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BCG vaccination is associated with decreased severity of tuberculosis in Pakistan

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ABSTRACT

Vaccination with Bacille Calmette–Guérin (BCG) is given at birth to protect against tuberculosis (TB) in Pakistan. The country ranks 6th amongst high-burden countries worldwide and has an incidence of 231/100,000 population. This was a cross-sectional multi-center hospital-based study. TB patients (n = 218) with pulmonary (PTB, n = 120) or extrapulmonary (ETB, 98) were recruited, and the presence of a BCG vaccination scar was documented. Cases were further classified into minimal, moderate and advanced PTB or less severe (L-ETB) or severe disseminated (D-ETB) disease. The association of age, gender and severity of TB infections with BCG vaccination of the individual TB cases was investigated.

No difference was found of the BCG vaccination status of PTB and ETB cases, or in relation to age or gender. Patients under 29 years of age comprised the largest group. There were more females with ETB than PTB. The largest group within ETB comprised those with tuberculous lymphadenitis (LNTB, 39%). A significantly greater number of LNTB cases had received BCG vaccinations than had those with pleural (unilateral) TB ($p = 0.004$), and tuberculous meningitis ($p = 0.027$) groups. Also, there were more immunized patients with pulmonary as compared with pleural disease ($p = 0.001$).

LNTB represents localized granulomatous disease and the observation of higher vaccination rates in this group suggests that BCG has protected against more severe forms of TB in this high-burden region.

Introduction

There were approximately 8.8 million cases of tuberculosis (TB) in 2010, mostly in the 22 high-burden countries where Pakistan ranks 6th with 34/100,000 deaths reported as a result of TB in 2011 and with an incidence of 231/100,000 [1]. Pakistan has a low incidence of HIV infection, and the incidence rate of TB in HIV-positive individuals is less than 1% [1]. In Pakistan, 82% of all TB cases are listed as pulmonary (PTB) with 18% as extrapulmonary (ETB) disease [1].

Vaccination with *Mycobacterium bovis* Bacille Calmette–Guérin (BCG) strain affords protection against TB in children, especially against the development of severe forms, such as, miliary TB and tuberculous meningitis [2–4]. In adults, BCG vaccination is thought to reduce the risk of TB, but there are

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variable reports as to its effectiveness in different populations [5,6].

The BCG vaccination program was initiated in Pakistan in 1949 [7]. BCG is administered at birth or in the first month after birth and has been part of the Extended Program of Immunization (EPI) program since 1970 [8,9]. BCG coverage is estimated to vary between 63% and 86% in children aged 12–23 months depending on the provincial region of their residence [10]. A national health survey of Pakistan revealed that only 21% of mothers were able to locate the vaccination cards of their children aged less than 23 months [10]. Due to limitations in obtaining physical records of vaccination records amongst participants, assessment of prior vaccination has in most cases been based on the evaluation of a BCG scar and on verbal examination.

There is limited data as to the rates of TB in vaccinated and unvaccinated children and adults in Pakistan. A study of 100 cases of TB in children under 15 years of age showed that the majority were vaccinated (76%); however, amongst abdominal TB cases, there was a larger proportion of unvaccinated as compared with vaccinated individuals suggesting that vaccination may have some beneficial effect in protection against disseminated extrapulmonary TB [11]. In another study, in 100 pediatric cases of tuberculous meningitis, it was observed that the majority of patients were vaccinated; however, there was a greater preponderance of tuberculomas amongst children who had not received the BCG vaccination [12]. In a recent study of 1000 cases of adult pulmonary TB, the rates of BCG vaccination were found to be 41% [13]. Thus far, no study has addressed the rates of BCG vaccination in Pakistani adults with respect to the severity of disease. This study investigated the association between the BCG vaccination in adult patients with pulmonary and extrapulmonary TB in relation to the severity of disease in each group.

Materials and methods

Study subjects

This was a cross-sectional observational study conducted between the period 2005 and 2009. The study was approved by the Ethical Review committees of The Aga Khan University Hospital and OJHA Institute for Chest Diseases, DOW University for Health Sciences, Karachi. Written informed consent was taken from each patient. A total of 218 patients were recruited from The Aga Khan University Hospital; Indus Hospital; OJHA Institute for Chest Diseases; DUHS University of Health Sciences; and the Orangi Urban Health Center, Karachi. A clinical history was taken from the patients, and those with chronic viral diseases such as hepatitis virus B and hepatitis virus C were excluded from the study. None of the patients had any history of human immunodeficiency virus (HIV) infection. Inclusion criteria were: patients with a confirmed TB diagnosis who had not received anti-tuberculous therapy (ATT); male or female; unrelated study subjects. Exclusion criteria were: pregnancy; co-morbid conditions compromising the immune system (such as diabetes mellitus, chronic renal failure, chronic liver disease or corticosteroid therapy) and patients with relapsed TB. Patients were aged 15 years and above except for two patients who were 13 years and three who were 14 years of age.

Patients were classified as pulmonary TB (PTB) or extrapulmonary TB (ETB) as per WHO guidelines for treatment of TB [14]. PTB patients were diagnosed by clinical examination, chest X-ray, sputum acid-fast bacillus (AFB) microscopy and/or AFB culture. Severity of PTB was classified as moderately advanced (PTB-mod) or far advanced (PTB-adv) PTB using a modified classification of the National Tuberculosis Association of the USA based on extent of lung tissue involvement [15]. Severity of ETB was assessed by WHO guidelines for clinical management of TB [14], according to which cases with tuberculous lymphadenopathy and unilateral pleural effusion were classified as less-severe ETB (L-ETB) and spinal, abdominal, ovarian and bilateral pleural effusion TB were classified as severe disseminated ETB (D-ETB). The diagnostic criteria used for each patient are provided in Table 1.

BCG strain

The Danish BCG strain 1331 (Copenhagen, State Serum Institute) was used in Pakistan up until the year 2007 [9]; therefore, this is the vaccine that would have been used for the study participants who were all born prior to this date.

Evaluation of BCG scar

The presence or absence of the vaccination was evaluated using the presence of a scar as proxy for BCG vaccination. The presence of a BCG scar was examined in the deltoid region. A verbal history regarding vaccination was taken from the patients.

Statistical analysis

The presence or absence of a BCG scar in patient cases was compared using a Chi-squared analysis. p values $\leqslant 0.05$ were considered to indicate significant differences between groups. A statistical analysis was performed using the Social Sciences Software Package version 11.0, USA.

Results

Study population

The presence of a BCG vaccination scar was investigated in 218 TB patients comprising 120 cases of PTB and 98 cases of ETB. The diagnostic criteria used to identify TB in each case are listed in Table 1.

The number of male and female patients with PTB and ETB were compared using Chi-squared analysis. It was found and it was observed that in the ETB group there were more females than males ($p = 0.043$) (Table 2). While in the cases of PTB, the proportion of each gender was comparable.

When rates of vaccination were compared between subjects with PTB and ETB, they were found to be approximately similar. Also, the proportion of vaccinated males and females in PTB and ETB cases were similar.

Table 1 – Diagnostic criteria for tuberculosis patients in the study.

Site	*n*	Abscess	Microscopy	Radiology	AFBC	Histopathology
PTB	120		54/66	120/120	22/28	11/14
L-ETB						
LNTB	38	1	4/10	7/29	3/9	34/34
Unilateral pleural	19		4/4	16/17	4/4	2/2
D-ETB						
Spine	14	9	1/3	7/8	3/5	4/4
Abdominal	9		2/4	3/4	1/3	3/3
Meninges	10		2/3	5/5	2/5	2/2
Miliary	3		1/1	3/3	N/A	1/1
Ovarian	2		N/A	1/1	1/2	1/2
Bilateral pleural	2		1/1	2/2	1/1	1/1
Vulval	1		N/A	N/A	N/A	1/1

In each case, the numbers denote the number tested positive out of the total tested in each category. PTB, pulmonary TB; L-ETB, less severe extrapulmonary TB; LNTB, tuberculous lymphadenitis; D-ETB, severe disseminated ETB.
Microscopy indicates the number of acid fast bacilli smear-positive cases; AFBC, AFB culture-positive cases; Histopathology, indicates those cases where histological staining revealed granulomatous lesions suggestive of *M. tuberculosis* infection; Radiology, indicates cases which showed a chest X-ray predictive of TB.

Table 2 – Demographic characteristics of tuberculosis patients.

Characteristic	TB patients *n* (% of 218)	PTB *n* (% of 120)	ETB *n* (% of 98)	*p*-Value
Gender				
Male	101 (46.3)	63 (52.5)	38 (38.7)	0.043*
Female	117(53.6)	57 (47.5)	60 (61.2)	
BCG scar (all cases)				
Yes	112 (51.4)	56 (46.6)	56 (57.1)	0.124
BCG scar (male)				
Yes	47 (21.5)	27 (22.5)	20 (20.4)	0.34
Age mean(±SD)	33.4(±16.2)	32.7(±15.7)	34(±16.7)	0.373
Age groups				
13–29	122 (55.9)	69(57.5)	53(54.1)	0.68
30–44	39 (17.8)	19(15.8)	20(20.4)	
⩾45	57 (26.1)	32(26.6)	25(25.5)	
Contact exposure				
Yes	74 (33.9)	40 (33.3)	34 (34.7)	0.871
Previous history of TB				
Yes	17 (7.8)	12 (10)	5 (95.1)	0.153

A significant difference between groups is indicated by '*' using Chi-squared test analysis.

Relationship of BCG vaccination with age and gender of patients with tuberculosis

When stratified into different age groups, it was observed that the patients were predominantly in the youngest age group of 13–29 years. Overall, TB patients had a median age of 33.4 years and 51% of them had received the BCG vaccination (Table 2). Next, the BCG vaccination was assessed in patients stratified into different age groups. It was observed that there were a higher number of BCG vaccines in the 30–44 year age group as compared with those who were aged 13–29 years, ($p = 0.037$, Fig. 1).

When gender differences were considered, it was observed that the numbers of male and female TB patients in each of the three age groups was comparable (data not shown). There was no difference between the numbers of males and females who had received BCG vaccinations across the age groups studied (data not shown).

Relationship of BCG vaccination with disease site and severity of TB

In order to examine the relationship between the severity of pulmonary and extrapulmonary disease and the BCG vaccination status of the patients, each group was studied separately and divided based on the clinical severity of TB. PTB was classified into minimal, moderate and advanced disease. No differences were observed between the proportions of vaccinated individuals with any of these PTB sub-groups (Table 3). ETB patients were classified into less severe localized

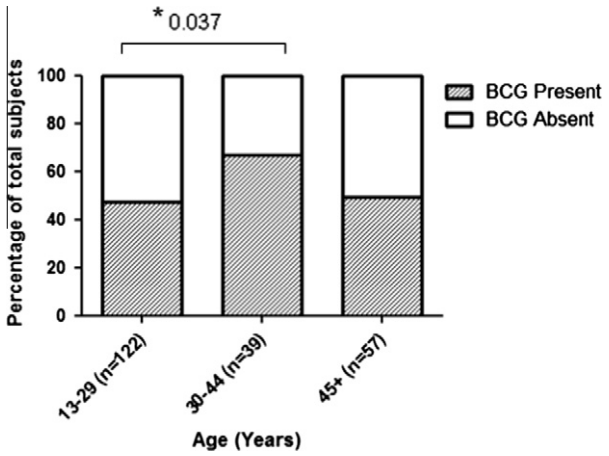

Fig. 1 – Frequency of BCG vaccination according to age of patients. The graphs depict the percentage of patients with tuberculosis who had a BCG scar (present, shaded bar) and in those individuals where there was no BCG scar (absent, clear bar) according to the different age groups of patients; $n = 122$, aged 13–29 years; $n = 39$, aged 30–44 years and $n = 57$, aged 45 years and over. '*' denotes a significantly higher value $p \leqslant 0.05$ between vaccinated individuals in the groups as analyzed by Chi squared test.

ETB (L-ETB) or severe disseminated ETB (D-ETB). L-ETB cases comprised a majority of patients with tuberculous lymphadenitis (LNTB) and unilateral-pleural TB. Overall, LNTB cases comprised 38.8% of all TB cases and 67% of L-ETB cases.

When gender was considered, the number of males and females in the L-ETB and D-ETB group was found to be comparable (Table 3). However, the number of female patients with D-ETB ($n = 27$) was approximately twice the number of male patients in the group ($n = 14$).

This study also investigated the possibility of any relationship between gender and vaccination in the sub-groups of TB patients and found no such correlation. It was observed that there was no gender difference amongst the TB cases as to who had received BCG vaccination.

The number of individuals with BCG scars within each class of TB patients was further compared. A significantly greater proportion of patients with PTB were vaccinated as compared with those who had pleural TB ($p = 0.001$). Also, a greater proportion of individuals with BCG scars were observed in the LNTB group as compared with those with pleural TB ($p = 0.004$) and D-ETB ($p = 0.012$) (Fig. 2).

Within the D-ETB group, the numbers of patients with TB at different sites were too few to be analyzed separately and were therefore pooled for further comparisons.

Discussion

In this study, it was observed that 41% of adults had received the BCG vaccination as assessed by the presence of a BCG scar. This proportion matches the percentage of 41% BCG vaccination in adults observed in another recent study from Pakistan [16].

The highest number of TB patients were aged 13–29 years and there was an equivalent number of vaccinated and unvaccinated individuals in this group, which may correlate with the 50% or so rates of BCG protection that have been shown in meta-analyses of vaccination studies [5]. It was observed that there was a higher proportion of vaccinated than unvaccinated individuals in groups aged 30–44 years as compared with the former age group. There is no discernible

Table 3 – BCG vaccination characteristics according to site of TB in patients.

Site of TB	Severity	*n* (%)	BCG scar present *n* (%)	*p* Value	Male, female *n*	BCG scar present		*p* Value
						Male *n* (%)	Female *n* (%)	
Pulmonary		103 (51.2)	56 (54.4)	0.084	56, 47	26 (46.2)	29 (61.7)	NS
	Minimal	15 (14.6)	5 (33.3)		7, 8	2 (28.6)	3 (37.5)	NS
	Moderate	65 (63.1)	37 (56.9)		36, 29	18 (50)	18 (62.1)	NS
	Advanced	23 (22.3)	8 (34.8)		13, 10	4 (30.8)	4 (40)	NS
Extrapulmonary		98 (48.8)	56 (57.1)		38, 60	20 (20.4)	36 (36.7)	NS
L-ETB		57 (58.2)	36 (63.2)		24, 33	13 (54.2)	23 (69.6)	NS
	Pleural (unilateral)	19 (19.4)	7 (36.8)	0.004*	12, 7	5 (41.7)	2 (28.6)	NS
	Lymph Node	38 (38.8)	29 (76.3)		12, 26	8 (66.6)	21 (80.8)	NS
D-ETB		41 (41.8)	20 (48.8)		14, 27	7 (50)	13 (48.1)	NS
	Abdominal	9 (9.2)	5 (55.5)		4, 5	2 (50)	3 (60)	NS
	Meningitis	10 (10.2)	4 (40)		6, 4	3 (50)	1 (25)	NS
	Spinal	14 (14.3)	7 (50)		2, 12	2 (100)	5 (41.7)	NS
	Miliary	3 (301)	1 (33.3)		2, 1	0	1 (100)	NS
	Pleural (bilateral)	2 (2.0)	1 (50)		0, 2	0	1 (50)	NS
	Vulval	1 (1.0)	1 (100)		0, 1	0	1 (100)	NS
	Ovarian	2 (2.0)	1 (50)		0, 2	0	1 (50)	NS

Information regarding extent of disease was not available for 17 PTB cases and these have been excluded from this table.
L-ETB, less severe extrapulmonary TB; D-ETB, severe disseminated extrapulmonary TB. The presence of a BCG scar between pulmonary and extrapulmonary groups was compared using Chi squared analysis. A significant difference between groups is indicated by '*', or $p > 0.05$ between groups using Chi-squared test analysis. NS; indicates no significant difference.

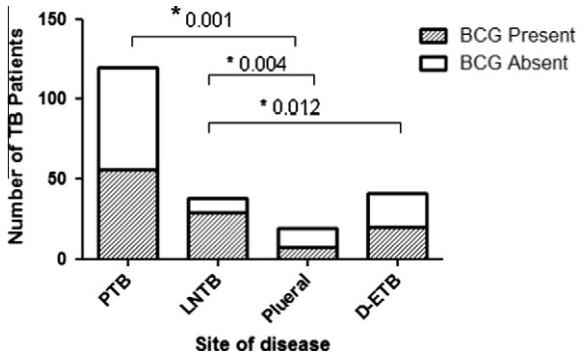

Fig. 2 – A larger proportion of patients with TB lymphadenitis have received BCG vaccination. The graphs depict the number of individuals where BCG scar was present (shaded bar) and those where it was absent (clear bar) according to the site of TB. PTB (n = 120), lymph node TB (LNTB, n = 38), pleural n = 19 and severe disseminated ETB (D-ETB, n = 41) cases. '*' denotes a significant difference $p < 0.05$ between the group as compared with LNTB. All analyses were performed by Chi squared test analysis.

explanation for this observation except that it is notable that the latter age group received the BCG vaccination during the initiation phase of the EPI program in Pakistan in the 1970s [8,9]. The patients were recruited from a private hospital (AKU), a government-run hospital (OJHA) and a not-for-profit charity hospital (Indus), so there should be no demographic bias within the cases selected. Perhaps the difference between groups could be attributed to the different sizes of the groups as there were 122 patients in the <29 year age group and 39 patients in the 30–44 year age group.

It was noted that while there was no gender difference in the number of patients with pulmonary disease, there were more females than males with extrapulmonary TB. Particularly, that in the D-ETB group there were twice as many females as male TB cases.

There was no difference found in the numbers of vaccinated and unvaccinated individuals with pulmonary disease. This correlates with previous reports that have shown that being BCG vaccinated is not associated with protection against pulmonary disease [3,17,18]. No difference was found in the numbers of individuals vaccinated based on their gender. The higher rates of pulmonary as compared with extrapulmonary TB fit with global trends [19]. It is thought that the BCG vaccination is most protective against severe disseminated tuberculosis and especially meningeal disease in childhood [2,20].

However, there is limited information regarding the severity of TB amongst being BCG vaccinated and unvaccinated individuals in adults. Amongst ETB patients, tuberculous lymphadenitis was found to be the most common form as has been reported previously [21,22]. Lymphadenitis is the most restricted form of TB as it comprises local granulomas with limited spread to other sites. Pleural disease although localized has a stronger pro-inflammatory profile and is likely to be clinically more acute [23]. The increased vaccination rate observed in patients with lymphadenitis as compared with pulmonary, pleural and severe disseminated ETB is suggestive of a protective effect of the BCG vaccination in this group.

Although BCG vaccination may itself result in mycobacterial disease, cases of BCG lymphadenitis occur within 24 months of vaccination [24]. As all the patients included in the cohort were vaccinated at birth, therefore association of lymphadenitis with BCG vaccination is unlikely.

This study has some limitations such that it relied upon the patient's own history for BCG vaccination and as such, some could not be recruited as they did not know their own vaccination status. In addition, the study relied upon the presence of a BCG vaccination scar as a proxy for vaccination. However, BCG scars may in some cases fade with time [25]. Also, as the persistence of scars has been shown to be lower in individuals who were vaccinated as infants under 1 month of age [26], therefore the rates of vaccination that were determined may be an underestimation of the study group.

Conclusions

Overall, the data of this study suggests that BCG vaccination may protect against more severe forms of TB and also lead to a preponderance of tuberculous lymphadenitis disease in a high-burden region.

Conflict of interest

None.

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