Effectiveness of single-dose rifampicin after BCG vaccination to prevent leprosy in close contacts of patients with newly diagnosed leprosy: A cluster randomized controlled trial

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A R T I C L E   I N F O

A B S T R A C T

Objective: To assess the effectiveness of single-dose rifampicin (SDR) after bacillus Calmette–Guérin (BCG) vaccination in preventing leprosy in contacts.
Methods: This was a single-centre, cluster-randomized controlled trial at a leprosy control programme in northwest Bangladesh. Participants were the 14 988 contacts of 1552 new leprosy patients who were randomized into the SDR – arm ($n = 7379$) and the SDR + arm ($n = 7609$). In the intervention group, BCG vaccination was followed by SDR 8–12 weeks later. In the control group, BCG vaccination only was given. Follow-up was performed at 1 year and 2 years after intake. The main outcome measure was the occurrence of leprosy.
Results: The incidence rate per 10 000 person-years at risk was 44 in the SDR – arm and 31 in the SDR + arm at 1 year; the incidence rate was 34 in the SDR – arm and 41 in the SDR + arm at 2 years. There was a statistically non-significant ($p = 0.148$; 42%) reduction for paucibacillary (PB) leprosy in the SDR+ arm at 1 year. Of all new cases, 33.6% appeared within 8–12 weeks after BCG vaccination.
Conclusions: In the first year, SDR after BCG vaccination reduced the incidence of PB leprosy among contacts by 42%. This was a statistically non-significant reduction due to the limited number of cases after SDR was administered. To what extent SDR suppresses excess leprosy cases after BCG vaccination is difficult to establish because many cases appeared before the SDR intervention.
Trial registration: Netherlands Trial Register: NTR3087.

Introduction

The global number of new leprosy cases has remained stable over the last decade (Anonymous, 2017a), indicating that transmission of *Mycobacterium leprae*, the causative agent of leprosy, is ongoing in many endemic countries. The basic intervention in leprosy control is multidrug therapy (MDT), but this appears insufficient to decrease new cases numbers and achieve the World Health Organization (WHO) target of reducing the burden of leprosy (Anonymous, 2018).

Close contacts of untreated leprosy cases are exposed considerably to *M. leprae*. Age of the contact, bacterial load of the index patient, and close physical and genetic distance are independent risk factors for the development of leprosy (Moet et al., 2006). Household contacts of newly diagnosed patients have a 10-fold higher risk of developing leprosy compared with the general population (Moet et al., 2008a); for different categories of neighbours and social contacts, this is three- to five-fold higher (Moet et al., 2006; Moet et al., 2008a).

Many studies on immunoprophylaxis (vaccination) and chemoprophylaxis aimed at preventing leprosy have focused primarily on contacts of leprosy patients. Bacillus Calmette–Guérin (BCG) vaccination is known as a vaccine against tuberculosis (TB) and is

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routinely given to infants as part of the neonatal immunization scheme in many parts of the world. Moreover, BCG is also recognized as protecting against leprosy (Merle et al., 2010; Setia et al., 2006). Several vaccine trials using BCG have established its protective effect against leprosy, often in combination with *M. leprae* or related *Mycobacterium* vaccines (Merle et al., 2010; Fine and Ponnighaus, 1988; Coppola et al., 2018; Kumar, 2017; Sharma et al., 2005; Richardus and Oskam, 2015). Brazil has officially recommended BCG since the early 1970s for household contacts of leprosy cases, as a booster to routine neonatal BCG vaccination against TB. Since 1991, the Brazilian Ministry of Health has advised two doses of BCG to be administered to household contacts. This policy was assessed in a cohort study in Brazil (Duppre et al., 2008), and showed 56% protection by a booster BCG vaccination. The risk of tuberculoid leprosy during the initial months was high among BCG-vaccinated contacts. Due to incomplete follow-up, the increased risk of paucibacillary (PB) leprosy in the first months after BCG requires further substantiation.

Regarding chemoprophylaxis, a study in Bangladesh (the COLEP trial) showed that a single dose of rifampicin (SDR) in contacts of newly diagnosed leprosy patients reduced the overall incidence of leprosy in the first 2 years by 57% (Moet et al., 2008b). Furthermore, this study showed that the effect of SDR depended on the BCG status of the contact (Schuring et al., 2009): if the contact had received BCG vaccination as part of a childhood vaccination programme, the protective effect of SDR was 80%. Contacts who received SDR without prior BCG vaccination had a protective effect of 58%. Recently, the WHO has included SDR as a recommendation in its guidelines for the diagnosis, treatment and prevention of leprosy (Anonymous, 2017b).

Based on earlier studies investigating BCG vaccination and SDR chemoprophylaxis in the prevention of leprosy among contacts, a trial was initiated to assess the efficacy of a combined strategy (the MALTALEP trial). The main objective of this trial was to assess the effectiveness of SDR given after BCG vaccination in preventing leprosy in close contacts of patients with newly diagnosed leprosy. More specifically, the aim was to determine whether possible excess cases in the first year after immunoprophylaxis, as observed previously in Brazil (Duppre et al., 2008), could be prevented by chemoprophylaxis.

Materials and methods

Trial design

The intervention was a cluster randomized controlled trial with two treatment arms, to study the effectiveness of single-dose rifampicin (SDR + arm) given after BCG vaccination in the prevention of leprosy among contacts of newly diagnosed leprosy patients, versus BCG vaccine alone (SDR – arm) (Figure 1). During the initial contact survey, BCG was given to all eligible contacts, followed by chemoprophylaxis with SDR 8–12 weeks later in those contact groups randomized to receive this (FU1). Follow-up examinations were performed at 1 year (FU2) and 2 years (FU3) after receiving BCG. The three follow-up time points were used to investigate whether contacts had developed leprosy (primary outcome measure). Also, contacts were examined for adverse events at the different follow-up points. Due to operational difficulties caused by political instability in the country, it was not always possible to provide SDR exactly 8 weeks after BCG, so the range was broadened to 8–12 weeks after BCG.

Eligibility criteria for participants

Newly diagnosed leprosy patients were included who had been diagnosed with leprosy according to the Rural Health Program

(RHP) guidelines, which follow those of the National Leprosy Control Programme (Anonymous, 1998; Anonymous, 2006). The diagnosis of leprosy was made when at least one of the cardinal signs was present: one or more skin lesions consistent with leprosy and with definite sensory loss; thickened peripheral nerve(s); and a positive skin smear result for acid-fast bacilli. Patients with negative smear results and five or fewer skin lesions were grouped as PB leprosy, and those with positive smear results or more than five skin lesions were grouped as multibacillary (MB) leprosy, according to the WHO treatment criteria. MDT was started according to the national guidelines. Within 2 weeks after newly diagnosed leprosy patients had received the second dose of MDT (4 weeks after the first dose), a household survey was performed. Contact groups were formed of around 10–15 persons for each patient.

Exclusion criteria for patients and contacts are summarized in the previously published methodology article (Richardus et al., 2013). Only close contacts were included, i.e. household contacts and next-door neighbours. Contacts were categorized according to their physical and genetic distance to the index patient. For physical distance, four categories were defined based on the local housing situation: shares a house and kitchen, shares a kitchen only, shares a house but not a kitchen (together called household contacts), and next-door neighbours. For genetic distance, two groups were defined: blood-related (parent, child, or sibling) and not blood-related or unclear (all others). Written informed consent was obtained from all patients and their contacts. For those who were illiterate, a thumb print was obtained. For minors under 16 years of age, the guardian's additional consent was obtained.

Study setting

The study was performed in the districts of Nilphamari, Rangpur, Thakurgaon, and Panchagarh in the northwest of Bangladesh. Patients entered the trial through the RHP of The Leprosy Mission International, Bangladesh (TLMI,B), based at the DBLM Hospital in Nilphamari, a referral hospital specialized in the detection and treatment of leprosy. The population of the four districts at the start of intake was around 7 000 000, and 800–900 new leprosy patients were detected per year (Anonymous, 2011). The prevalence rate of HIV in adults aged 15 to 49 years in Bangladesh in 2018 was <0.1 (UNAIDS).

Interventions

The BCG vaccine was applied by trained research assistants to all included contacts (0.1 ml of BCG vaccine by intradermal injection). Two different BCG strains were used in the trial (and in routine neonatal vaccination in Bangladesh). The Indian vaccine was used between 2011 and 2015 (Moscow strain 361) and the Japanese vaccine in 2016 and 2017 (Tokyo strain 172). These are freeze-dried glutamate BCG vaccines composed of 0.5 mg/ampoule live bacteria of Calmette–Guérin (as approximately 70% moist bacteria) and 2.0 mg/ampoule sodium glutamate (as a stabilizer). The BCG vaccine was stored at the Government Immunisation Programme facilities.

Rifampicin comes in capsules of 150 mg, and the dosage used was the same as that recommended in the guidelines of the National Leprosy Control Programme of Bangladesh and the RHP (Table 1).

Outcomes

The primary outcome measure was the number of new leprosy patients emerging from the contact groups. The proportions of new
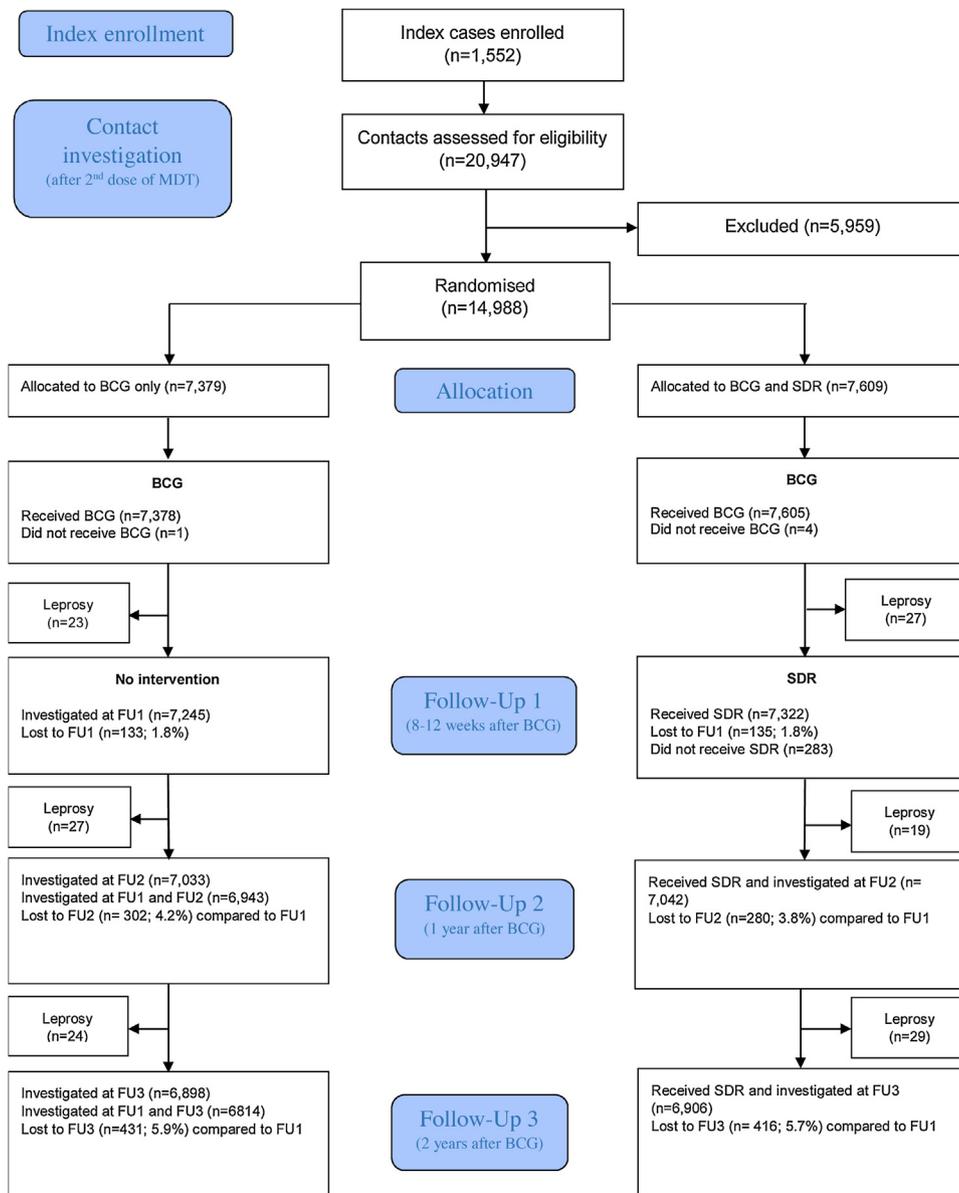
Figure 1. Flow of participants through the trial (MALTALEP study).

leprosy patients were compared between the two arms of the trial after 1 and 2 years.

Sample size

In the earlier COLEP trial (Moet et al., 2008b), the incidence rate (IR) of leprosy among household contacts and direct neighbours was found to be 40 per 10 000 per year in the untreated group over the first 2 years. It was hypothesized that in contacts receiving BCG only, this number would be similar in the first year or possibly slightly increased. Also based on the previous trial, a 50% reduction

through the SDR intervention was expected (IR of 2 per 1000). Based on these figures (with two-sided $\alpha = 0.05$, power $= 0.80$), a total of about 10 000 contacts would be necessary in each group to detect reliably the expected protective effect of the BCG plus SDR combination of 50%, considering an expected 10% loss to follow-up of contacts.

Intake took place between July 2012 and January 2017. The intake took longer than originally planned, since the required number of contacts according to the power calculation had not yet been reached. Nevertheless, it was necessary to end recruitment in 2017 for budgetary reasons. Follow-up after 2 years was completed in January 2019.

Interim analyses and stopping guidelines

As the trial was not blinded, it was possible to assess the outcomes during the study. This was done annually. The main stopping criterion was the occurrence of more serious adverse reactions to BCG vaccination among contacts than described in the literature.

Table 1
Dosage of rifampicin chemoprophylaxis according to age and body weight.

Age/weight	Dose of rifampicin
Adult >35 kg	600 mg
Adult <35 kg	450 mg
Child 10–14 years	450 mg
Child 5–9 years	300 mg

In the first year of the trial, we found an unexpectedly high proportion of healthy contacts of patients (0.4%) presenting with PB leprosy within 12 weeks after receiving the BCG vaccination (i.e., in the timeframe before SDR was given) (Richardus et al., 2015). Since it was too early in the trial to draw definite conclusions about this finding, the study was continued according to the protocol.

Randomization

Each contact group was allocated randomly to one of the two study arms (arm 1: BCG only; arm 2: BCG plus SDR) by means of a computer-generated random sequence with a 1:1 ratio for each arm. A block size of 10 was used. A randomization table was created with 2000 sequential study numbers (one for each contact group). Each study number received a random number generated in MS Excel and this was fixed. The table was then sorted by block number and random number. Within each block of 10 study numbers, the highest five random numbers were assigned SDR, the lowest five were assigned no SDR. The allocation was generated by the database manager (RF); participants were enrolled by field staff. On inclusion of a new index patient, the local database manager (KK) entered the index into the database. Randomization into an arm of the trial was achieved by automatically assigning each next study number to the contact group, thus assigning the pre-allocated randomization group of the study number.

Blinding

Blinding was not possible because there were no placebo capsules of rifampicin available and we were not able to locate any company that could produce these especially for this trial.

Statistical methods

For the calculation of the primary outcome measure, we started at FU1, the time when SDR was provided in the treatment arm (SDR +) of the trial. Contacts who developed leprosy after BCG vaccination, but before FU1, were not included in the calculation of the primary outcome measure. IRs per 10 000 person-years at risk (PYAR) were calculated for year 1 (FU2) and year 2 (FU3) of follow-up. The numbers at risk were calculated by adding the number of new cases of leprosy to the number of contacts without leprosy at the same follow-up moment. The probability of developing leprosy at 2 years was converted to the IR assuming a constant hazard during the period (rate $= -\log(1 - \text{leprosy/total})/2$). To obtain confidence intervals (CI), we applied the standard errors of the probability of developing leprosy ($\sqrt{1/\text{leprosy} + 1/\text{no leprosy}}$) around the log(rate). Additionally, the number needed to treat for BCG + SDR was estimated. A significance level of 5% was used in all tests.

The statistical analyses were done using SAS 9.4. Techniques for the analysis of survey samples were used to account for clustering at the level of the index patient in the sample. Bivariate associations were investigated using proc surveyfreq and the Rao–Scott Chi-square test instead of the Pearson Chi-square test.

Additional analyses

The effectiveness of BCG alone and BCG with SDR was investigated in different subgroups and odds ratios (OR) were reported, which are comparable to relative risks due to the low prevalence of leprosy. Additionally, the number needed to treat (NNT) per subgroup of contacts was reported. Clustering was accounted for through the proc survey logistic instead of ordinary logistic regression.

Results

A total of 1552 index patients were included, of whom 1077 (70%) were PB leprosy patients and 475 (30%) were MB patients. The intake of PB leprosy index patients was intentionally ended when around 1000 had been included, to ensure an intake of at least 300 MB patients. The number of participants in each arm of the trial is shown in Figure 1. A total of 20 947 eligible household contacts were identified. Reasons for exclusion were steroid use ($n = 9$), pregnancy ($n = 241$), liver disease or jaundice ($n = 70$), malignancies ($n = 7$), history of or under treatment for TB ($n = 122$), history of leprosy ($n = 462$), leprosy patient or suspect at intake ($n = 228$), refusal of informed consent ($n = 1136$), under 5 years old ($n = 1900$), residing temporarily in the area ($n = 1314$), or suffering from another serious illness ($n = 673$). Some contacts were excluded because they had more than one exclusion criterion. HIV was not tested within the trial, but when reported, was used as an exclusion criterion. After exclusion, 14 988 contacts entered the trial.

The contacts in both arms of the trial were well-balanced (Table 2). Of the 14 988 contacts included, 7245 contacts in the SDR − arm were checked at FU1, 7033 at FU2, and 6898 at FU3 (Figure 1). A total of 7322 contacts in the SDR + arm received SDR at FU1; 7042 were checked at FU2 and 6906 at FU3. Of the 7322 contacts randomized to receive SDR, 283 did not receive it for various reasons. These contacts were not included in the effect calculations.

Among the included contacts, 27 new leprosy patients were found in the first year (at FU2) in the SDR − arm, and 19 in the SDR + arm. Subsequently, 24 new patients were found in the second year (at FU3) in the SDR − arm, and 29 in the SDR + arm (Tables 3–5). The IR of leprosy per 10 000 PYAR was 44 in the SDR − arm and 31 in the SDR + arm at 1 year, and 34 in the SDR − arm and 41 in the SDR + arm at 2 years. The reduction in incidence of leprosy in the SDR + group compared to the SDR − group was 42% (95% CI − 13% to 70%); Rao–Scott Chi-square = 2.1 (df = 1), $p = 0.148$. The overall NNT was 714 (95% CI −2000 to 313) for PB leprosy in the first year. The reduction in new PB leprosy cases in the BCG + SDR group occurred in the first year after treatment; in year 2, no statistically significant difference in the number of new PB leprosy cases was found between the groups.

Supplementary Material Tables S1 and S2 show the effect of BCG only and BCG with SDR prophylaxis by variable category 1 and 2 years after BCG vaccination. No significant differences of interest were found. A negative NNT indicates a statistically non-significant difference.

Table 6 shows the number of new cases at the different follow-up points including FU1 at 8–12 weeks after BCG. This table shows that 50 out of a total of 149 new cases (33.6%) occurred within 3 months after BCG vaccination. All except one of these were PB leprosy cases. Later in the trial, more MB cases arose (eight MB cases after 1 year and six after 2 years).

The rate of documented adverse events after BCG in the trial was low (0.34%) and comparable to rates reported in studies from other countries (Krysztopa-Grzybowska et al., 2012; Dourado et al., 2003; Turnbull et al., 2002; Grange, 1998). These complications consisted primarily (80%) of skin ulcerations, which are known, common and benign adverse events after BCG vaccination; we have described these previously (Richardus et al., 2018). Except for the orange urine discolouration caused by rifampicin, no adverse events were reported after SDR.

Discussion

In the first year after the provision of SDR to contacts who had first received BCG vaccination, the number of PB leprosy patients

Table 2
Baseline characteristics at intake of contacts of newly diagnosed leprosy patients (N = 14 988) by treatment allocation.[a]

Variable	BCG (n = 7379)	%	BCG and SDR (n = 7609)	%	p-Value
Age at intake (in years)					
5–14	2203	29.85	2302	30.25	0.68
15–29	2051	27.80	2113	27.77	
30–44	1586	21.49	1610	21.16	
≥45	1539	20.86	1584	20.82	
Sex					
Male	3358	45.51	3407	44.78	0.27
Female	4021	54.49	4202	55.22	
Genetic distance to index patient					
Blood-related	1662	22.52	1647	21.65	0.34
Not blood-related (or unclear)	5717	77.48	5962	78.35	
Type of leprosy in index patient					
Paucibacillary	5009	67.88	5367	70.53	0.31
Multibacillary	2370	32.12	2242	29.47	
BCG scar					
Present	4201	56.93	4369	57.42	0.67
Absent	3172	42.99	3236	42.53	
Unknown	6	0.08	4	0.05	
Physical distance to index patient					
Household contact	2192	29.71	2117	27.82	0.09
Neighbour	5187	70.29	5492	72.18	

BCG, bacillus Calmette–Guérin; SDR, single dose of rifampicin.
[a] Values are numbers and percentages of total numbers of contacts.

Table 3
Analysis of all cases of leprosy in contacts of patients with newly diagnosed leprosy.[a]

Treatment	Leprosy	No leprosy	Total number at risk	Incidence rate per 10 000 PYAR	95% CI
BCG					
1 year FU	27	7250	7277	44	30–64
2 year FU	24	7118	7142	34	23–50
1–2 years FU	51				
BCG and SDR					
1 year FU	19	7228	7247	31	20–48
2 year FU	29	7087	7116	41	28–59
1–2 years FU	48				

PYAR, person-years at risk; CI, confidence interval; BCG, bacillus Calmette–Guérin; SDR, single dose of rifampicin; FU, follow-up.
[a] Numbers are provided by treatment arm at 1 and 2 years of follow-up, with incidence rates per 10 000 PYAR (95% CI).

Table 4
Analysis of PB leprosy in contacts of patients with newly diagnosed leprosy.[a]

Treatment	PB leprosy	No leprosy	Total number at risk	Incidence rate per 10 000 PYAR	95% CI
BCG					
1 year FU	24	7253	7277	39[b]	26–58
2 year FU	24	7118	7142	34	23–50
1–2 years FU	48				
BCG and SDR					
1 year FU	14	7233	7247	23[b]	13–38
2 year FU	23	7093	7116	32	22–49
1–2 years FU	37				

PB, paucibacillary; PYAR, person-years at risk; CI, confidence interval; BCG, bacillus Calmette–Guérin; SDR, single dose of rifampicin; FU, follow-up.
[a] Numbers are provided by treatment arm at 1 and 2 years of follow-up, with incidence rates per 10 000 person-years at risk (95% confidence interval).
[b] Overall reduction in incidence of PB leprosy in the SDR+ group in year 1: 42% (95% CI −13% to 70%); Rao–Scott Chi-square = 2.1 (df = 1), p = 0.148; overall number needed to treat = 714 (95% CI −2000 to 313).

Table 5
Analysis of MB leprosy in contacts of patients with newly diagnosed leprosy.[a]

Treatment	MB	No leprosy	Total number at risk	Incidence rate per 10 000 PYAR	95% CI
BCG					
1 year FU	3	7274	7277	4.9	1.6–15
2 year FU	0	7142	7142	0.00	–
1–2 years FU	3				
BCG and SDR					
1 year FU	5	7242	7247	8.1	3.4–20
2 year FU	6	7110	7116	8.4	3.8–19
1–2 years FU	11				

MB, multibacillary; PYAR, person-years at risk; CI, confidence interval; BCG, bacillus Calmette–Guérin; SDR, single dose of rifampicin; FU, follow-up.
[a] Numbers are provided by treatment arm at 1 and 2 years of follow-up, with incidence rates per 10 000 person-years at risk (95% confidence interval).

Table 6
New leprosy cases among contacts of newly diagnosed leprosy cases identified according to the time points of diagnosis.

	8–12 weeks	1 year	2 years	Total
BCG				
PB	23	24	24	71
MB	0	3[a]	0	3
BCG and SDR				
PB	26	14	23	63
MB	1	5	6	12
Total	50	46	53	149

BCG, bacillus Calmette–Guérin; PB, paucibacillary; MB, multibacillary; SDR, single dose of rifampicin; BI, bacterial index; BL, borderline lepromatous; BT, borderline tuberculous.

[a] Only one new MB leprosy case had a BI of 2+ (BL); the rest of the MB cases were smear-negative (MB BT).

was reduced by 42% compared to the group that did not receive SDR. No additional effect of SDR was seen in the second year. A large proportion (33.6%) appeared within 8–12 weeks after vaccination, the window period between vaccination and the provision of SDR.

By providing rifampicin (a bactericidal drug) at 8–12 weeks after BCG vaccination, we envisaged the prevention of new leprosy cases among contacts in the first year after BCG vaccination. This was described in Brazil by Duppre et al. (2008), who showed that the risk of PB leprosy was high during the initial months among those contacts vaccinated with BCG: among the 58 new cases detected during 18 years of contact follow-up, leprosy was diagnosed in 21 of these contacts (36%) relatively soon after vaccination (2–10 months); 18 out of these 21 contacts had PB leprosy. We also found an unexpectedly high proportion of new PB leprosy cases following BCG vaccination; however, this phenomenon had already occurred in the period between BCG vaccination and SDR provision. This time interval was selected in order to ensure that rifampicin would not affect the efficacy of BCG, which is a live vaccine. At the time of conceptualization of the trial, we had no indication to expect that this would occur this early after BCG. Most trials have only included long-term follow-up, often starting 1 year after vaccination. The Brazilian trial (Duppre et al. (2008)) diagnosed the new leprosy cases 2–10 months after BCG vaccination, which was also later than what was found in our trial. In previous studies, either the number of cases was too low to confirm early 'induction' of leprosy after BCG (Karonga Prevention Trial Group, 1996; HW W, 1960), or it was not specified when exactly leprosy occurred after vaccination (Lwin et al., 1985; Bagshawe et al., 1989). So, at the time SDR was provided in the current study, most excess cases had probably already become manifest.

What would have been the result of the trial if SDR had been given before BCG vaccination? There was no published evidence to support our decision on the order of BCG and SDR. We simply followed the logic of the primary research question regarding whether SDR would suppress the excess cases after BCG vaccination and designed the study in that order. Also, the intervention strategy considered the bactericidal effect of SDR on live bacteria such as BCG. In hindsight, it may have been preferable to first provide SDR, and this should be explored in a future study.

The level of protection offered by SDR in the present study was 42%, which is less than the level reported in the COLEP study (57%) conducted 10 years previously in the same population (Moet et al., 2008b). However, our contact population only included household and first neighbour contacts, while the COLEP study also included second neighbours and social contacts. The further contacts are physically removed from the index case, the more pronounced is the effect of SDR in protecting against leprosy. This is probably due to a lower exposure rate and hence a lower bacterial load of these

further distanced contacts, rendering a single dose of rifampicin more effective (Moet et al., 2008b; Feenstra et al., 2012). Immunological screening of the effect of SDR on *M. leprae* infection in contacts could provide insight into the extent, how fast, and how durable *M. leprae* infection is reduced by this single dose of antibiotic.

The observations from this trial give rise to interesting hypotheses regarding the immunological mechanisms underlying the effect of BCG vaccination given to contacts of newly diagnosed leprosy cases. It is possible that BCG accelerates pro-inflammatory T-helper 1 (Th1) immunity to *M. leprae* antigens, thereby revealing incipient forms of PB leprosy. Alternatively, BCG vaccination is also known to induce trained immunity and thereby non-specifically activates protective innate responses (Arts et al., 2018; Kleinnijenhuis et al., 2012). In a previous study (Richardus et al., 2018), we showed that BCG vaccination induced significant Th1-type immunity (higher levels of interferon gamma) in those who presented with high local inflammation responses, implicating that efficient protection against *M. leprae* is dependent on an adequate Th1 response (Ottenhoff, 2012), although the concomitant inflammation may result in collateral tissue damage (Geluk, 2018).

This study investigated the effect of BCG with or without SDR in one highly endemic area in the Indian sub-continent with a specific PB:MB ratio (2:1 instead of the usual 1:1 reported worldwide) (van Hooij et al., 2016; van Hooij et al., 2018; van Hooij et al., 2019), a low socio-economic status, and specific demographic, genetic, and cultural characteristics. Whether BCG would give similar protection in other areas of the world is questionable. Furthermore, in Bangladesh the Moscow strain 361 and Tokyo strain 172 are used; elsewhere, the use of other BCG strains for vaccination could lead to different results (Fine, 1995; Zhang et al., 2013).

This trial was not designed to establish the protective effect of BCG against leprosy. It was assumed that this is a given based on the literature (Merle et al., 2010; Karonga Prevention Trial Group, 1996; Cunha et al., 2008); therefore an arm without BCG was not included in the trial. However, we doubt that the protective effect of BCG alone was large in this study. The IR of leprosy at 2 years among the household contacts and next-door neighbours in the non-intervention arm in the COLEP study was 39.35 per 10 000 PYAR (Moet et al., 2008b). The IR was 33.72 per 10 000 PYAR in the BCG-only arm at 2 years in the MALTALEP trial. This implies a 14.3% reduction in leprosy incidence by BCG vaccination compared to no intervention. A Brazilian trial (Duppre et al., 2008) showed that the protection conferred by a booster BCG vaccination was 56% and was not substantially affected by previous BCG vaccination. More specifically, this effect was 83–85% for the indeterminate and MB forms of leprosy, but a non-significant effect of 26% was found for the PB leprosy forms. This might explain the lack of effect of BCG in our trial when compared to no intervention; in Bangladesh, most patients have the PB form of leprosy (Anonymous, 2017a).

In a subgroup analysis (**Supplementary Material**), we found no significant difference in the development of leprosy between revaccinated (BCG scar-positive) versus primary vaccinated (BCG scar-naïve) contacts. In their meta-analysis, Merle et al. (Merle et al. (2010)) also found no statistical difference in BCG protection against leprosy between studies in which individuals were vaccinated once and studies in which individuals received a booster vaccination on top of the neonatal vaccination.

There may be better alternatives to BCG vaccination as immunoprophylaxis in leprosy, with new candidate leprosy vaccines in the pipeline, such as MIP (Sharma et al., 2005; Kumar, 2017) and LepVax (Duthie et al., 2018). The MIP vaccine has only been evaluated in Uttar Pradesh, India, with both patients and contacts vaccinated. The protective efficacy was 68%, 60%, and 28% after 3, 6, and 9 years, respectively (Sharma et al., 2005). For

LepVax, post-exposure prophylaxis tested in nine-banded armadillos appeared safe, and unlike BCG, it diminished the neurological disruptions caused by *M. leprae* infection (Duthie et al., 2018). Further trials are needed to investigate these vaccines before they can be introduced in the field.

A strength of this trial is that it was randomized and controlled and field-based. An extensive number of leprosy contacts were included (*n* = 14 988). Also, because it was based in a leprosy-endemic area, implementation was close to clinical field practice. The loss to follow-up was less than 6%, which was lower than expected. A limitation is that it was not possible to make it double-blind (placebo was not available), which may have biased the results. Even when using a harmless dose of a dissimilar vitamin pill to prevent participants from knowing whether or not they had been given an intervention, this would not have prevented bias by the field staff, since they would have known the difference. For instance, the field staff may expect and look more closely for signs and symptoms of leprosy in those who have not received SDR. Furthermore, a limitation was that intake took longer than expected and therefore we could not reach the 10 000 contacts per arm we set out to include, leading to less power and therefore less statistically significant results.

In conclusion, it is difficult to establish the extent to which SDR suppresses excess leprosy cases among contacts in the year after BCG vaccination. Based on this study, we cannot recommend BCG vaccination followed by SDR as a routine intervention in leprosy control. However, we do advise contact surveys followed by SDR to eligible contacts of new leprosy cases. Recently, the WHO included SDR in the guidelines for its leprosy elimination strategy (Anonymous, 2017b). Implementation studies on the effectiveness of SDR as leprosy post-exposure prophylaxis (LPEP) are currently ongoing (Barth-Jaeggi et al., 2016; Steinmann et al., 2018).

Author contributions

All authors contributed to the design of the study and manuscript preparation. All authors have read and approved the final manuscript.

Conflict of interest

The authors declare that they have no competing interests. The BCG vaccine was provided free of charge by the Government of Bangladesh.

Ethical approval

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

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.08.035.

References

Anonymous. WHO expert committee on leprosy. World Health Organ Tech Rep Ser 1998;874:1–43.

Anonymous. Global strategy for further reducing the leprosy burden and sustaining leprosy control activities 2006-2010. Operational guidelines. Lepr Rev 2006;77(3) IX, X, 1–50.

Anonymous. Bangladesh bureau of statistics: Bangladesh population & housing census 2011. 2011 Available from: http://www.bbs.gov.bd/site/page/47856ad0-7e1c-4aab-bd78-892733bc06eb/-. [Accessed 20 April 2019].

Anonymous. Global leprosy update, 2016: accelerating reduction of disease burden. Releve Epidemiol Hebd 2017a;92(35)501–19 [published Online First: 2017/09/02].

Anonymous. Guidelines for the diagnosis, treatment and prevention of leprosy. New Delhi: World Health Organization, Regional Office for South-East Asia; 2017.

Anonymous. Global leprosy update, 2017: reducing the disease burden due to leprosy. Wkly Epidemiol Rec 2018;35(93):445–56.

Arts RJW, Moorlag S, Novakovic B, Li Y, Wang SY, Oosting M, et al. BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. Cell Host Microbe 2018;23(1)89–100.e5, doi:http://dx.doi.org/10.1016/j.chom.2017.12.010 [published Online First: 2018/01/13].

Bagshawe A, Scott GC, Russell DA, Wigley SC, Merianos A, Berry G. BCG vaccination in leprosy: final results of the trial in Karimui, Papua New Guinea, 1963-79. Bull World Health Organ 1989;67(4)389–99 [published Online First: 1989/01/01].

Barth-Jaeggi T, Steinmann P, Mieras L, van Brakel W, Richardus JH, Tiwari A, et al. Leprosy post-exposure prophylaxis (LPEP) programme: study protocol for evaluating the feasibility and impact on case detection rates of contact tracing and single dose rifampicin. BMJ Open 2016;6(11)e013633, doi:http://dx.doi.org/10.1136/bmjopen-2016-013633 [published Online First: 2016/11/20].

Coppola M, van den Eeden SJF, Robbins N, Wilson L, Franken K, Adams LB, et al. Vaccines for leprosy and tuberculosis: opportunities for shared research, development, and application. Front Immunol 2018;9:308, doi:http://dx.doi.org/10.3389/fimmu.2018.00308 [published Online First: 2018/03/15].

Cunha SS, Alexander N, Barreto ML, Pereira ES, Dourado I, Maroja Mde F, et al. BCG revaccination does not protect against leprosy in the Brazilian Amazon: a cluster randomised trial. PLoS Negl Trop Dis 2008;2(2)e167, doi:http://dx.doi.org/10.1371/journal.pntd.0000167 [published Online First: 2008/02/14].

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(4)399–402 [published Online First: 2003/05/06].

Duppre NC, Camacho LA, da Cunha SS, Struchiner CJ, Sales AM, Nery JA, et al. Effectiveness of BCG vaccination among leprosy contacts: a cohort study. Trans R Soc Trop Med Hyg 2008;102(7)631–8, doi:http://dx.doi.org/10.1016/j.trstmh.2008.04.015 [published Online First: 2008/06/03].

Duthie MS, Pena MT, Ebenezer GJ, Gillis TP, Sharma R, Cunningham K, et al. LepVax, a defined subunit vaccine that provides effective pre-exposure and post-exposure prophylaxis of M. leprae infection. NPJ Vaccines 2018;3:12, doi:http://dx.doi.org/10.1038/s41541-018-0050-z [published Online First: 2018/04/06].

Feenstra SG, Pahan D, Moet FJ, Oskam L, Richardus JH. Patient-related factors predicting the effectiveness of rifampicin chemoprophylaxis in contacts: 6 year follow up of the COLEP cohort in Bangladesh. Lepr Rev 2012;83(3)292–304 [published Online First: 2013/01/30].

Fine PE. Variation in protection by BCG: implications of and for heterologous immunity. Lancet 1995;346(8986)1339–45 [published Online First: 1995/11/18].

Fine PE, Ponnighaus JM. Leprosy in Malawi. 2. Background, design and prospects of the Karonga Prevention Trial, a leprosy vaccine trial in northern Malawi. Trans R Soc Trop Med Hyg 1988;82(6)810–7 [published Online First: 1988/01/01].

Geluk A. Correlates of immune exacerbations in leprosy. Semin Immunol 2018;39:111–8, doi:http://dx.doi.org/10.1016/j.smim.2018.06.003 [published Online First: 2018/06/29].

Grange JM. Complications of bacille Calmette-Guerin (BCG) vaccination and immunotherapy and their management. Commun Dis Public Health 1998;1(2)84–8 [published Online First: 1998/06/30].

HW W. BCG-induced activations. Int J Lepr 1960;28(2):179–81.

Karonga Prevention Trial Group. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed Mycobacterium leprae vaccine for prevention of leprosy and tuberculosis in Malawi. Karonga Prevention Trial Group. Lancet 1996;348(9019)17–24 [published Online First: 1996/07/06].

Kleinnijenhuis J, Quintin J, Preijers F, Joosten LA, Ifrim DC, Saeed S, et al. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. Proc Natl Acad Sci U S A 2012;109(43)17537–42, doi:http://dx.doi.org/10.1073/pnas.1202870109 [published Online First: 2012/09/19].

Krysztopa-Grzybowska K, Paradowska-Stankiewicz I, Lutynska A. The rate of adverse events following BCG vaccination in Poland. Przegl Epidemiol 2012;66(3)465–9 [published Online First: 2012/12/13].

Kumar S. India resurrects forgotten leprosy vaccine. Science 2017;356(6342)999, doi:http://dx.doi.org/10.1126/science.356.6342.999 [published Online First: 2017/06/10].

Lwin K, Sundaresan T, Gyi MM, Bechelli LM, Tamondong C, Garbajosa PG, et al. BCG vaccination of children against leprosy: fourteen-year findings of the trial in Burma. Bull World Health Organ 1985;63(6)1069–78 [published Online First: 1985/01/01].

Merle CS, Cunha SS, Rodrigues LC. BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. Expert Rev Vaccines 2010;9(2)209–22, doi:http://dx.doi.org/10.1586/erv.09.161 [published Online First: 2010/01/30].

Moet FJ, Pahan D, Schuring RP, Oskam L, Richardus JH. Physical distance, genetic relationship, age, and leprosy classification are independent risk factors for leprosy in contacts of patients with leprosy. J Infect Dis 2006;193(3)346–53, doi:http://dx.doi.org/10.1086/499278 [published Online First: 2006/01/03].

Moet FJ, Schuring RP, Pahan D, Oskam L, Richardus JH. The prevalence of previously undiagnosed leprosy in the general population of northwest bangladesh. PLoS Negl Trop Dis 2008a;2(2)e198, doi:http://dx.doi.org/10.1371/journal.pntd.0000198 [published Online First: 2008/02/28].

Moet FJ, Pahan D, Oskam L, Richardus JH. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. BMJ 2008b;336(7647)761–4, doi:http://dx.doi.org/10.1136/bmj.39500.885752.BE [published Online First: 2008/03/12].

Ottenhoff TH. New pathways of protective and pathological host defense to mycobacteria. Trends Microbiol 2012;20(9)419–28, doi:http://dx.doi.org/10.1016/j.tim.2012.06.002 [published Online First: 2012/07/13].

Richardus JH, Oskam L. Protecting people against leprosy: chemoprophylaxis and immunoprophylaxis (vaccination). Clin Dermatol 2015;33(1):19–25.

Richardus RA, Alam K, Pahan D, Feenstra SG, Geluk A, Richardus JH. The combined effect of chemoprophylaxis with single dose rifampicin and immunoprophylaxis with BCG to prevent leprosy in contacts of newly diagnosed leprosy cases: a cluster randomized controlled trial (MALTALEP study). BMC Infect Dis 2013;13:456, doi:http://dx.doi.org/10.1186/1471-2334-13-456 [published Online First: 2013/10/04].

Richardus RA, Butlin CR, Alam K, Kundu K, Geluk A, Richardus JH. Clinical manifestations of leprosy after BCG vaccination: an observational study in Bangladesh. Vaccine 2015;33(13)1562–7, doi:http://dx.doi.org/10.1016/j.vaccine.2015.02.017 [published Online First: 2015/02/24].

Richardus R, van Hooij A, van den Eeden SJF, Wilson L, Alam K, Richardus JH, et al. BCG and adverse events in the context of leprosy. Front Immunol 2018;9:629, doi:http://dx.doi.org/10.3389/fimmu.2018.00629 [published Online First: 2018/04/20].

Schuring RP, Richardus JH, Pahan D, Oskam L. Protective effect of the combination BCG vaccination and rifampicin prophylaxis in leprosy prevention. Vaccine 2009;27(50)7125–8, doi:http://dx.doi.org/10.1016/j.vaccine.2009.09.054 [published Online First: 2009/09/30].

Setia MS, Steinmaus C, Ho CS, Rutherford GW. The role of BCG in prevention of leprosy: a meta-analysis. Lancet Infect Dis 2006;6(3)162–70, doi:http://dx.doi.org/10.1016/s1473-3099(06)70412-1 [published Online First: 2006/02/28].

Sharma P, Mukherjee R, Talwar GP, Sarathchandra KG, Walia R, Parida SK, et al. Immunoprophylactic effects of the anti-leprosy Mw vaccine in household contacts of leprosy patients: clinical field trials with a follow up of 8-10 years. Lepr Rev 2005;76(2)127–43 [published Online First: 2005/07/26].

Steinmann P, Cavaliero A, Aerts A, Anand S, Arif M, Ay SS, et al. The Leprosy Post-Exposure Prophylaxis (LPEP) programme: update and interim analysis. Lepr Rev 2018;89:102–16.

Turnbull FM, McIntyre PB, Achat HM, Wang H, Stapledon R, Gold M, et al. National study of adverse reactions after vaccination with bacille Calmette-Guerin. Clin Infect Dis 2002;34(4)447–53, doi:http://dx.doi.org/10.1086/338462 [published Online First: 2002/01/18].

UNAIDS https://aidsdatahub.org/sites/default/files/country_review/Bangladesh-2019-UNAIDS-data.pdf (Accessed 30 September 2019).

van Hooij A, Tjon Kon Fat EM, Richardus R, van den Eeden SJ, Wilson L, de Dood CJ, et al. Quantitative lateral flow strip assays as user-friendly tools to detect biomarker profiles for leprosy. Sci Rep 2016;6:34260, doi:http://dx.doi.org/10.1038/srep34260 [published Online First: 2016/09/30].

van Hooij A, Tjon Kon Fat EM, Batista da Silva M, Carvalho Bouth R, Cunha Messias AC, Gobbo AR, et al. Evaluation of Immunodiagnostic Tests for Leprosy in Brazil, China and Ethiopia. Sci Rep 2018;8(1)17920, doi:http://dx.doi.org/10.1038/s41598-018-36323-1 [published Online First: 2018/12/19].

van Hooij A, van den Eeden S, Richardus R, Tjon Kon Fat E, Wilson L, Franken K, et al. Application of new host biomarker profiles in quantitative point-of-care tests facilitates leprosy diagnosis in the field. EBioMedicine 2019;, doi:http://dx.doi.org/10.1016/j.ebiom.2019.08.009 [published Online First: 2019/08/20].

Zhang W, Zhang Y, Zheng H, Pan Y, Liu H, Du P, et al. Genome sequencing and analysis of BCG vaccine strains. PLoS One 2013;8(8)e71243, doi:http://dx.doi.org/10.1371/journal.pone.0071243 [published Online First: 2013/08/27].