

ORIGINAL ARTICLE

CLINICAL MANAGEMENT OF LOCALIZED BCG ADVERSE EVENTS IN CHILDREN

Thais das Neves Fraga MOREIRA(1), Maria Isabel de MORAES-PINTO(2), Beatriz Tavares COSTA-CARVALHO(2), Anete Sevciovic GRUMACH(3) & Lily Yin WECKX(1)

SUMMARY

BCG adverse events (BCG-AE) are rare conditions with no well-established treatment. This study aims to describe clinical characteristics and outcome of localized BCG-AE. Children with BCG-AEs who were treated at the Reference Center for Special Immunobiologicals of the Federal University of São Paulo from 2009 to 2011 were included. Patients were followed monthly until 3 months after healing. One hundred and twenty-seven patients with localized BCG-AE were followed: 67 (52.7%) had suppurative lymphadenitis; 30 (23.6%) injection-site abscess; five (3.9%) had enlarged lymph node > 3 cm; four (3.1%) had ulcer > 1 cm; and one (0.8%) had a local bacterial infection. Five patients (3.9%) had more than one BCG-AE simultaneously. Fifteen patients (11.8%) had atypical manifestations: seven wart-like lesions; five BCG reactivations; two other dermatologic lesions and one with vasomotor phenomenon. Isoniazid was used in 96 patients with typical BCG-AE (85.7%) until lesion resolution which took place 3.1 months later (in median); the healing rate was 90.6%. Patients with atypical manifestations had an individual approach. Regarding the outcome, 105/112 patients with typical AE and 13/15 patients with atypical AE had resolution of BCG-AE. Localized BCG-AE caused by BCG Moreau RJ had positive outcome when treated with a short course of isoniazid. Atypical BCG-AE are not infrequent.

KEYWORDS: BCG vaccine; Adverse event; Therapeutics; *Mycobacterium bovis*.

INTRODUCTION

BCG has been used safely in more than one billion people to prevent meningeal and miliary tuberculosis (TB) in children¹. However, BCG strains currently in use differ in drug resistance and reactogenicity profile resulting in conflicting published data regarding efficacy and safety^{2,3,4}.

Adverse events after BCG have been described since its introduction and can be classified as localized (regional lymphadenitis, injection site abscess, an ulcer larger than 1 cm or other local manifestation) or disseminated manifestations⁵. The first events can occur in healthy individuals or as part of an immunological reconstitution inflammatory syndrome (IRIS) in HIV patients. By contrast, disseminated BCG disease which is a rare condition, usually affects either HIV-infected children or those with primary immunodeficiencies^{6,7,8,9}.

One poorly understood topic is the best treatment for BCG adverse events (BCG-AE). In localized reactions, surgical procedures, fine needle aspiration and/or anti-tuberculosis drugs are globally used, although scientific evidence¹⁰ is weak. In disseminated disease, various anti-tuberculosis drug regimens are used^{11,12}.

In Brazil, intradermal BCG Moreau *Rio de Janeiro* is recommended at birth to all neonates, with more than 99% coverage¹³. Since 2005, reporting of adverse events following immunization (AEFI) in Brazil is mandatory and the Reference Centers for Special Immunobiologicals (CRIE) provide technical support for vaccine adverse event management throughout the country¹⁴.

This study aims to describe the clinical aspects and the outcome of patients with localized BCG adverse events.

MATERIALS AND METHODS

This study was conducted from 2009 to 2011 and included patients under 10 years old, presenting with BCG adverse events, who were seen routinely at the Reference Center (CRIE) and/or were identified by the AEFI surveillance system in the city of Sao Paulo. They were followed up by one of the authors (TNFM).

Mild inflammatory reaction after BCG vaccination such as erythema, vesicle, small ulcer (< 1 cm) or mild lymph nodes enlargement (< 3 cm) were considered expected reactions within normal BCG vaccination evolution, and were excluded.

(1) Reference Center for Special Immunobiologicals, Division of Pediatric Infectious Diseases, Federal University of São Paulo, São Paulo, SP, Brazil.

(2) Department of Pediatrics, Federal University of São Paulo, São Paulo, SP, Brazil

(3) Outpatient Clinic of Recurrent Infections, Faculty of Medicine ABC, Santo André, SP, Brazil.

Correspondence to: Thais das Neves Fraga Moreira. E-mail: tnmoreira@yahoo.com.br

The 2008 Brazilian Ministry of Health criteria for BCG-AE were employed in this study. Adverse events were classified as localized BCG-AE (typical BCG-AE) - regional enlarged lymph node > 3 cm, suppurative lymphadenitis, ulcer > 1 cm, injection site abscess, bacterial infection at injection site, lupus vulgaris lesion and keloid scar - or manifestation caused by BCG dissemination. Any local manifestation not included in the 2008 Brazilian Guidelines was analyzed and, if considered possibly associated with BCG, it was classified as an atypical manifestation¹⁴.

At the first visit, a questionnaire was filled in with demographic and clinical data on adverse events, BCG vaccination data, previous infections, hospital admissions and risk factors for immunodeficiency.

Treatment of BCG adverse events was based on the Brazilian Guidelines in use¹⁴. Isoniazid 10 mg/kg/day was proposed to individuals with suppurative lymphadenitis, ulcer larger than 1 cm and injection site abscess until complete resolution. Bacterial local infection was treated with oral antibiotics. Regional enlarged lymph nodes larger than 3 cm diameter received no specific treatment unless there was fluctuation or suppuration during the follow-up. Patients with atypical manifestations had an individual approach according to clinical characteristics.

Complete blood count and liver function evaluation were performed only for children who took isoniazid for more than three months, took more than one anti-tuberculosis drug, had symptoms suggestive of toxicity during follow-up or reported previous hepatic diseases.

Patients were followed monthly until 3 months after lesion resolution. In this study, criteria for healing used were complete ulcer or abscess resolution and, in previous enlarged lymph nodes, size < 1 cm without drainage. Patients without complete lesion resolution after 6 months were considered as "treatment failure" and a second therapeutic approach was employed.

Microsoft Office Access 2007 and Excel 2010 were used to build the main database and for descriptive analyses, respectively.

This study was approved by the Ethics Committee of the Federal University of *São Paulo* (protocol:1293/09).

RESULTS

One hundred and twenty-seven patients with BCG-AE were included in the study: 112 with typical BCG-AE and 15 with atypical manifestations. No manifestation caused by BCG dissemination was observed during the study. Seventy patients (55.1%) were recruited through the surveillance system and 57 (44.9%) through spontaneous demand, and the latter were reported to the surveillance system.

The BCG-AE occurred in 97.6% of the patients after first dose of the vaccine. Only three (2.4%) had BCG-AE after a second BCG dose. No vertical exposure to HIV infection was reported by parents.

Typical BCG-AE

Among 112 patients with typical BCG-AE, 67 had suppurative lymph nodes; 30 had injection site abscesses; five had non suppurative lymph nodes larger than 3 cm; five had more than one simultaneous event; four

had ulcers larger than 1 cm and one presented with a bacterial infection at the injection site (Fig. 1).

The median age for BCG vaccination was two days and the first symptoms occurred at a median age of 2.5 months, but varied according to the type of BCG-AE. Demographic characteristics of patients are described in Table 1.

During the study period, 15 out of 112 patients with typical AE-BCG had hospital admissions due to infectious conditions with a total of 20 admissions, all of them unrelated to BCG-AE. Causes of admission were: sepsis (five admissions), respiratory infection⁹, diarrhea² and other clinical conditions⁴. In this group, the hospitalization coefficient index for infectious conditions was 59.5 admissions/1,000 children/year.

Isoniazid was used in 96 (85.7%) patients with typical AE and 87 (90.6%) had a complete resolution in a median period of 5.2 months. The median period of treatment was 3.1 months (minimum 0.3 - maximum 8.3).

Only five patients with typical BCG-AE had therapeutic failure with isoniazid (Table 2): in two cases, surgical excisions were performed without complications, one patient received multiple drugs treatment because the BCG strain isolated from the injection site abscess was resistant to isoniazid and two were lost to follow-up.

Eight patients with typical BCG-AE did not receive treatment because they arrived at the Center already in the healing phase.

Treatment was well tolerated and was not associated with any relevant clinical manifestation or laboratory abnormalities. A small increment in the levels of aspartate aminotransferase (AST) (< 3 x normal serum levels; 32 to 106 U/L) was observed in 20 of 36 (35.5%) children examined. All of them had normalization of liver enzymes after discontinuation of medication.

One patient had already been diagnosed with the Chediak-Higashi syndrome, a primary immunodeficiency, at the time the child was included in the study. He had a suppurative lymph node that healed after 3 months of isoniazid. He was submitted to a hematopoietic stem cell transplantation at 26 months of age without BCG reactivation.

One patient with suppurative lymph node died due to respiratory failure during the follow-up. No etiological agent was identified but clinical information suggested a viral respiratory infection.

Summarizing the outcome among 112 patients with typical BCG-AE: 105 healed (87 with isoniazid, three after a second approach because of isoniazid failure, seven with alternative treatments prescribed in other services, eight with no intervention), one died and six patients were lost to follow-up (including two presenting with isoniazid failure).

Atypical BCG-AE

Fifteen patients (11.8%) had atypical manifestations after BCG: seven, wart-like lesion at injection site; five BCG scar reactivations; two other local dermatologic lesions and one patient presenting with vasomotor phenomenon (Fig. 2). Three patients had a known immunosuppressive condition prior to BCG-AE diagnosis (Table 3).



Fig. 1 - Typical BCG adverse event manifestations. A- lymph node with fluctuation. B- suppurative lymph node with fistulization. C- Ulcer > 1 cm. D- injection site abscess (cold abscess).

Patients with atypical manifestations were submitted to an individual therapeutic approach according to the clinical characteristics. All seven patients with wart-like lesions had isoniazid treatment prescribed: two patients did not take the drug and three patients took the drug for less than 30 days due to a rapid lesion improvement (Fig. 2). Two patients maintained isoniazid with a gradual lesion resolution including one patient who was submitted to liver transplantation due to cirrhosis caused by tyrosinemia (Table 3).

Two patients presented BCG reactivation after liver transplantation and were treated with isoniazid for six months. No other antituberculosis drug was used to avoid hepatotoxicity. One patient succumbed to sepsis (clinically not suggestive of a BCG complication, and no etiological agent was identified) and one had BCG-AE resolution after six months of treatment.

The other three patients with BCG reactivation did not have an immunodeficiency condition, and they did not receive any treatment during the follow-up. Two of them had a spontaneous resolution after a few days and one was lost to follow-up.

The neonate who had a vasomotor phenomenon presented with a sudden red skin color around the BCG injection site on her right arm, some minutes after BCG administration (Fig. 2). That was followed some

minutes later by a pale yellow skin color. It had a spontaneous resolution after one hour and a normal BCG evolution was observed.

Two other local dermatologic lesions were described as atypical BCG-AE. They are reported in Table 3 and shown in Figure 2.

DISCUSSION

From 2009 to 2011, 574,529 BCG vaccine doses were administered in *São Paulo* city and 278 adverse events after BCG were reported to the surveillance system, which results in a rate of 48 BCG-AE reported/100,000 doses¹⁵. This study describes the clinical characteristics and outcomes of patients with BCG-AE and represents a significant proportion (45.7%) of adverse events reported in *São Paulo* city. It also confirms lymphadenitis and injection site abscess as the main manifestations of localized BCG-AE and describes the outcome with isoniazid treatment.

The main localized adverse event manifestations mentioned in the literature, as in this study, were suppurative lymph nodes and injection site abscesses but the incidence rate may vary from 35/100,000 to 2,500/100,000 according to the vaccine strain, age at vaccination or number of previous doses^{5,16,17}. Despite being based on a passive reporting system, the rate of BCG-AE in this study is in agreement with the

Table 1
Demographic characteristics of patients with loco-regional BCG adverse events with typical manifestations

Characteristics	Suppurative lymph node (67)	Site injection abscess (30)	Non suppurative lymph node > 3 cm (5)	More than one diagnosis (5)	Ulcer > 1 cm (4)	Bacterial infection at injection site (1)	Total (112)
Male gender (%)	45/67 (67.2)	10/30 (33.3)	4/5 (80.0)	4/5 (80.0)	2/4 (50.0)	1/1 (100.0)	66 (58.9)
Prematurity (gestational age < 37weeks)	10/66 (15.1)	5/30 (16.7)	0	0	0	0	15/111 (13.5)
Median birth weight in g (P25-P75)	3190 (2765- 3532)	3203 (2908 - 3450)	3280 (3035-3529)	3315 (3207-3541)	3295 (2944-3552)	N.A.*	3225 (2855-3540)
Patients with low weight (Z score W/A < -2SD)	6/65 (9.2)	0	0	0	1/4 (25)	0	7/110 (6.3)
Median age at BCG vaccination in days (P25-P75)	2 (1.0 – 5.0)	4 (1.0 – 10.5)	1 (0 – 5.0)	2 (0 – 20.0)	2.2 (1.7- 3.2)	0	2 (1.0 – 6.0)
Median age at first symptoms in months (P25-P75)	1.8 (1.0 -2.8)	3.8 (2.7-5.7)	2.2 (1.2 -3.0)	3.0 (2.3-6.3)	4.5 (2.6- 6.8)	N.A.*	2.5 (1.4 - 3.8)
Median age at first visit in months (P25- P75)	4.6 (3.2 -7.8)	9.9 (6.4 – 15.2)	11.2 (8.8-15.2)	7.4 (5.4 – 8.2)	9.1 (6.9-10.2)	N.A.*	6.3 (3.6-10.9)
Known immunodeficiency disease	1/67 (1.5)	0	0	0	0	0	1/112 (0.9)

*Not applicable

prospective multicenter study by Lotte *et al.* and with previous Brazilian studies^{5,17,18}. To the best of our knowledge, this is the largest prospective study focus on BCG-AE performed in Brazil.

Patients with typical BCG-AE had similar demographic characteristics compared to those described in the general Brazilian population, including the prematurity rate¹⁹. The only exception was the admission rate due to infectious causes, which was higher than the one that had been previously described. A study in *São Paulo* city conducted from 2002 to 2006 showed a hospitalization coefficient index for all causes (including perinatal diseases, prematurity, infectious diseases and others) of 36.07 to 40.01/1,000 in < 1 year contrasting with 59.5/1,000 hospitalization coefficient index for the infectious conditions only found in our study²⁰. These findings highlight the importance of studies that analyze the immunological response of this specific group of patients.

The age at first symptoms with typical AE-BCG in our study (median 2.5 months) is in agreement with the literature¹⁶. Some patients had been previously treated in other health units, which can explain the delay between the initial symptoms and the age at the first visit to our center (median 6.3 months).

Localized BCG-AE can be the first symptom of a primary immune

defect^{7,12} or part of an immune reconstitution inflammatory syndrome (IRIS) manifestation²¹. The risk of disseminated disease in these groups can be extremely high^{6,22}. In our setting, no HIV-exposed child was identified which was expected considering that the rate of HIV infection in children below 5 years of age in *São Paulo* city was 2.5/100,000 inhabitants during the study period²³.

No disseminated disease was identified in the study and the only patient with primary immunodeficiency had a positive outcome. The exact incidence of primary immunodeficiency in Brazil is unknown. The Latin American Society for Immunodeficiency has recently set up a registry to report all diagnosed primary immune deficiencies²⁴.

There is no consensus on the best treatment for BCG-AE either in healthy or immunodeficient patients. A recent systematic review on BCG disease treatment highlighted the small number of randomized controlled studies and concluded that it is unclear whether oral antibiotics (isoniazid, erythromycin, or a combination of isoniazid plus rifampicin) are effective or not for the resolution of BCG-induced disease¹⁰. The divergence between studies may be explained by the different profile of BCG strains and the different treatment goal. Of note, BCG Moreau RJ is highly sensitive to isoniazid².

Most of the studies published about treatment have focused on BCG

Table 2
Treatment and final outcome of patients with typical BCG adverse events

Characteristics	Suppurative lymph node	Injection site abscess	Non suppurative lymph node > 3 cm	More than one diagnosis	Ulcer > 1 cm	Bacterial infection	Total
No drug treatment	4/67 (6.0)	3/30 (10.0)	1/5 (20.0)	0/5	0/4	1/1 (100)	9/112 (8.0)
Median time for spontaneous healing in months	5.87 and 2.6*	13.2 and 3.0*	5.17	---	---	---	5.52
Isoniazid treatment (%)	58/67(86.6)	25/30 (83.3)	4/5 (80.0)	5/5 (100)	4/4 (100)	---	96/112 (85.7)
Median period of isoniazid use in months	3.17	2.93	5.10	2.07	1.82	---	3.07
Median period for resolution with isoniazid in months	5.2	6.2	5.2	6.25	3.3	N.A.	5.2
Other previous treatment (%)	5/67(7.5)	2/30 (6.7)	0	0	0	----	7/112 (6.2)
Healing with isoniazid (%)	53/58 (91.4)	22/25 (88.0)	4/4 (100.0)	5/5 (100.0)	3/4 (75.0)	----	87/96 (90.6)
Therapeutic failure with isoniazid (%)	3/58 (5.2)	2/25 (8.0)	0	0	0	----	5/96 (5.2)
Healing after second therapeutic approach (%)	2/3 (66.7)	1/2 (50.0)	0	0	0	----	3/4 (75.0)
Patients lost to follow-up (%)	3/67 (4.5)	2(6.6)	0	0	1 (25.0)	0	6/112 (5.3)
Deaths (%)	1(1.5)	0	0	0	0	0	1/112 (0.9)

* Only 2 patients with available data



Fig. 2 - Atypical BCG adverse events. A and B show wart-like lesions in two different patients. C- vasomotor phenomenon. D- undefined lesion (cutaneous sarcoidosis? foreign body granuloma?). E- post inflammatory hypopigmentation. F- BCG scar reactivation after influenza vaccine.

Table 3
Clinical aspects, treatment and outcomes of patients with atypical BCG-AE

Gender	Age at BCG (d)	Age at first symptoms (mo)	Clinical aspects	Underlying conditions	Final AE diagnosis	Treatment (mo)	Outcome
M	14	69.6	Erythema and edema (2 cm) at BCG scar	Influenza vaccine in the right arm 3 cm under BCG scar 1 d before symptoms	BCG reactivation	None	Healing (3 d)
F	2	6.2	Erythema, edema (1 cm) and secretion at BCG scar	Exanthema subitum 2 d after symptoms	BCG reactivation	None	Healing (10 d)
M	6	46.3	Edema and secretion at BCG scar	-----	BCG reactivation	None	Lost to follow-up
F	2	6.5	Erythema, edema (1 cm) and secretion at BCG scar	Liver transplantation for biliary atresia 1 mo before symptoms	BCG reactivation	Isoniazid	Died of sepsis (not related to BCG)
M	1	8.9	Erythema, edema (1 cm) and secretion at BCG scar	Liver transplantation for biliary atresia 15 d before symptoms	BCG reactivation	Isoniazid (6.0)	Healing (6 mo)
F	1	6.7	Solid raised lesion with wart-like appearance at BCG injection site	-----	Wart-like lesion	Isoniazid (0.3)	Healing (0.3 mo)
M	1	3.5	Solid raised lesion (base 0.5cm)	Tyrosinemia, Liver cirrhosis and liver transplantation during treatment	Wart-like lesion	Isoniazid (6.0)	Healing (1 mo)
M	1	2.0	Solid raised lesion (0.5x0.5x0.6cm)	-----	Wart-like lesion	Isoniazid (4.1)	Healing (4.1 mo)
M	66	6.1	Solid raised lesion (1.2x1.2x0.5cm)	Prematurity	Wart-like lesion	None	Healing (1.9 mo)
M	1	0.5	Solid raised lesion (1.4x1.4x0.2cm)	-----	Wart-like lesion	Isoniazid (1.0)	Healing (1.0 mo)
M	1	1.0	Solid raised lesion (0.8x0.5x0.2cm)	Prematurity	Wart-like lesion	Isoniazid (0.5)	Healing (0.5 mo)
F	31	4.1	Solid raised lesion (0.8x0.5x0.5 cm)	-----	Wart-like lesion	None	Healing (5.0 mo)
F	7	1.4	Ecematous plaque (2.5 cm) surrounding BCG scar with induration and erythema. Biopsy: non caseous granulomas without surrounding lymphocytes (naked tubercles). Acid-fast bacilli: negative. Culture: negative	Atopic dermatitis	Undefined lesion (cutaneous sarcoidosis? Foreign body granuloma?)	Topic corticosteroid and anti-histaminic (3)	Healing (2.1 mo)
F	1	1.1	Well circumscribed white macule surrounding BCG scar	Down syndrome, hypothyroidism	Post inflammatory hypopigmentation	Moisturizing cream (6.0)	Healing (6 mo)
F	2	2.0	Yellow skin color on right arm within minutes of BCG vaccination	-	Vasomotor phenomenon	None	Recovery (1 h)

lymphadenitis. The average time for clinical resolution of suppurative lymph nodes, without intervention, has been reported as 8.7 months²⁵.

In our study, the use of isoniazid was considered safe and was given to 85.7% of patients with localized adverse events and 90.6% of them healed. The mean period for resolution of the suppurative lymph node group in our study was 5.2 months, what may suggest isoniazid as a good

option in this situation. This hypothesis should be tested in randomized controlled studies in the future.

Only one patient developed isoniazid resistance during the treatment and she was successfully treated with anti-tuberculosis drugs association.

Another treatment reported for lymphadenopathy is fine needle

aspiration. A controlled randomized study comparing fine needle aspiration and no intervention in BCG lymphadenitis suggests the superiority of this procedure. However, 7.7% of children in the intervention group had lymph nodes aspirated more than once²⁶. In our study, the failure rate with isoniazid treatment was 4.2%. There are no studies comparing the isoniazid treatment with the fine needle aspiration.

Lymph node excision was performed in two patients due to isoniazid failure. Excision proved to be a useful intervention in this group. No surgical complications were observed.

An unexpected finding was that almost 12% of our patients presented atypical BCG-AE. In the literature, there are uncommon cutaneous complications after BCG, including foreign body granuloma caused by monosodium glutamate, delayed granuloma formation, sarcoidosis, BCG scar reactivation and others^{27,28,29}.

BCG scar reactivation has been associated with Kawasaki disease³⁰. Our study describes the BCG scar reactivation after exantema subitum and influenza vaccine, suggesting that other non-specific stimuli might trigger the BCG reactivation³¹. No patients presented clinical signs suggestive of Kawasaki syndrome in this study.

BCG reactivation can also be a result of an immunosuppressive status⁶. Two patients in our study presented with BCG scar reactivation after liver transplantation. Studies are needed to define the best management in this specific group.

In our study, we classified as wart-like lesion a painless solid raised lesion sometimes covered with a crust. Unfortunately, no histopathological assessment could be performed for better characterization. Five out of seven patients with wart-like lesions healed without treatment or after less than one month of isoniazid, suggesting that this is a benign cutaneous reaction.

BCG-Moreau *Rio de Janeiro* strain is used in Brazil to vaccinate 3 million children annually and data on the management of these adverse events contribute to public vaccination programs¹⁵. This study analyzed a homogeneous group of patients with localized BCG-AE after vaccination in their first month of life. It was conducted in a setting with low HIV infection rate. Patients were classified and treated with the standard protocol and were followed-up by the same investigator. This gives credibility to our findings for similar scenarios, although it may not represent the behavior of other BCG strains.

Randomized controlled studies are needed to compare the natural course of BCG-AE and the benefits of different modalities of treatment according to the sensitivity profile of the BCG strains. The occurrence of primary immune deficiency among patients with localized BCG-AE should also be assessed in future studies as these conditions cannot be completely ruled out in our follow-up.

In conclusion, localized BCG adverse events caused by Moreau *Rio de Janeiro* strain have a high cure rate when treated with a short course of isoniazid. Treatment failure is uncommon, and in these situations antibiotic resistance or other differential diagnoses should be considered. Atypical BCG-AEs are not infrequent and should be approached individually.

ACKNOWLEDGEMENTS

We thank the Department of Surveillance in Health (*Coordenação de Vigilância em Saúde - COVISA*) of São Paulo city and the São Paulo State Immunization Program (*Programa Estadual de Imunizações - SP*) for collaborate in this research.

This study was funded by the *Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP)*, Brazil, process number 11/21754-8.

REFERENCES

1. Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PE, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. *Clin Infect Dis*. 2014;58:470-80.
2. Kolibab K, Derrick SC, Morris SL. Sensitivity to isoniazid of Mycobacterium bovis BCG strains and BCG disseminated disease isolates. *J Clin Microbiol*. 2011;49:2380-1.
3. Ritz N, Curtis N. Mapping the global use of different BCG vaccine strains. *Tuberculosis (Edinb)*. 2009;89:248-51.
4. World Health Organization. Global Vaccine Safety. WHO vaccine reaction rates information sheets. [cited 2012 Dec 12]. Available from: http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html
5. 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*. 1988;63:47-59.
6. Hesseling AC, Rabie H, Marais BJ, Manders M, Lips M, Schaaf HS, et al. Bacille Calmette-Guérin vaccine-induced disease in HIV-infected and HIV-uninfected children. *Clin Infect Dis*. 2006;42:548-58.
7. Mazzucchelli JT, Bonfim C, Castro GG, Condino-Neto AA, Costa NM, Cunha L, et al. Severe combined immunodeficiency in Brazil: management, prognosis and BCG-associated complications. *J Invest Allergol Clin Immunol*. 2014;24:184-91.
8. Norouzi S, Aghamohammadi A, Mamishi S, Rosenzweig SD, Rezaei N. Bacillus Calmette-Guérin (BCG) complications associated with primary immunodeficiency diseases. *J Infect*. 2012;64:543-54.
9. Global Advisory Committee on Vaccine Safety, 3-4 December 2009. *Weekly Epidemiol Rec*. 2010;85:29-36.
10. Cuello-García CA, Pérez-Gaxiola G, Jiménez Gutiérrez C. Treating BCG-induced disease in children. *Cochrane Database Syst Rev*. 2013;CD008300.
11. Bernatowska EA, Wolska-Kusnierz B, Pac M, Kurenko-Deptuch M, Zwolska Z, Casanova JL, et al. Disseminated bacillus Calmette-Guérin infection and immunodeficiency. *Emerg Infect Dis*. 2007;13:799-801.
12. Marciano BE, Huang CY, Joshi G, Rezaei N, Carvalho BC, Allwood Z, et al. BCG vaccination in patients with severe combined immunodeficiency: complications, risks, and vaccination policies. *J Allergy Clin Immunol*. 2014;133:1134-41.
13. Brasil. Ministério da Saúde. Calendário nacional de vacinação. [cited 2014 Jun]. Available from: <http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/leia-mais-o-ministerio/197-secretaria-svs/13600-calendario-nacional-de-vacinacao>.
14. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Programa Nacional de Imunização. Manual de vigilância epidemiológica de eventos adversos pós-vacinação. 2ª ed. Brasília: Ministério da Saúde; 2008. [cited 2014 Jun]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/manual_pos_vacinacao.pdf

15. Brasil. Ministério da Saúde. DATASUS. Imunizações - Doses aplicadas - Brasil. [cited 2014 Jun]. Available from: <http://tabnet.datasus.gov.br/cgi/tabcgi.exe?pn/cnv/dpniuf.def>
16. Dommergues MA, de La Rocque F, Guy C, Lécuyer A, Jacquet A, Guérin N, et al. Local and regional adverse reactions to BCG-SSI vaccination: results of a large community trial. *Vaccine.* 2009;27:6967-73.
17. Dourado I, Rios MH, Pereira SM, Cunha SS, Ichihara MY, Goes JC, et al. Rates of adverse reactions to first and second doses of BCG vaccination: results of a large community trial in Brazilian schoolchildren. *Int J Tuberc Lung Dis.* 2003;7:399-402.
18. de Souza GR, Sant'Anna CC, Lapa e Silva JR, Mano DB, Bethlem NM. Intradermal BCG vaccination complications – analysis of 51 cases. *Tubercle.* 1983;64:23-7.
19. World Health Organization. Born too soon: the global action report on preterm birth. Geneva: WHO; 2012. [cited 2016 Jun 21]. Available from: http://www.who.int/pmnch/media/news/2012/preterm_birth_report/en/
20. Ferrer AP, Sucupira AC, Grisi SJ. Causes of hospitalization among children ages zero to nine years old in the city of São Paulo, Brazil. *Clinics (Sao Paulo).* 2010;65:35-44.
21. Rabie H, Violarì A, Duong T, Madhi SA, Josipovic D, Innes S, et al. Early antiretroviral treatment reduces risk of bacille Calmette-Guérin immune reconstitution adenitis. *Int J Tuberc Lung Dis.* 2011;15:1194-200.
22. Deeks SL, Clark M, Scheifele DW, Law BJ, Dawar M, Ahmadipour N, et al. Serious adverse events associated with bacilli Calmette-Guérin vaccine in Canada. *Pediatr Infect Dis J.* 2005;24:538-41.
23. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Boletim Epidemiológico HIV-AIDS. 2013. [cited 2016 Jun 27]. Available from: <http://www.aids.gov.br/publicacao/2013/boletim-epidemiologico-aids-e-dst-2013>
24. Latin Society for Immunodeficiencies. LASID registry. [cited 2016 Jun 27]. Available from: http://www.lasid.org/index.php?option=com_content&view=article&id=91&Itemid=72&lang=en
25. Ramos D, Oliveira C, Fernandes R, Mação P, Januário G, Gata L, et al. BCG adenitis: a 6-year review. Poster session presented at: 33rd Annual Meeting of the European Society for Paediatric Infectious Diseases; 2015 May 12-16; Leipzig, Germany.
26. Banani SA, Alborzi A. Needle aspiration for suppurative post-BCG adenitis. *Arch Dis Child.* 1994;71:446-7.
27. Chiu YK, Huang CC, Jeng J, Shiea J, Chen WJ. Foreign body granuloma caused by monosodium glutamate after BCG vaccination. *J Am Acad Dermatol.* 2006;55 (Suppl 2):S1-5.
28. Keijsers RR, Bovenschen HJ, Seyger MM. Cutaneous complication after BCG vaccination: case report and review of the literature. *J Dermatolog Treat.* 2011;22:315-8.
29. Bellet JS, Prose NS. Skin complications of Bacillus Calmette-Guérin immunization. *Curr Opin Infect Dis.* 2005;18:97-100.
30. Sireci G, Dieli F, Salerno A. T cells recognize an immunodominant epitope of heat shock protein 65 in Kawasaki disease. *Mol Med.* 2000;6:581-90.
31. Kakisaka Y, Ohara T, Katayama S, Suzuki T, Sasai S, Hino-Fukuyo N, et al. Human herpes virus type 6 can cause skin lesions at the BCG inoculation site similar to Kawasaki Disease. *Tohoku J Exp Med.* 2012;228:35.

Received: 22 January 2016

Accepted: 27 May 2016