with good outcomes. There were more variations in

management and outcome of suppurative lymphadenitis and the optimal approach remains uncertain. Although BCG vaccination was associated with only mild morbidity and no mortality but in our study one child died due to disseminated complication. A higher incidence of suppurative lymphadenitis than expected was observed. All children were treated conservatively without sequelae or complications. Most of the infants who had BCG complication they were given BCG (Danish strain 1331). The number of patients decreases when the health authority changed the type of BCG to Japanese strain.

Recommendations

Although BCG is a safe vaccine, an intense education programme should be implemented to ensure the correct vaccine administration and dosage in the vaccination of new-born infants. It is clear that increasing the dose of BCG vaccine increase the chance of complication. Non suppurative and Suppurative lymphadenitis should be treated conservatively. Although it is benign, the time of recovery can be long. In this case parent should know that recovery could take few months.

Development of a more sensitive assay to test the reactogenicity of the BCG vaccine may help reduce the occurrence of such outbreaks and improve public confidence in the nation's vaccination programme.

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Abbreviation

BCG: Bacille Calmette-Guérin
S.R: site reaction
S.L: suppurative lymphadenitis
Non S.L: Non suppurative lymphadenitis
Systemic R: systemic reaction

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