

The incidence of BCG Lymphadenitis in Iraq, 2015-2022

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Abstract

Background: BCG vaccine is the only licensed vaccine for tuberculosis (TB) prevention and has been widely administered in Iraq, with a coverage rate of 96% among one-year-olds. BCG lymphadenitis, a common complication, occurs in two forms: non-suppurative (self-limiting) and suppurative (with inflammation and pus). Despite its significance, no prior studies have examined its incidence in Iraq.

Objective: To describe the incidence and characteristics of BCG lymphadenitis in children (≤ 2 years) in Iraq from 2015 to 2022.

Patients and Methods: A descriptive cross-sectional study reviewed TB surveillance data from 2015-2022, analyzing demographic, diagnostic, and treatment outcomes of children diagnosed with BCG lymphadenitis. Data were presented as frequencies and percentages.

Results: Out of 344 cases, 64.5% were male, and the highest incidence was in 2018 (67 cases). Most cases were from Baghdad (35.2%). Diagnosis was bacteriologically confirmed in 51.2% of cases, with 80.8% achieving successful treatment outcomes. The overall incidence ranged from 1 to 6 per 100,000 vaccinated children, with a notable prevalence among total TB cases in 2021 (1.24%).

Conclusions:

The low incidence of BCG lymphadenitis in Iraq may be attributed to the vaccine strain (Tokyo 172), experienced vaccinators, and proper handling. Recommendations include improving side-effect reporting systems and involving private healthcare in surveillance.

Keywords: BCG vaccine, lymphadenitis, tuberculosis, Iraq, incidence, pediatric.

Introduction:

Bacille Calmette-Guérin (BCG) vaccine is the only licensed vaccine for prevention of TB disease. The BCG vaccine was developed almost 100 years ago. It is widely used and prevents severe forms of TB in children. ⁽¹⁾ According to WHO, BCG immunization coverage among 1-year-olds in Iraq is 96%. ⁽²⁾ BCG-related complications can be subdivided into local (vaccine area) or regional (adjacent lymph-node) vaccine-related complications referred to as BCGitis, versus distant (affecting one site) or disseminated (affecting > 1 site and/or blood) BCG infection, referred to as BCGosis. ⁽³⁾ As in all immunization programs, the adverse events following immunization with BCG vaccines should be monitored and recorded. The following events are important after BCG vaccination: injection site abscesses, BCG lymphadenitis, disseminated BCG diseases and osteitis/osteomyelitis. ⁽⁴⁾

BCG lymphadenitis is the most common complication of BCG vaccination. Two forms of BCG lymphadenitis can be recognized in its natural course—simple or non-suppurative lymphadenitis, which usually regresses spontaneously over a period of few weeks, and suppurative BCG lymphadenitis distinguished by the development of fluctuations in the swelling, with erythema and oedema of overlying skin. ⁽⁵⁾

BCG Lymphadenitis is more common in patients with genetic defects that impair their ability to fight mycobacterial infections which are referred to as inborn errors of immunity (IEIs), with the highest rates of complications in patients with Mendelian susceptibility to mycobacterial disease (MSMD). ⁽⁶⁾

Patients with isolated axillary (or supraclavicular/cervical) lymph node enlargement without fever or other constitutional symptoms within two years of BCG vaccination were clinically diagnosed with BCG lymphadenitis. Puncture of enlarged lymph nodes or acid-fast

stain of secretions is helpful in the diagnosis of BCG lymphadenitis. ⁽⁷⁾

In Iraq, it has been no previous study examining the incidence of BCG Lymphadenitis. In an Omani study, the most common complication of BCG-vaccine related complications was isolated BCG lymphadenitis which occurred in 85% of children. ⁽⁸⁾ In Saudi Arabia, the incidence of BCG lymphadenitis is 0.4-1 per 1,000 vaccinated children. ⁽⁹⁾ The incidence of BCG lymphadenitis in Singapore was reported to be 3.16 per 1000 vaccinees in 2011. ⁽¹⁰⁾ Another study in Denmark found that the risk of non-suppurative regional lymphadenitis was 6.1 per 1000 and suppurative lymphadenitis was 4.7 per 1000. ⁽¹¹⁾

The aim of the study is to analyze the incidence dynamics of BCG related lymphadenitis among children (age ≤ 2 years) in Iraq from 2015 to 2022.

This study included all children (age ≤ 2 years) who clinically and laboratory confirmed diagnosed BCG lymphadenitis from January 2015 to December 2022 from the Iraqi NTP database.

Justifications of the study:

- 1- No similar study in Iraq.
- 2- BCG related lymphadenitis is one of the most frequent complications of BCG vaccine.
- 3- Increased case notification of BCG lymphadenitis reported from Iraqi governorates.

Objectives of the study:

- 1- To describe patients' characteristics related to BCG lymphadenitis.
- 2- To determine the incidence of BCG lymphadenitis from the total BCG vaccinated children
- 3- To determine the proportion of BCG lymphadenitis from the total TB Children (<15y) patients.
- 4- To determine the proportion of BCG lymphadenitis from the total TB patients.

BCG vaccine reported by NTP during the period 2015-2022.

Patients and Methods of the study:

Study included all children less than 2 years reported with lymphadenitis as a complication of

The TB surveillance data for the years 2015 to 2022 were reviewed in National Tuberculosis Institute which is the hosting health facility for the of National Tuberculosis Program-Iraq.

A descriptive cross-sectional study, for data from TB surveillance data bank was reviewed for cases of BCG lymphadenitis.

Data Collection and Tools: Data from Excel spread sheets for our sample was reviewed, their characteristics were examined (Gender, referral site, residence area, Chest Symptoms, HIV Status, and outcome) and Method of diagnosis (clinically diagnosed or bacteriologically confirmed). Then we presented these data as frequencies, percentages using tables and graphs.

Results:

A total of 344 children who have BCG Lymphadenitis from 2015 to 2022 were enrolled in this study. Majority of them were Males (N=222, 64.53%). The Females were (N=122, 35.47%). The Highest number of cases were registered in 2018 (N=67), while the lowest were registered in 2017 (N=9).

When coming to Residence, most of the cases were found in Baghdad (N=121, 35.17%).

Northern area hosted the lowest number of cases (N=25, 7.27%). The Remaining cases reside in the Middle (N=51, 14.83%), Mid Euphrates (N=99, 28.78%) and Southern regions (N=48, 13.95%).

The Majority of the cases do not have chest symptoms (N=306, 88.95%). Only (N=38, 11.05%) have reported Chest symptoms.

According to the Method of Diagnosis, more than half of the cases were Bacteriologically Confirmed (N=176, 51.6%). The remaining were Clinically Diagnosed (N=168, 48.84%).

All of the cases (N=344, 100%) have Negative HIV.

Regarding the Referral Site, most of cases were referred from Private clinics (N=206, 59.88%). Small number were referred by Self (N=13, 3.78%). The Remaining (N=125, 36.34%) were referred by Public Sector.

As per Treatment Outcome, (N=278, 80.82%) of the cases have successful outcome. (N=3, 0.87%) die, (N=3, 0.87%) are lost to follow up and only (N=1, 0.29%) was transferred. The remaining cases (N=59, 17.15%) have no documented outcome (table 1).

Table 1. Distribution of the children with BCG Lymphadenitis according to socio-demographic characteristics from 2015 – 2022:

Year		2015	2016	2017	2018	2019	2020	2021	2022	Total (N)	Total (%)
Gender	M	9	12	6	47	32	41	41	34	222	64.53%
	F	12	9	3	20	26	11	24	17	122	35.47%
Residence	North	0	0	0	7	4	5	6	3	25	7.27%
	Middle	0	0	0	7	13	6	15	10	51	14.83%
	Baghdad	21	21	9	21	14	10	15	10	121	35.17%
	Mid Euphrates	0	0	0	17	20	20	19	23	99	28.78%
	South	0	0	0	15	7	11	10	5	48	13.95%
Chest Symptoms	Yes	1	0	0	7	8	6	10	6	38	11.05%
	No	20	21	9	60	50	46	55	45	306	88.95%
Method of Diagnosis	Bacteriologically Confirmed	8	12	7	28	32	31	32	26	176	51.16%
	Clinically Diagnosed	13	9	2	39	26	21	33	25	168	48.84%
HIV Status	Positive	0	0	0	0	0	0	0	0	0	0.00%
	Negative	21	21	9	67	58	52	65	51	344	100.00%
Referral Site	Self	2	3	0	5	2	1	0	0	13	3.78%

	Public	8	7	5	22	23	19	23	18	125	36.34%
	Private	11	11	4	40	33	32	42	33	206	59.88%
Treatment outcome	Successful	20	20	3	63	57	51	50	14	278	80.82%
	Death	1	0	0	0	1	0	1	0	3	0.87%
	Lost to follow up	0	0	0	3	0	0	0	0	3	0.87%
	Transfer	0	0	0	1	0	0	0	0	1	0.29%
	Other	0	1	6	0	0	1	14	37	59	17.15%

In 2015, 21 children develop BCG Lymphadenitis out of 897,811 Vaccinated Children (0.002%). In 2016, the number was also 21 out 878,585 (0.002%). In 2017, the lowest number was registered 9 out of 989,139 (0.001%). The Majority of cases were registered in 2018; 67 out

of 1,025,109 vaccinated children (0.007%). In 2019, 58 out of 1,061,257 (0.005%). In 2020, 52 out of 1,044,477 (0.005%). In 2021, 65 out of 1,036,584 (0.006%) and in 2022 the cases were 51 out of 1,046,337 vaccinated children (0.005%) as shown in table 2.

Table 2. Incidence of BCG Lymphadenitis among vaccinated children in Iraq 2015-2022:

Year	Total Vaccinated Children	Children develop BCG Lymphadenitis	Incidence (%)
2015	897,811	21	0.002%
2016	878,585	21	0.002%
2017	989,139	9	0.001%
2018	1,025,109	67	0.007%
2019	1,061,257	58	0.005%
2020	1,044,477	52	0.005%
2021	1,036,584	65	0.006%
2022	1,046,337	51	0.005%

In 2015, 21 Children developed BCG Lymphadenitis out of 7,245 TB patients (0.29%). In 2016, also 21 children registered out of 6,507 (0.32%). The lowest reported cases and prevalence were recorded in 2017; 9 out of 6,899 (0.13%). In 2018, highest number of cases recorded; 67 out of 6,369 (1.05%). In 2019, it was

58 out of 6,024 (0.96%). In 2020, 52 out of 4,474 (1.16%). The highest recorded prevalence was recorded in 2021, 65 cases out of 5,248 total cases (1.24%) and in 2022; 51 out of 6,125 (0.83%) were recorded as shown in table 3.

Table 3. Prevalence of BCG Lymphadenitis among Total TB patients in Iraq 2015 – 2022:

Year	Total TB Patients	Children develop BCG Lymphadenitis	Prevalence out of registered TB cases in Iraq (%)
2015	7,245	21	0.29%
2016	6,507	21	0.32%
2017	6,899	9	0.13%
2018	6,369	67	1.05%
2019	6,024	58	0.96%
2020	4,474	52	1.16%
2021	5,248	65	1.24%
2022	6,125	51	0.83%

In 2015, 21 Children developed BCG Lymphadenitis out of 576 total TB children patients (3.65%). In 2016, also 21 children registered out of 525 (4.00%). The lowest reported cases and prevalence were recorded in 2017; 9 out of 560 (1.61%). In 2018, highest number of cases recorded; 67 out of 547 (12.25%). In 2019, it was

58 out of 512 (11.33%). In 2020, 52 out of 342 (15.20%). The highest recorded prevalence was recorded in 2021, 65 cases out of 404 total cases (16.09%) and in 2022; 51 out of 431 (11.83%) were recorded as shown in table 4.

Table 4. Prevalence of BCG Lymphadenitis among Total TB in children (<15 y) in Iraq 2015- 2022

Year	Total TB in Children (<15y)	Children develop BCG Lymphadenitis	Prevalence out of all TB case among children <15 (%)
2015	576	21	3.65%
2016	525	21	4.00%
2017	560	9	1.61%
2018	547	67	12.25%
2019	512	58	11.33%
2020	342	52	15.20%
2021	404	65	16.09%
2022	431	51	11.83%

Discussion

BCG vaccination is overall safe and should be considered in the process of TB elimination. The incidence of BCG lymphadenitis is influenced by host and vaccine related factors. A number of factors such as the age of the child, the technique of vaccination, the BCG strain, the dose, potency, viability and immunogenicity of the vaccine, and prior exposure to mycobacterial antigens are

implicated in the pathogenesis of lymphadenitis.⁽¹²⁾

An Indian study demonstrated that one of commonest sites of involvement in patients presenting with BCG complications were lymph nodes, which is 93% of all other sites⁽¹³⁾. Similar to our study, lymphadenitis has been the most commonly reported BCG-related disease in many studies that included clinical and laboratory diagnosed cases.⁽¹⁴⁾⁽¹⁵⁾

Most of the studies found that males are most affected by BCG Lymphadenitis, Al Waili *et al* found that males were 73% ⁽⁸⁾, Soh *et al* saw that males were 61% and females were 39%. ⁽¹⁰⁾ A study by Hegde V and his colleagues demonstrated that male gender predominated in 75% of cases. ⁽¹²⁾ Also, Alfawaz *et al* showed that males who develop post BCG vaccine complications were more than Females ⁽¹⁶⁾. Yadav *et al* concluded that 68.9% of study's patients were males. ⁽¹³⁾ It may be related to genetic role in the development of this complication.

The Incidence of BCG Lymphadenitis in Iraq is between 1 to 6 per 100,000 vaccinated children as shown in results above. This incidence is approximate to some of the reviewed studies in the region and internationally. The general incidence of BCG lymphadenitis was 173 per 1,000,000 doses in Shanghai from 2010 to 2019. ⁽⁷⁾ Cuello-García *et al* found that vaccine-induced infection has occasionally been reported with an incidence of approximately 1:10,000–1:1,000,000 ⁽¹⁷⁾. Another study in Oman showed that the incidence rate varied from 0.0 to 14.5 cases per 100,000 (average 9.2 per 100,000) vaccinated neonates. ⁽¹⁴⁾

Our study showed that the bacteriologically-confirmed cases were more than a half. This is the opposite of what is found in a study in India in which MTBC was detected in lymph node excision biopsy/bronchoalveolar lavage/pus specimens in 47.7% of the cases. ⁽¹³⁾ This is probably because of different guidelines and

techniques used to diagnose the cases between countries.

As per outcome, our study showed more than 80% successful outcome, a result similar to many studies such as a Chinese study that showed recovery rate is about 94% in Shanghai ⁽⁷⁾. Also, high percentages of cases were ultimately recovered well in similar study. ⁽¹⁴⁾

In our study, there was no case of BCG Lymphadenitis reported in HIV-infected children, perhaps due to the implementation of antenatal screening programs and the low incidence of pediatric HIV in our country. A result also found in other studies. ⁽¹⁴⁾

Strengths of our study lie in being the first study to demonstrate the Incidence of BCG Lymphadenitis in Iraq while limitations of the Study are, Being a record-based study, incomplete and inaccurate data, clinical details, and some other details was noticed in some cases.

Conclusions

Low incidence of lymphadenitis in our study compared to regional and international studies, can be probably due to a low immunogenic vaccine (Tokyo 172 strain) the strain that used for years in Iraq, proper technique used in our facilities, highly experienced vaccinator and proper vaccine storage and handling available at our health institutions. So we recommend enhancing BCG side effects reporting system, for example including private health care sector in such reporting.

REFERENCES:

- (1) WHO. Global tuberculosis report 2023. WHO; 2023.
- (2) The Global Health Observatory [website]. Geneva: World Health Organization; 2023 ([https://www.who.int/data/gho/data/indicators/indicator-details/GHO/bcg-immunization-coverage-among-1-year-olds\(-\)](https://www.who.int/data/gho/data/indicators/indicator-details/GHO/bcg-immunization-coverage-among-1-year-olds(-))). Accessed on 21-01-2024.
- (3) Ying W, Sun J, Liu D, Hui X, Yu Y, Wang J, Wang X. Clinical characteristics and immunogenetics of BCGosis/BCGitis in Chinese children: a 6-year follow-up study. *PloS one*. 2014 Apr 10;9(4):e94485.
- (4) WHO. Recommendations to assure the quality, safety and efficacy of BCG vaccines,; 2013 ([https://cdn.who.int/media/docs/default-source/biologicals/vaccine-standardization/bcg-\(tuberculosis\)/trs-979-annex-3-bcg-vax.pdf](https://cdn.who.int/media/docs/default-source/biologicals/vaccine-standardization/bcg-(tuberculosis)/trs-979-annex-3-bcg-vax.pdf)). Accessed on 22-01-2024.
- (5) Goraya JS, Viridi VS. Bacille Calmette-Guérin lymphadenitis. *Postgrad Med J*.

- 2002 Jun;78(920):327-9. doi: 10.1136/pmj.78.920.327. PMID: 12151684; PMCID: PMC1742390.
- (6) Mahdavian SA, Fallahi M, Jamee M, Marjani M, Tabarsi P, Moniri A, *et al* Effective anti-mycobacterial treatment for BCG disease in patients with Mendelian Susceptibility to Mycobacterial Disease (MSMD): a case series. *Annals of Clinical Microbiology and Antimicrobials*. 2022 Mar 1;21(1):8.
- (7) Jing Wang, Feng Zhou, Ming-Bo Jiang, Zhen-hui Xu, Yi-hong Ni, Qiang-Song Wu. Epidemiological characteristics and trends of *Bacillus Calmette–Guérin* lymphadenitis in Shanghai, China from 2010 to 2019, *Human Vaccines & Immunotherapeutics*, 2022 18:1, DOI: 10.1080/21645515.2021.1938922
- (8) Al Waili B, Al Mufarajii N, Al Hashmi S, Al Ajmi A, Al Sukaiti N. *Bacillus Calmette–Guérin* vaccine-related complications in children in Oman. *Annals of Saudi Medicine*. 2021 Jan;41(1):24-30. DOI: 10.5144/0256-4947.2021.24
- (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. *European Review for Medical & Pharmacological Sciences*. 2016 Sep 1;20(17).
- (10) Soh SB, Han PY, Tam KT, Yung CF, Liew WK, Tan NW, *et al*. Investigations into an outbreak of suppurative lymphadenitis with BCG vaccine SSI® in Singapore. *Vaccine*. 2014 Oct 7;32(44):5809-15.
- (11) Nissen TN, Birk NM, Kjærgaard J, Thøstesen LM, Pihl GT, Hoffmann T, *et al*. Adverse reactions to the *Bacillus Calmette–Guérin* (BCG) vaccine in newborn infants—an evaluation of the Danish strain 1331 SSI in a randomized clinical trial. *Vaccine*. 2016 May 11;34(22):2477-82.
- (12) Hegde V. BCG lymphadenitis. *Journal of Evolution of Medical and Dental Sciences*. 2014 Aug 4;3(32):8782-6.
- (13) Yadav RM, Dalvi A, Gupta M, Bargir UA, Shabrish S, Aluri J, *et al*. Spectrum of inborn errors of immunity in a cohort of 90 patients presenting with complications to BCG vaccination in India. *Scandinavian Journal of Immunology*. 2021 May;93(5):e13010A.
- (14) Al Busaidi N, Kp P, Al-Jardani A, Al-Sukaiti N, Al Tamemi S, Al-Rawahi B, *et al*. The spectrum of bacille calmette–guérin diseases in children—a decade of data from neonatal vaccination settings. *Vaccines*. 2021 Feb 13;9(2):150.
- (15) 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.
- (16) Alfawaz TS, Alshehri M, Alshahrani D. BCG related complications: A single center, prospective observational study. *International Journal of Pediatrics and Adolescent Medicine*. 2015 Jun 1;2(2):75-8.
- (17) Cuello-García CA, Pérez-Gaxiola G, Gutiérrez CJ. Treating BCG-induced disease in children. *Cochrane Database of Systematic Reviews*. 2013(1).