original article

Bacillus Calmette-Guérin vaccine-related complications in children in Oman

Badria Al Waili,[a] Nasra Al Mufarajii,[a] Samiyah Al Hashmi,[a] Abdullah Al Ajmi,[b] Nashat Al Sukaiti[a]

From the [a]Department of Pediatrics, Royal Hospital, Muscat, Oman; [b]Department of Orthopedics, Khoula Hospital, Mina Al Fahal, Muscat, Oman

Correspondence: Dr. Badria Al Waili · Department of Pediatrics, Royal Hospital, Muscat 1771, Oman · T: +968 99237852 · badriaalwaili@gmail.com · ORCID: https://orcid.org/0000-0003-4872-561X

Citation: Al Waili B, Al Mufarajii N, Al Hashmi S, Al Ajmi A. Bacillus Calmette-Guérinvaccine-related complications in children. Ann Saudi Med 2021; 41(1): 24-30. DOI: 10.5144/0256-4947.2021.24

Received: July 13, 2020

Accepted: November 14, 2020

Published: February 4, 2021

Funding: None.

BACKGROUND: Bacillus Calmette-Guérin (BCG) vaccine-related complications are frequently observed in children in Oman. There are a few regional studies on BCG complications, but none from Oman.

OBJECTIVE: Evaluate the spectrum of BCG-vaccine related complications and immune status in Omani children.

DESIGN: Retrospective cross-sectional study.

SETTING: Referral tertiary hospital.

METHODS: Children aged younger than 13 years old and with complications of BCG vaccination recorded from 2006-2018 were included in this study. Clinical characteristics, treatment, immune workup and outcome were reviewed from hospital records.

MAIN OUTCOME MEASURES: Different BCG vaccine-related complications categorized by the site of involvement.

SAMPLE SIZE: 226.

RESULTS: Of the 226 children had BCG-vaccine related complications, 99% received BCG vaccine immediately after birth. The median age of presentation was 4 months. The most common complication was isolated BCG lymphadenitis (85%, n=192), followed by BCG-related osteomyelitis (10.2%, n=23) and disseminated BCG infection (4.9%, n=11). The median age of presentation of disseminated BCG was 5 months, with different organs involved. Out of 11 children with disseminated BCG infection, 72.7% (n=8) had primary immune deficiency (PID), including chronic granulomatous disease (CGD, n=5), severe combined immunodeficiency (SCID) (n=2); 1 patient had Mendelian susceptibility to mycobacterial disease (IFNGR2 deficiency); 2 patients with PID not yet identified and the 1 with a non-specific PID had blood or saliva samples sent for whole-exome sequencing.

CONCLUSION: Because of the spectrum of BCG vaccine-related complications, including the most severe in children with PID, we suggest that delaying the BCG vaccine from birth to 6 months may prevent disseminated BCG diseases and their complications in children with PID because any PID will have been identified before 6 months. Further studies are needed to guide this recommendation.

LIMITATIONS: Single center-based study that may not provide a full overview of all BCG vaccine-related complications in Oman. Unavailability of details of some microbiological results and an inability to determine the detailed management for all patients.

CONFLICT OF INTEREST: None.

Bacillus Calmette-Guérin (BCG) vaccine is a usually safe vaccine commonly used in specific areas of the world. It is a live attenuated vaccine composed of a strain of *Mycobacterium bovis*, and is given to newborn or children as primary prophylaxis to prevent tuberculosis (TB) especially TB meningitis and miliary TB. In 1974, the World Health Organization recommended incorporation of the BCG vaccine into the global Expanded Program of Immunization (EPI).[1] In Oman, BCG vaccination was initiated in 1981.[2] In endemic countries, all newborns, except those born to mothers with HIV or with a family history of primary immune deficiency (PID), receive the vaccine in the first day of life or a few months after birth.

BCG-related lymphadenitis, a localized adverse reaction, is one of the most common complications of BCG vaccine. There is no specific definition of BCG-related lymphadenitis, but most investigators define it as the development of ipsilateral regional lymph node enlargement after administration of BCG vaccination.[3-5] Most studies report different rates of this complication. Oman has a low incidence of TB and high BCG coverage as it is given to all newborns in their first day of life unless contraindicated. According to the EPI program about 1.9% of all newborns who received the vaccine develop isolated BCG lymphadenitis.[6]

Disseminated BCG infection is a rare complication. One study in Saudi Arabia estimated a rate from 0.1 to 4.3 per one million in vaccinated children.[3] Several studies have proposed the following diagnostic criteria for disseminated BCG infection.[5,7-9] Disseminated BCG infection is defined as systemic symptoms of fever, weight loss or irritability and two or more sites of BCG complications beyond the site of injection (involving lymph node, skin, bone or liver) with a documented isolation of *Mycobacterium bovis* and a histological finding on the tissue biopsy.

The diagnosis of BCG-related complications is usually by clinical features. Additional tests include interferon-gamma release assay , a specific test for *M tuberculosis*, which is obtained from a blood sample, along with a chest x-ray, which can be used as screening tools to differentiate other causes of disease from *M tuberculosis*. The acid fast bacilli (AFB) test is another test obtained from patient tissues either by aspiration or surgery,[3,6] but a negative mycobacterial culture cannot exclude BCG-related complications.

The presence of severe complications after BCG vaccination can suggest an underlying primary or secondary immunodeficiency. Several immunodeficiency diseases can increase the susceptibility to mycobacterial infection. These conditions include severe combined immunodeficiency disease (SCID), CGD, and Mendelian susceptibility to mycobacterial diseases (MSMD), involving Interleukin 12 (IL-12)/interferon-gamma pathway defects.[1,10] These diseases were noted mostly in countries with a higher consanguinity rate, such as Oman, Saudi Arabia and Iran.[11] The aim of this study was to evaluate the spectrum of BCG vaccine-related complications and immune status among Omani children.

PATIENTS AND METHODS

In this retrospective cross-sectional study, we included children younger than 13 years of age who were attended by or referred to the pediatric infectious diseases services for BCG vaccine-related complications in the form of local or systemic complications. The data are from the hospital records of the Royal Hospital, Muscat, Oman from 2006-2018. BCG vaccine-related complications were classified as localized lymphadenitis, distant osteomyelitis or disseminated BCG infection. Lymphadenitis was further subdivided as suppurative or nonsuppurative. The European Society for Primary Immunodeficiencies defines disseminated BCG infection as the presence of systemic symptoms with documented involvement of more than two sites distal to the BCG vaccination site involving the skin, a lymph node, the lungs, bone, or the liver. Data was collected on a spreadsheet that included patient age, history, physical findings, inflammatory markers, microbiological findings of AFB stain and TB culture with sensitivities, management modalities like required medications and/or surgery and the immunological blood workup findings. Confidentiality and patient privacy were maintained throughout the process. Ethical approval was obtained from the Scientific Research Committee of the Royal Hospital.

Data entry was performed using Microsoft Office Excel (version 2007). The data was reviewed by a second investigator to ensure data accuracy. IBM SPSS version 22 was used for data analysis (Armonk, New York, United States: IBM Corp). Categorical variables are described as percentages and continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR). Statistical significance was set at P=.05.

RESULTS

Of the 226 children with BCG vaccine-related complications from 2006 to 2018, 164 (73%) were male with a male-to-female ratio of 2.6:1.0.The patients were referred from different hospitals, so the total number who received vaccinations is unknown, but the current policy

is to vaccinate all children (http://www.bcgatlas.org/). The median (IQR) age at presentation was 4 months (4 months, range 0.3-40 months) for 225 of the children (one child was 10 years old) (**Figure 1**). Infants constituted 77.4% (n=175) of the sample (age ≤ 6 months). All but three participants received the BCG vaccine immediately after birth. BCG lymphadenitis was present in 192 patients (85.0%), BCG vaccine-related osteomyelitis in 23 patients (10.2%) and disseminated BCG infection in 11 patients (4.9%).

BCG lymphadenitis

BCG site reactions such as discharge; ulcer or abscess occurred in 22 patients (9.7%). Among those with isolated lymphadenitis, left axillary lymph node involvement was the most common, found in 171 of 192 patients (89%). The other lymph nodes were left supraclavicular (n=18), left infraclavicular (n=1) and right axillary lymph node (n=2) (**Figure 2**). All of these patients had no recurrence of infection and had normal growth parameters in follow up. The median (IQR) size of the enlarged lymph node in the longest axis was 2.0 (1) centimeters and range of 1 to 6 centimeters.

Most children (85.4%) had lymph nodes ≤3 centimeters. The mean duration of lymph node enlargement was 3.8 months with a range of 5 days to 10 months. Nonsuppurative lymphadenitis was found in 131 patients (68%) and suppurative lymphadenitis in 61 patients (32%). Children with nonsuppurative lymphadenitis were managed conservatively. Five patients of 131 with nonsuppurative lymphadenitis (4%) required surgery for persistent lymph node swelling beyond 6 months. Among children with suppurative lymphadenitis, needle aspiration (60.7%, n=37), incision and drainage (16.3%, n= 10) or surgical excision (19.7%, n=12) were required.

BCG vaccine-related osteomyelitis

BCG vaccine-related osteomyelitis presented as a bony swelling and involved different sites in 23 patients. Fever was reported in 6 patients (26.1%). Most of these patients presented with chest wall osteomyelitis (34.8%, n=8) including ribs or sternum, and upper limbs osteomyelitis (34.8%, n=8) including commonly the left side (n=5) more than the right side (n=3). Seven patients (30.4%) had lower limb osteomyelitis involving different sites. BCG-related osteomyelitis was confirmed by positive TB culture of *Mycobacterium bovis* in 13 of 23 patients (56.5%) of which AFB was positive in 70% (9/13). Two patients had positive *M tuberculosis* Complex PCR with rifampicin sensitivity and 8 patients with positive histopathology showed necrotizing granuloma. Mean C-reactive protein (CRP) was 10 mg/L, with range of 0-53 and mean (SD) erythrocyte sedimentation rate was 20 (12) mm/hour with a range of 4-48.

All patients with osteomyelitis were started with four antimycobacterial chemotherapy agents including isoniazid, rifampicin, ethambutol, and pyrazinamide prior to identification of *Mycobacterium bovis*. Pyrazinamide was stopped after the identification of the BCG strain. Ciprofloxacin was used in three patients. Isoniazid and rifampicin were continued for the entire treatment duration, while the other agents were stopped after 2 to 4 months if there was marked clinical improvement. The

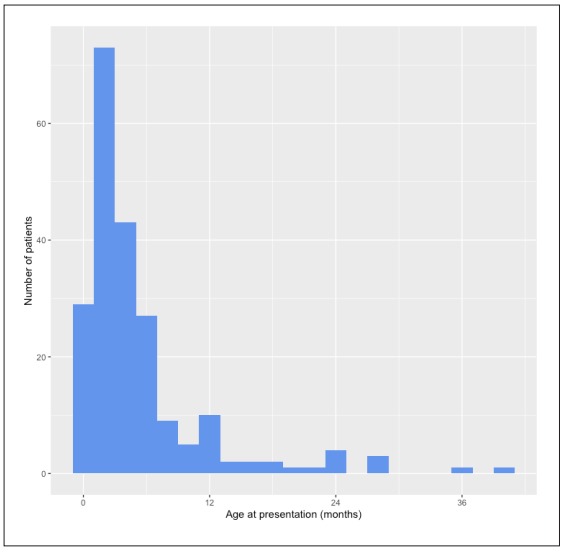

Figure 1. Age distribution of 225 of the patients (median 4 months, interquartile range 4 months; excludes one patient with age at presentation of 10 years).

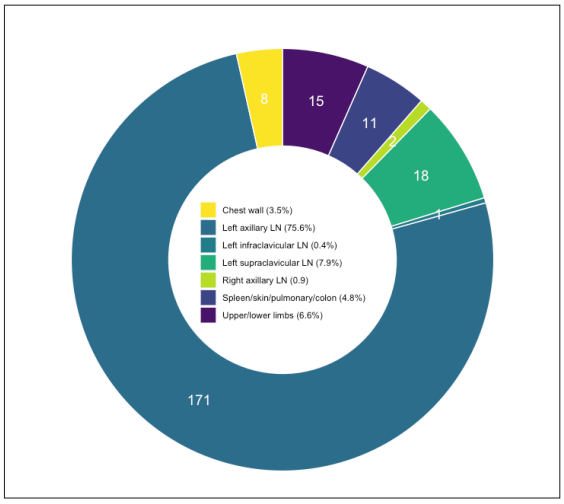

Figure 2. Common sites of BCG vaccine-related complications (n=226).

median (IQR) duration of anti-TB treatment was 12 (6) months and the range was 3-30 months.

All patients required biopsy and surgical debridement and all patients showed complete recovery except for one patient who had an ankle deformity. Immune workup was done in 17 of 23 patients and all were normal including on the HIV and interleukin 12/interferon-gamma tests.

Disseminated BCG infection

Disseminated BCG infection was diagnosed in 11 patients (4.9%); 3 males and 8 females, who were term and received BCG vaccine at birth (**Table 1**). The median (IQR) at presentation was 5 (9.25) months with a range from 1.0 to 28 months.

All patients underwent biopsy and the findings showed necrotizing granuloma. TB culture was positive in four patients and showed BCG strain. On the other hand, two patients had a positive *M tuberculosis* Complex PCR and five patients had positive AFB with no growth on TB culture. Mean (SD) duration of mycobacterial chemotherapy was 14 (6) months, ranging from 6 to 18 months. All patients required surgery.

Immune workups were done in all children with disseminated TB infection. Five children had CGD and two had SCID, one had MSMD, caused by IFNGR2 deficiency, and one had other non-specific primary immunodeficiencies. Two patients had blood or saliva samples sent for whole exome sequencing (sent to Centogene Laboratory in Germany [*https://www.centogene.com/*] for whole exome sequencing). The organs involved in in patients with CGD (patient 1 to 5 in **Table 1**) were variable in each patient. Three patients had lymph node involvement and necrotizing consolidation and/or cavitary lesions in the lungs, confirmed by positive *Mycobacterium tuberculosis* Complex PCR using bronchoalveolar lavage. One patient had spleen and skin involvement along with left axillary lymphadenitis and lung infiltrates. Two patients had chest wall osteomyelitis and lung infiltrates. All those patients had an immune workup which revealed CGD.

The first patient with SCID had disseminated BCG infection that involved multiple organs including the lungs, colonic tissue, spleen, skin and right knee septic arthritis (Patient 6). She harbored a pathogenic mutation in the IL7R gene. Her course of treatment was challenging as she needed an urgent hematopoietic stem cell transplant. The second patient had JAK3 deficiency and developed lung infiltrates and a small liver lesion (Patient 7). Moreover, another patient who had PID not yet identified developed BCG lymphadenitis complicated with multiple brain lesions seen on brain magnetic resonance imaging suggestive of tuberculoma (Patient 9). His whole exome sequencing sent to Centogene laboratory was normal with no mutations. Another patient (Patient 8), diagnosed with IFNGR2 deficiency, developed a disseminated BCG infection with bilateral axillary lymphadenitis and hepatosplenomegaly. There were two other patients with a normal basic immune workup (Patients 10 and 11). The BCG infection involved lymphadenitis and the right parotid lymph node in one patient, and 6th rib osteomyelitis, mediastinal lymph nodes, and hepatomegaly in the other patient. As of publication, these patients were still under immunological workup.

DISCUSSION

BCG vaccine-related complications are variable and can involve different sites of the body, with left axillary BCG lymphadenitis being the most common site. There have been no studies of BCG vaccine-related complications in Oman until now. This study showed the spectrum of these complications in children attending the Royal Hospital over a period of 13 years. Isolated BCG lymphadenitis was present in 85% of patients, BCG-related osteomyelitis in 10.2% and disseminated BCG infection in 4.9%. Similar results were noted in a study conducted in Riyadh by Al Fawaz et al, where 90% had regional lymphadenitis, 3% had disseminated BCG infection and 7% had a local vaccine reaction only.[3] In the current study, unilateral left axillary lymphadenitis was the most common site involved, a finding similar to that noted in previous studies.[2-5] Although the different treatment modalities and guidelines in treating BCG-related complications differ, the mainstay of treatment in isolated non-suppurative lymphadenitis is observation. The indication for surgical excision is variable, but the most common indication is persistent enlarged lymph nodes without regression beyond 6 to 9 months or progression more than 3 centimeters in size.[5] Treatment in children with suppurative lymphadenitis necessitates the use of antibiotics if there is a secondary bacterial infection. Needle aspiration has been recommended for suppurative lymphadenitis to avoid spontaneous rupture and sinus formation.[4,5] Another study showed that needle aspiration reduces time to clinical cure.[12] Incision and drainage was less practiced in our study, while other studies showed that incision and drainage resulted in persistent wound drainage and deforming scars.[4,5,13]

The prevalence of BCG osteomyelitis is variable, from 1 to 700 per million vaccinated children.[2,4] In our study, 23 patients with BCG osteomyelitis presented mostly with bony swelling. Fever was not noted in 7

Table 1. Disseminated BCG vaccine-related complications, treatment and outcome in 11 patients.

Patient number	Age at presentation (months)	BCG complications		Treatment	Treatment duration (months unless noted otherwise)	Type of immunodeficiency	Outcome
		Left axillary lymphadenitis (regional)	Site of dissemination				
1	24	Negative	Mediastinal LN, pulmonary, L cervical LN; LN biopsy: granuloma; AFB-, TB culture+	No treatment		CGD	Transferred to other hospital
2	5	Positive	Pulmonary, R inguinal LN; lung biopsy: multiple epithelioid granulomas with minimal central necrosis and hilar pyogenic inflammation; AFB-, TB culture+	4 antimycobacterial drugs,	18	CGD	Lung infiltrates Improved with clinical improvement
3	3	Positive	Pulmonary, L axillary LN; bronchial lavage; AFB+, TB culture-	4 antimycobacterial drugs	9	CGD	Lung infiltrates Improved with clinical improvement
4	2	Positive	Pulmonary with cavitary lung lesion, splenic lesions; LN biopsy: TB culture+ for M bovis sensitive to INH, RIF, EMB, gastric aspirate AFB+	4 antimycobacterial drugs	18	CGD	Lung and splenic lesions improved
5	1	Positive	Pulmonary, R 5th finger osteomyelitis; Rib bone biopsy: AFB+, TB culture-	4 antimycobacterial drugs	2 years	CGD	Lung and bony lesions improved
6	11	Negative	Pulmonary, colon, spleen, skin, R knee septic arthritis; R knee biopsy: AFB+, TB culture M bovis sensitive to INH, RIF, EMB, MTB PCR+	5 antimycobacterial drugs, and interferon gamma	Duration not documented	SCID: IL7R gene (c.616C>T (p.Arg206, exon 5)	Persistent; HSCT planned
7	2	Positive	Pulmonary, small liver abscess; bronchial lavage: AFB+, MTB PCR+	4 antimycobacterial drugs	Duration not documented	SCID: JAK3 deficiency c.1613 G>A (p.Gly538>Asp) [[AUTHOR: verify > in p.Gly538>Asp)]]:	Died of DLBCL

Patient number	Age at presentation (months)	BCG complications		Treatment	Treatment duration (months unless noted otherwise)	Type of immunodeficiency	Outcome
8	5	Positive	Liver, spleen; LN biopsy: AFB+, TB culture M bovis sensitive to INH, RIF, EMB	4 antimycobacterial drugs	6	IFNGR2 deficiency c.175+102del in relation to start ATG, exon 1	Improved
9	12	Positive	L shoulder ulcers, CNS tuberculoma; Skin ulcer biopsy: AFB+, TB culture M bovis sensitive to INH, RIF, EMB	4 antimycobacterial drugs	12	PID – not yet identified	Improved clinically and radiologically
10	1.3	Positive	R parotid; parotid biopsy: necrotizing granulomatous lesions with fistula formation; AFB-, TB culture-	3 antimycobacterial drugs	12	PID – not yet identified	Improved
11	28	Negative	L chest wall, osteomyelitis, lung, liver; lung biopsy: granuloma with central necrosis; AFB-, TB culture-	4 antimycobacterial drugs	18	PID – not yet identified	Improved

LN: lymph node, L: left, R: right, INH: isoniazid, RIF: rimfampin, EMB: ethambutol; MTB PCR: , CGD: chronic granulomatous disease, PID: primary immune deficiency. DLBCL: diffuse large B-cell lymphoma; HSCT: hematopoietic stem cell transplantation.

of 23 patients (30.4%) with BCG osteomyelitis. The most commonly affected site in our study was the chest wall, with osteomyelitis involving either rib or sternum (34.8%, n=8), and upper limbs (34.8%, n=8). In contrast to these findings, other studies have shown that extremity bones, mainly the lower limbs, are more commonly involved with BCG osteomyelitis than the axial skeleton.[2,14]

Al Azri et al reported a case of BCG osteomyelitis of the right hip bone in an 8-month old infant, confirmed by PCR, as a BCG strain of *M tuberculosis* and characteristic histopathology. The patient required two surgical operations and completed 12 months of antimycobacterial agents.[2] Another case report by Avcu et al showed BCG osteomyelitis of the distal femur in a 22-month old treated with surgical debridement and 12 months of antimycobacterial therapy.[15]

Disseminated BCG infection is a rare, yet serious complication. It is mostly associated with immunodeficiency, but can occur in healthy, immune-competent children.[13,16-18] Various immunodeficiency conditions have been associated with increased susceptibility to disseminated mycobacterial infections. Those conditions are secondary immunodeficiency, primary immunodeficiencies such as SCID and CGD, hyper-IgM syndrome, and defects of the IL12-IFNγ axis (MSMD).[13] In our study, 8 of 11 (72.7%) children with disseminated lymphadenitis had PID, including one with MSMD (confirmed with IFNGR2). CGD was the most common PID, presenting with disseminated BCG complications (n=5). In contrast, in a study of 10 patients with disseminated BCG in a 15-year long study in Singapore, all had PID.[19] The median age of presentation was 5.5 months (range 0.8-35.5) compared to 4 months (9.5, range 0.3-40 months) in our study. They reported 4 patients with SCID, 3 patients with MSMD, 1 patient with anhidrotic ectodermal dysplasia with PID, 1 patient with combined immunodeficiency, and one patient with a STAT-1 gain-of-function mutation.[19] Patients reporting with isolated BCG osteomyelitis had an apparently normal immunological evaluation.[2,14] Multiple case reports have described disseminated BCG infection in children with different types of SCID including IL7R gene mutation and JAK3 deficiency.[11,12,18] Preparation SCID patients with disseminated BCG infection for transplant was a real challenge in one of our patients. Al Mousa noted the same, reporting that the most challenging part of treatment of disseminated BCG infection in children with SCID is the risk of flare up after the transplant.[11] Therefore, modification of the transplant procedure is recommended to control the inflammatory response of *Mycobacterium bovis*. There are no clear guidelines

on the most suitable treatment for disseminated BCG disease, however, aggressive therapy with at least four anti-mycobacterial agents is recommended.[9,11]

Although BCG vaccination is important in TB endemic areas, the spectrum of complications ranges from isolated lymphadenitis to disseminated BCG infection. Therefore, early identification of children with PID prior to vaccination either by doing neonatal screening or deferring BCG vaccination until the age of 6 months is the key to prevent BCG vaccine-related complications in these children. In Oman, it is been found that the median age of onset and diagnosis of SCID patients were 54 and 135 months, respectively.[20] Further studies are needed to guide this recommendation. Because our study was single center, the data may not provide a full overview of all BCG vaccine-related complications in Oman. Because our study was retrospective, details of microbiological results were sometimes unavailable as was the ability to determine the detailed management for all patients.

REFERENCES

1. BCG_Vaccine_rates_information_sheet.pdf [Internet]. [cited 2018 Oct 21]. Available from:http://www.who.int/vaccine_safety/initiative/tools/BCG_Vaccine_rates_information_sheet.pdf

2. Al-Azri MS, Manarang J, Al-Mufargi Y. Bacille Calmette-Guérin Vaccine-Induced Tuberculous Hip Osteomyelitis in an Infant. Sultan Qaboos Univ Med J. 2017 Aug;17(3):e358–62.

3. Alfawaz TS, Alshehri M, Alshahrani D. BCG related complications: A single center, prospective observational study. Int J Pediatr Adolesc Med. 2015 Jun 1;2(2):75–8.

4. Venkataraman A, Yusuff M, Liebeschuetz S, Riddell A, Prendergast AJ. Management and outcome of Bacille Calmette-Guérin vaccine adverse reactions. Vaccine. 2015 Oct 5;33(41):5470–4.

5. Elsidig N, Alshahrani D, Alshehri M, Alzahrani M, Alhajjar S, Aljummah S, et al. Bacillus Calmette–Guérin vaccine related lymphadenitis in children: Management guidelines endorsed by the Saudi Pediatric Infectious Diseases Society (SPIDS). Int J Pediatr Adolesc Med. 2015 Jun 1;2(2):89–95.

6. Paul G, Al-Maani AS, Kurup PJ. Management of Infants and Children who are Contacts of Contagious Tuberculous Patients. Sultan Qaboos Univ Med J. 2013 Nov;13(4):477–85.

7. ESID - European Society for Immunodeficiencies [Internet]. [cited 2018 Oct 21]. Available from: https://esid.org/Working-Parties/Clinical-Working-Party/Resources/Diagnostic-criteria-for-PID2#Q2

8. Al-Mousa H. An infant with disseminated bacillus Calmette-Guerin infection (BCGitis). Int J Pediatr Adolesc Med. 2014 Dec 1;1(2):89–92.

9. Bukhari E, Alaklobi F, Bakheet H, Alrabiaah A, Alotibi F, Aljobair F, et al. Disseminated bacille Calmette-Guérin disease in Saudi children: clinical profile, microbiology, immunology evaluation and outcome. Eur Rev Med Pharmacol Sci. 2016;20(17):3696–702.

10. Al-Hammadi S, Alsuwaidi AR, Alshamsi ET, Ghatasheh GA, Souid A-K. Disseminated Bacillus Calmette-Guérin (BCG) infections in infants with immunodeficiency. BMC Res Notes. 2017 May 5;10.

11. Al-Mousa H. An infant with disseminated bacillus Calmette-Guerin infection (BCGitis). Int J Pediatr Adolesc Med [Internet]. 2014 Dec 1 [cited 2018 Oct 23];1(2):89–92. Available from: http://www.sciencedirect.com/science/article/pii/S2352646714000490

12. Cuello-García CA, Pérez-Gaxiola G, Jiménez Gutiérrez C. Treating BCG-induced disease in children. Cochrane Database Syst Rev. 2013 Jan 31;(1):CD008300.

13. Lee PP. Disseminated Bacillus Calmette-Guérin and Susceptibility to Mycobacterial Infections-Implications on Bacillus Calmette-Guérin Vaccinations. Ann Acad Med Singapore. 2015 Aug;44(8):297–301.

14. Chiu N-C, Lin M-C, Lin W-L, Wang S-Y, Chi H, Huang L-M, et al. Mycobacterium bovis BCG–Associated Osteomyelitis/Osteitis, Taiwan - Volume 21, Number 3—March 2015 - Emerging Infectious Diseases journal - CDC. [cited 2020 Feb 16]; Available from: https://wwwnc.cdc.gov/eid/article/21/3/14-0789_article

15. Al-Hammadi S, Alsuwaidi AR, Alshamsi ET, Ghatasheh GA, Souid A-K. Disseminated Bacillus Calmette-Guérin (BCG) infections in infants with immunodeficiency. BMC Res Notes. 2017 May 5;10.

16. Amanati A, Pouladfar G, Kadivar MR, Sanaei Dashti A, Jafarpour Z, Haghpanah S, et al. A 25-year surveillance of disseminated Bacillus Calmette-Guérin disease treatment in children in Southern Iran. Medicine (Baltimore). 2017 Dec;96(52):e9035.

17. Santos A, Dias A, Cordeiro A, Cordinhã C, Lemos S, Rocha G, et al. Severe axillary lymphadenitis after BCG vaccination: alert for primary immunodeficiencies. J Microbiol Immunol Infect. 2010 Dec;43(6):530–7.

18. Sadeghi-Shabestari M, Rezaei N. Disseminated bacille Calmette-Guérin in Iranian children with severe combined immunodeficiency. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2009 Nov;13(6):e420-423.

19. Rina Yue Ling Onga, Su-Wan Bianca Chanb,g , Siu Jun Chewc , Woei Kang Liewb , Koh Cheng Thoond, et al. Disseminated Bacillus-Calmette-Guerin infections and primary immunodeficiency disorders in Singapore: A single Center 15 year retrospective review. International Journal of Infectious Diseases 97 (2020) 117–125.

20. Al Sukaiti N, Ahmed K, Alshekaili J, Al Kindi M, Cook MC, Farsi TA. A Decade Experience on Severe Combined Immunodeficiency Phenotype in Oman, Bridging to Newborn Screening. Front Immunol [Internet]. 2021 [cited 2021 Jan 27];11. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2020.623199/full