Preventing Leprosy: Epidemiological and immunological aspects of chemo- and immunoprophylaxis in leprosy patients' contacts

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CHAPTER 4

Clinical manifestations of leprosy after BCG vaccination: an observational study in Bangladesh

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Abstract

Background: Although BCG is used as a vaccine against tuberculosis, it also protects against leprosy. Previous evaluation over 18 years of an intervention of two doses BCG for 3536 household contacts of leprosy patients showed that 28 (23%) out of 122 contacts diagnosed with leprosy, developed symptoms 2-10 months after vaccination. This study describes contacts of leprosy patients in Bangladesh who developed leprosy within 12 weeks after receiving a single BCG dose.

Methods: A cluster RCT in Bangladesh aims to study the effectiveness of the BCG vaccine versus BCG in combination with single dose rifampicin (SDR) given 2 to 3 months after BCG, in the prevention of leprosy among contacts of newly diagnosed leprosy patients. During the first 1,5 years of this ongoing trial we identified contacts who developed leprosy within the first 12 weeks after receiving BCG vaccination, the timeframe before SDR is given.

Results: We identified 21 contacts who developed leprosy within 12 weeks after BCG vaccination among 5,196 vaccinated contacts (0.40%). All 21 cases presented with paucibacillary (PB) leprosy, including children and adults. About half of these cases had previously received BCG vaccination as indicated by the presence of a BCG scar; 43% presented with signs of nerve function impairment and/or Type 1 (reversal) reaction, and 56% of the index patients had multibacillary (MB) leprosy.

Conclusion: An unexpectedly high proportion of healthy contacts of leprosy patients presented with PB leprosy within 12 weeks after receiving BCG vaccination, possibly as a result of boosted cell-mediated immunity by homologues of *M. leprae* antigens in BCG. Various immunological mechanisms could underlie this phenomenon, including an immune reconstitution inflammatory syndrome (IRIS). Further studies are required to determine whether BCG vaccination merely altered the incubation period or actually changed the course of the infection from self-limiting, subclinical infection to manifest disease.

Key words: leprosy, BCG, contacts, *M. leprae,* prevention, prophylaxis

Introduction

Mycobacterium bovis Bacillus Calmette-Guérin (BCG) remains the only available vaccine against tuberculosis (TB) today. It is routinely administered to infants in many countries worldwide and confers significant protection against severe forms of TB, mostly miliary and meningeal in young infants. BCG-induced immunity has been shown to decline with time and is generally thought to last no more than 10-15 years, differs between ages and endemic areas, and offers poor protection against contagious pulmonary TB in adulthood [1-4].

Despite being known primarily as a vaccine against TB, BCG also protects against leprosy (caused by *Mycobacterium leprae*), especially when given to household contacts of leprosy patients [5 6]. In fact, to date, BCG has been shown to be the best available vaccine for prevention of leprosy, superior to other mycobacterium containing vaccines, including combination vaccines with BCG and *M. leprae* specific vaccines [7 8]. The rationale for the use of BCG as a vaccine against leprosy relies on the occurrence of many highly homologous antigens present in the *M. bovis* genome (the progenitor for the BCG vaccine) and the *M. leprae* and the *M. tuberculosis* genomes [9 10], which induce cross-reactive, protective immune responses to *M. leprae* following BCG vaccination.

Because of BCG's protective effects against leprosy, Brazil has officially recommended BCG since the early 1970s for household contacts of leprosy cases, as a boost to routine BCG vaccination in new-borns as a TB prophylactic vaccine. Since 1991, the Brazilian Ministry of Health has advised two doses of BCG to be administered to both current household contacts and contacts of index cases who were diagnosed within the previous five years. This policy was assessed in a cohort study of 3536 contacts of 1,161 leprosy patients in Brazil [11], showing that the protection conferred by a booster BCG vaccination was 56% and was not substantially affected by previous BCG vaccination. Among the 122 new cases detected during 18 years of contact follow-up, leprosy was diagnosed in 28 of these contacts (23%) relatively soon after vaccination (2-10 months). Due to incomplete follow-up, the study needs to be interpreted with caution, and in particular the increased risk of tuberculoid leprosy in the first months after BCG vaccination needs further substantiation.

The COLEP study in Bangladesh showed that the use of a single dose of rifampicin (SDR) in contacts of newly diagnosed leprosy patients reduced the overall incidence of leprosy in the first two years by 57% [12]. Furthermore, this study showed that the effect of SDR depended on the BCG status of the contact: If the contact had received BCG vaccination as part of a childhood vaccination program (as established by the presence of a BCG-scar), the protective effect of SDR was 80% [13]. And if not, the protective effect of BCG alone was 57%.

In view of the above findings regarding BCG vaccine and SDR in contacts of leprosy patients, a cluster randomized controlled trial was initiated in Bangladesh in 2012 with the aim to study the effectiveness of the BCG vaccine versus BCG in combination with SDR given 2 to 3 months after BCG, in the prevention of leprosy among contacts of newly diagnosed leprosy patients [14]. In this trial special attention is given to the occurrence of clinical manifestations of leprosy in the first 12 weeks after the contacts received BCG vaccination, the timeframe before SDR is given. Here we report the occurrence of 21 cases of leprosy (among 5,196 vaccinated contacts) during this first period after BCG vaccination and describe the characteristics of these patients and their disease symptoms. Furthermore, the possible underlying immunological mechanisms and implications for public health practice are discussed.

Methods

The study is part of the MALTALEP trial [14] that is currently conducted in the districts of Nilphamari, Rangpur, Thakurgaon and Panchagarh in northwest Bangladesh. Leprosy patients are recruited into the trial through the Rural Health Program (RHP) of The Leprosy Mission International Bangladesh (TLMIB), located in Nilphamari; a referral centre specialized in the detection and treatment of leprosy. The population of the four districts is around 7,000,000 (2011 census [15]) and approximately 600 new leprosy patients were detected per year between 2011 and 2013. The population in the four districts is mainly rural, but also includes six main towns.

The MALTALEP trial is a cluster randomized controlled trial. The aim is to study the effectiveness of the BCG vaccine alone versus BCG in combination with single-dose rifampicin (SDR) in the prevention of leprosy among contacts of newly diagnosed leprosy patients. Full details of the trial protocol were described previously (9). In summary, contact groups of approximately 15 persons are established for each of the 1,300 newly diagnosed leprosy patients (index cases) included in the trial, which will result in roughly 20,000 contacts in total. The contact groups are divided randomly over the two arms of the trial with approximately 10,000 contacts each. Contacts who have been diagnosed with leprosy in the past, are diagnosed at the intake examination (i.e. co-prevalent cases) or are clinically considered to be leprosy suspects at intake examination, are excluded from the trial. All contacts are screened by trained and experienced health workers at intake, to ensure they had no apparent signs of leprosy at the time of intake. After written informed consent was obtained, BCG was administered to all subjects (i.e. healthy contacts) followed by SDR 8-12 weeks later in the intervention group. Subsequent follow-up takes place one year and two years after intake. The primary outcome is the occurrence of clinical leprosy within two years of intake. Individuals who are suspected to have leprosy at any of the follow-up time points or who present to a health clinic between follow-ups are sent to the specialised leprosy hospital in Nilphamari or a local clinic for confirmation of their disease by a specialist clinician and for treatment. Intake for the trial was started in August 2012 and is expected to be completed in 2015.

In this paper we report on incidental observations during the ongoing trial of all new leprosy cases among healthy contacts who were diagnosed within 12 weeks after receiving BCG (and before receiving SDR) between December 2012 and May 2014. We present demographic and clinical data of the patients as recorded in our database as a routine procedure for the purpose of the trial.

Results

A total of 21 contacts (0.40%) were diagnosed with leprosy within 12 weeks after receiving BCG vaccination, out of 5,196 contacts who had received BCG and were screened after 8-12 weeks.

Table 1 shows the characteristics of the healthy contacts who developed leprosy within 12 weeks after BCG vaccination. Of these contacts, 10 (48%) were male and 11 (52%) female. Table 2 shows the characteristics of the contacts who received BCG vaccination but who did not develop leprosy. The differences between the groups do not show statistical significance (P>0.05) due to the low number of contacts with leprosy, but some of the observed group characteristics are worth noting. The male-female distribution is also nearly equal in this group (47% and 53%, respectively). The average age at registration was 29 years (range: 10 – 70 years) among the contacts who developed leprosy, and 28 years (range: 5 – 90 years) in the group of contacts who did not develop leprosy. There were 8 children (≥ 5 to < 16 years of age) who developed leprosy within 12 weeks after BCG vaccination, representing 38% of the new cases. Among the contacts who did not develop leprosy, 34% were children. Nine (43%) of the new patients were household contacts to the index patient, sharing either the same kitchen or roof, or both. The remaining 12 (57%) were direct neighbours of the index patient. In the group of contacts who did not develop leprosy, 31% were household contacts of the index patient, a lower proportion. Nine contacts who developed leprosy (43%) were known to be blood relatives to the index patient, 3 were other relatives (unclear if blood relative or not), or in-laws. In the group of contacts who did not develop leprosy, 25% were blood relatives to the index patient. Twelve (57%) contacts developing leprosy had probably received BCG for the first time or no sufficient response was induced upon initial vaccination, since no BCG scar was observed. The other 9 (43%) had a BCG scar and were thus revaccinated. In the group of contacts that did not develop leprosy, the proportion with a BCG scar was higher (56%). These differences are also apparent in the proportion of leprosy among household contacts (0.55%) and neighbours (0.34%), blood related (0.69%) and not blood related relatives (0.30%), and those with (0.31%) and without (0.53%) a BCG scar (Table 2).

The average time from BCG to first suspicion of leprosy by the field staff was 9 weeks (range: 3-11 weeks) (Table 1). Two of these contacts came to a clinic on their own initiative before the planned follow-up time, because they detected leprosy patches themselves (3 and 9 weeks after BCG). When asking the contacts how long after having received BCG the patch had appeared, 7 contacts could not provide a clear answer as to when they first discovered a patch or they had only noticed it at follow-up time point when the staff pointed it out. The remaining 14 recalled having first seen the patch between 2 and 11 weeks after receiving BCG, although few could recollect an accurate date.

Table 1. Characteristics of new cases of leprosy among contacts within 12 weeks of BCG vaccination.

Contact No.	Age	Sex	Blood relation to index*	Contact level**	BCG scar (Y/N)	Time from BCG to patient first noticing patch (in weeks)	Time from BCG to first suspicion of leprosy by clinician (in weeks)	Smear result (BI)	Classification (Ridley Jopling)	Nerve involvement (Y/N)	Reversal reaction (Y/N)
1	24	F	N	H	Y	Unknown	10	negative	TT	N	N
2	10	F	N+	N	Y	10	10	negative	TT	N	N
3	11	F	Y	H	N	Unknown	9	refused	BT	N	N
4	40	M	N	N	Y	Unknown	10	negative	BT	N	N
5	60	F	Y	N	N	Unknown	10	negative	BT	Y	N
6	70	M	N	N	N	2	10	negative	TT	N	N
7	12	F	Y	H	Y	7	9	refused	TT	N	N
8	40	F	N	N	N	10	10	negative	BT	N	N
9	55	M	Y	N	N	Unknown	9	negative	BT	Y	Y
10	34	M	Y	N	N	4	9	negative	BT	N	Y
11	12	F	N+	H	Y	Unknown	10	negative	BT	Y	N
12	35	F	Y	H	N	11	11	negative	TT	N	N
13	38	M	N	N	N	4	9	negative	BT	N	N
14	27	F	N	N	Y	4	9	negative	BT	N	Y
15	15	F	N	N	Y	2	9	negative	BT	Y	N
16	16	M	Y	H	Y	Unknown	9	negative	I	N	N
17	12	M	Y	H	Y	10	10	negative	I	N	N
18	12	M	N+	H	N	4	10	negative	I	N	N
19	12	M	N	N	N	4	10	negative	BT	Y	N
20	22	M	Y	H	N	3	3	negative	BT	Y	N
21	60	F	N	N	N	4	9	negative	TT	N	Y

*Blood related contact: child (son/daughter), parent (father/mother), brother or sister; +Other relative: unclear if blood related or not**H: household contact; sharing either the same roof or kitchen, or both; N: neighbour living next door to patient`s house.

Table 2. Characteristics of contacts with leprosy within 12 weeks after BCG vaccination, compared to those contacts who received BCG vaccination but who did not develop leprosy.

Contact characteristics	Contacts with leprosy		Contacts without leprosy		All contacts	Contacts with leprosy****
	N	% ***	N	%***	N	%***
Number	21	-	5175	-	5196	0.40%
Male	10	48%	2426	46.9%	2436	0.41%
Female	11	52%	2749	53.1%	2760	0.40%
< 16 years	8	38%	1742	33.7%	1750	0.46%
≥ 16 years	13	62%	3433	66.3%	3446	0.38%
Household contact*	9	43%	1620	31.3%	1629	0.55%
Neighbour**	12	57%	3555	68.7%	3567	0.34%
Blood related	9	43%	1301	25.1%	1310	0.69%
Not blood related or unknown	12	57%	3874	74.9%	3886	0.30%
BCG scar	9	43%	2906	56.2%	2915	0.31%
No BCG scar	12	57%	2269	43.8%	2281	0.53%
Average age at registration	29 years		28 years			

*Household contact: sharing either the same roof or kitchen, or both
**Neighbour next to patient
*** χ^2 test: none of the differences in percentages between the two groups are statistically significant (P>0.05)
****Contacts that developed leprosy in each subgroup as a percentage of the total number of contacts in the same subgroup

All contacts with leprosy were classified as paucibacillary (PB). According to the Ridley-Jopling classification [16], 6 (29%) contacts were classified as tuberculoid (TT), 12 (57%) as borderline tuberculoid (BT), and 3 (14%) as indeterminate (I). Six contacts (29%) presented with nerve involvement, but only one had disability (partial foot drop). This contact (#9 in Table 1) asserted that the foot drop was present before BCG vaccination, but it was not noted by the staff at contact registration time. Possibly he was a co-prevalent case incorrectly registered at intake. The fact that he did not recover on steroids indicates that it was possibly a late-stage nerve function impairment. All known skin smears were negative, two contacts refused skin smears (because of young age).

Of the 21 contacts who developed leprosy after BCG, 4 (19%) had Type 1 (or reversal) reaction requiring steroids on initial presentation, including the patient described above with neuritis and partial foot drop. Three other patients (14%) who had no nerve involvement presented with a red, hot, swollen, anaesthetic patch indicating a mild Type 1 reaction. One of these had a second episode of reaction during the study requiring steroids and responded well. In July 2014, 6 of the contacts completed multidrug therapy without having any signs of reaction. Others were still on treatment.

Table 3 shows the characteristics of the 18 index patients of the contacts diagnosed with leprosy in the first 12 weeks after BCG vaccination. In the case of two index patients, multiple contacts were found with leprosy within 12 weeks (2 and 3 contacts, respectively). Of the remaining 16 index patients each had one contact that developed leprosy. The average age at registration of the index patient was 33 years (of which 3 index cases were younger than 16 years). This resembles closely the average age (35 years) of all new patients that were registered by the Rural Health Program in 2013 (data not shown). Among the index patients 8 (44%) were male and 10 (56%) female. In the group of all patients registered in 2013, the percentage of males and females was nearly equal. Of 18 index patients, 8 (44%) were classified as PB and 10 (56%) as MB leprosy. In the group of all patients registered in 2013, these percentages were the other way around, 66% and 34% for PB and MB, respectively. According to the Ridley-Jopling classification, all index patients were BT, except for one borderline lepromatous (BL) and one lepromatous (LL) patient. The bacterial index (BI) for most index patients was negative except for the one BL patient with a BI of 4 and the LL patient with a BI of 6. One patient refused to have a smear taken. In the 16 index patients symptoms were detected at an average of 38 months before diagnosis (range 5 to 120 months). The duration of delay was 18 months (range 1 to 264 months) in the group of patients registered in 2013. At intake six contacts (other than the contacts who were found to have leprosy at 8-12 weeks after BCG) of four index cases gave a history of leprosy in the past, but no details were available. One family represented an exception to this finding: the father was a smear positive MB case who was released from treatment in 1985 and restarted MB-MDT in 2013, and thus probably was the primary source of infection. One of his sons was the index case at intake of the trial and one of the other sons developed leprosy within 12 weeks after BCG vaccination. In this family there were two more family members with a history of leprosy. The father is included in Table 3 as one of the 3 contacts ever found with leprosy.

Table 3. Characteristics of the index cases according to new cases found among healthy contacts (see Table 1 for serial number of the new cases).

Index patient No.	Contact patient No.	Sex	Age	Classification (PB/MB)	Classification (Ridley-Jopling)	Smear result (BI)	Duration of symptoms before diagnosis (in months)	No. of contacts found at intake who ever had leprosy	No. of co-prevalent cases (contacts found with leprosy at intake)
1	1	M	23	MB	BL	4	36	1	0
2	2	F	55	PB	BT	0	12	0	0
3	3	F	30	MB	BT	0	72	0	0
4	4	M	26	PB	BT	0	not available	0	0
5	5	F	13	PB	BT	0	12	0	0
6	6	M	29	PB	BT	0	12	0	0
7	7	F	16	PB	BT	not taken	24	1	0
8	8	M	19	PB	BT	0	24	1	0
9	9	M	61	MB	BT	0	36	0	0
10	10	M	27	MB	LL	6	12	0	0
11	11	F	50	MB	BT	0	84	0	0
12	12	M	9	MB	BT	0	5	0	0
13	13	F	45	MB	BT	0	84	0	0
	14								
	15								
14	16	M	27	MB	BT	0	12	0	0
15	17	F	65	PB	BT	0	12	0	0
	18								
16	19	F	51	MB	BT	0	120	0	0
17	20	F	11	MB	BT	0	not available	3	1
18	21	F	40	PB	BT	0	48	0	0

Discussion

We found that 21 out of 5,196 (0.4%) healthy contacts of newly diagnosed leprosy patients in the ongoing BCG intervention trial in Bangladesh developed clinical evidence of leprosy within 12 weeks after receiving BCG. All these 21 contacts presented with PB forms of leprosy (I, TT and BT), with a nearly equal number of males and females, and including both children and adults. Nearly half (43%) presented with signs of nerve function impairment and/or Type 1 reaction. Among the contacts with leprosy there was a high number with MB index cases (56%) and with a long average duration of symptoms before diagnosis, possibly indicating that these contacts experienced a high level of exposure over a long time.

The reported prevalence of leprosy in the four districts of northwest Bangladesh in 2013 was 0.74 per 10,000 population and the new case detection rate 0.84 per 10,000 (source: Rural Health Program). Considering the high prevalence of leprosy in this area, it is not surprising that there are many people with subclinical leprosy, some of whom may present clinical signs and symptoms for the first time after receiving BCG. Since all of these 21 cases were tuberculoid forms of leprosy, the increase of *M. leprae*-reactive cellular immunity may result from boosting of cell-mediated immunity by homologues *M. leprae* antigens present in BCG. Alternatively, BCG vaccination has been shown to induce epigenetic reprogramming of innate cells leading to increased cytokine production in response to related and nonrelated pathogens for up to 3 months after vaccination, a phenomenon called trained immunity [17].

Past studies have shown sporadically that BCG may induce clinical expression of leprosy skin lesions in the short term [18 19]. It fact, this phenomenon was discussed as early as 1960, when an editorial in the International Journal of Leprosy addressed 'BCG-induced activations' and referred to two case reports in the French literature in 1958 [18]. Data from the Karonga Prevention Trial between 1986 and 1989 in Malawi indicated that protection against leprosy is afforded by a repeated BCG vaccination, even during the first year after revaccination, but that the case series is too small to confirm early 'induction' of leprosy after BCG [20]. The main reason for paucity of information in literature about this issue is that most trials only include long-term follow-up, often starting 1 year after vaccination. Taking into account in particular the data described for BCG vaccination of contacts in Brazil [11], we anticipated a probable increase in new leprosy patients in the first year after BCG, although we had not expected this to occur as early (within 12 weeks) after BCG vaccination, as was observed in the current study. Düppre et al. [11] hypothesized that the accelerated manifestations of tuberculoid leprosy after BCG vaccination found in their study in Brazil, reflected the influence of BCG in catalyzing the existing anti-mycobacterial immunity in subjects infected with *M. leprae* before or

immediately after BCG vaccination. In line with the Brazilian study, we also found predominantly tuberculoid forms of leprosy. The incidence rate in the Brazilian study in the first year was higher among the contacts without a BCG scar than among those with a scar. We found a similar tendency in our study, although the difference was not very large. Finally, among the contacts who developed leprosy soon after BCG, there was a relative high number of contacts with manifestations of Type 1 reaction, which was not described in the Brazilian study.

Live vaccines, in particular BCG, have a nonspecific beneficial effect on overall mortality when administered early in life, more than can be explained by the targeted infection [21]. In fact children with a scar or a positive skin test resulting from BCG vaccination, exhibit an overall reduction in child mortality of around 50% [22]. In adults, immunization with BCG causes increased levels of pro-inflammatory cytokines TNF and IL-1β in response to BCG-related stimuli that is maintained for up to three months after vaccination [23]. The adaptive immune response after BCG vaccination is clearly Th1-skewed and results in *Mtb*- and *M. leprae*-specific, IFN-γ producing $CD4^+$ T cells that provide an early response to these mycobacteria and are associated with some degree of protection [24]. However, as is evident from several studies, the IFN-γ response induced by BCG vaccination does not correlate with protection [25-27]. In addition, Th17 helper cells producing IL-17 and IL-22 are produced as well which are beneficial for protection against pathogens at mucosal sites [28].

In 1989, Bagshawe et al. [29] also already hypothesized that prevailing immunity to mycobacterial antigens is largely responsible for clinical manifestations of PB leprosy and that the non-specific immune stimulation induced by BCG vaccination can precipitate clinical signs and symptoms of leprosy in people incubating the disease and cause upgrading of established lesions, especially in indeterminate or borderline leprosy. In the Karimui trial in Papua New Guinea [29], a 47% protection against clinical leprosy by BCG was demonstrated. However, they provided evidence for accelerated manifestation of tuberculoid leprosy in children vaccinated when under 5 years of age. In our study, children less than 5 years old were excluded, but we observed this phenomenon among all other ages.

Among the index cases in our study more than half had MB leprosy, with an average duration of symptoms before diagnosis of over three years, compared with 18 months in all newly registered leprosy patients in the Rural Health Program in 2013. We also found that in the group of 21 contacts that developed leprosy, a higher proportion were blood relative and/or a household contact of the index patient than in the group of contacts that did not develop leprosy. These factors represents a high level of exposure over a long duration and possibly increased susceptibility for leprosy, but definite conclusions on the relationship between level of exposure and chance of contacts to develop

leprosy soon after BCG vaccination cannot be drawn until the trial is completed and immunological and gene expression data are available.

Presentation of leprosy as part of an immune reconstitution inflammatory syndrome (IRIS) in HIV infected individuals or AIDS patients starting their highly antiretroviral active (HAART) therapy has been described [30 31]. Previously, Deps et al. [30] proposed the case definition for IRIS in leprosy as leprosy and/or Type 1 reaction and erythema nodosum leprosum (ENL or Type 2 reaction) developing within 6 months after initiation of HAART. They found that 89.5% of the leprosy/IRIS cases presented a histopathological diagnosis of TT or BT leprosy. The mean time until onset of IRIS after initiating HAART was 8.7 weeks. Fifty-seven percent of the leprosy patients presented within 8-12 weeks after initiating HAART [31]. Two main forms of leprosy as IRIS occurring in the first few months of HAART were identified [30]. The first type is an inflammatory 'unmasking' of a previously untreated *M. leprae* infection, the second (less commonly occurring) is a paradoxical clinical deterioration in pre-existing leprosy during which the patient developed HAART-associated Type 1 reaction. We propose that a comparable process leads to presentation of clinically apparent leprosy after BCG vaccination of contacts of leprosy patients.

In our trial we found an unexpectedly high proportion of new leprosy patients among apparently healthy household contacts of leprosy patients in the first 12 weeks after receiving BCG vaccination. When all follow-up data of the trial are available, we will compare PB/MB proportions in new cases arising among contacts at different time points after BCG vaccination and in a group without BCG vaccination. If a higher proportion of contacts present with PB leprosy in the first 12 weeks after BCG and later (in the following 1-2 years) a higher proportion of contacts present with MB leprosy, this would support the theory that BCG accelerates the immune response and reveals highly immunologically active forms of subclinical leprosy first. In fact BCG vaccination given to household contacts of leprosy patients could actually identify this important group, who will then receive proper treatment at an early stage. However this does not imply that BCG should be seen as a legitimate diagnostic test for pre-clinical leprosy. Further investigation including analysis of the cytokine/chemokine range induced after BCG vaccination [32], is necessary to understand this phenomenon. Differentiation of the patients through epidemiological and immunological studies will be undertaken, in order to carefully consider the implications of giving BCG vaccination to contacts of newly diagnosed leprosy patients as immunoprophylaxis as part of a leprosy control programme.

Ethical approval

The national Research Ethics Committee (Bangladesh Medical Research Council) has approved the study protocol (Ref no. BMRC/NREC/2010-2013/1534).

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Conflicts of interest

The authors declare that they have no conflict of interest.

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