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

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Citation

Richardus, R. A. (2020, February 4). *Preventing Leprosy: Epidemiological and immunological aspects of chemo- and immunoprophylaxis in leprosy patients' contacts*. Retrieved from https://hdl.handle.net/1887/84691

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Author: Richardus, R.A.
Title: Preventing Leprosy: Epidemiological and immunological aspects of chemo- and immunoprophylaxis in leprosy patients' contacts
Issue Date: 2020-02-04

CHAPTER 6

6

Effectiveness of BCG vaccine with or without single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: a cluster randomized controlled trial (MALTALEP study)

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International Journal of Infectious Diseases November 2019, Volume 88, pages 65-72

ABSTRACT

Objective: To assess the effectiveness of SDR after BCG-vaccination in preventing leprosy in contacts.

Design: Single-centre, cluster-randomized controlled trial.

Setting: Leprosy control programme in northwest Bangladesh.

Participants: 14,988 contacts of 1,552 new leprosy patients; randomized in the SDR- arm (7,379) and SDR+ arm (7,609).

Interventions: Intervention group: BCG-vaccination followed by SDR 8-12 weeks later. Control group: BCG only. Follow-up: at one and two years after intake.

Main outcome measure: 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+ at 1 year, and 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 PB leprosy in the SDR+ arm at 1 year. Of all new cases, 33.6% appeared within 8-12 weeks after BCG-vaccination.

Conclusion: In the first year, SDR after BCG-vaccination reduced PB leprosy incidence among contacts by 42%. This was a statistically non-significant reduction due to the limited number of cases after SDR was administered. To which extent SDR suppresses excess leprosy cases after BCG-vaccination is difficult to establish because many 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[1], indicating that transmission of *Mycobacterium leprae* (*M. 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 WHO target of reducing the burden of leprosy[2].

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 development of leprosy[3]. Household contacts of newly diagnosed patients have a ten-fold higher risk to develop leprosy compared with the general population[4]; for different categories of neighbours and social contacts this is three to five-fold higher[3 4].

Many studies regarding immunoprophylaxis (vaccination) and chemoprophylaxis aiming to prevent leprosy focused primarily on contacts of leprosy patients. Bacillus Calmette-Guérin (BCG) vaccination is known as a vaccine against tuberculosis and is 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[5 6]. Several vaccine trials using BCG have established its protective effect against leprosy, often in combination with *M. leprae* or related mycobacterium vaccines[5 7 8 9 10 11]. 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[12], 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 (acronym: COLEP) showed that a single dose of rifampicin (SDR) in contacts of newly diagnosed leprosy patients reduced the overall incidence of leprosy in the first two years with 57%[13]. Furthermore, this study showed that the effect of SDR depended on the BCG-status of the contact[14]: if the contact had received BCG-vaccination as part of a

childhood vaccination program, the protective effect of SDR was 80%. Contacts that received SDR without prior BCG vaccination had a protective effect of 58%. Recently, the WHO has included SDR as recommendation in their guidelines [15].

Based on earlier studies with BCG-vaccination and SDR chemoprophylaxis in preventing leprosy among contacts, a trial was initiated to assess the efficacy of a combined strategy (acronym: MALTALEP). The main objective of this trial was to assess the effectiveness in preventing leprosy in close contacts of patients with newly diagnosed leprosy of SDR given after BCG-vaccination, and specifically to determine whether possible excess cases in the first year after immunoprophylaxis, as observed previously in Brazil[12], can 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). At 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 at one year (FU2) and two years (FU3) after receiving BCG. The three follow-up moments 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 we broadened the range to 8 to 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 Program[16 17]. 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. We grouped patients with negative smear results and five or less skin lesions as PB leprosy, and those with positive smear results or more than five skin lesions as multibacillary (MB) leprosy according to the WHO treatment criteria. MDT was started according to the national guidelines. Within two weeks after newly diagnosed leprosy received the second dose of MDT (four 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 our methodology article[18]. 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 we defined four categories based on the local housing situation: shares a house and kitchen; shares a kitchen only; shares a house but not kitchen (together called household contacts); and next-door neighbours. For genetic distance we defined two groups: 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 illiterate people a thumb print and for minors under 16 years of age, the guardian's additional consent was obtained.

Study setting. The study was in the districts of Nilphamari, Rangpur, Thakurgaon and Panchagarh in northwest 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[19]. The prevalence rate of HIV in adults aged 15 to 49 in Bangladesh in 2018 was <0,1[20].

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/ampule live bacteria of Calmette-Guérin (as approximately 70% moist bacteria) and 2,0 mg/ampule 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 is the same as recommended in the guidelines of the national leprosy control program of Bangladesh and RHP (Table 1).

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

Outcomes. The primary outcome measure was the number of new leprosy patients emerging from the contact groups. The proportions between the two arms of the trial is compared after one and two years.

Sample size. In the earlier COLEP trial[13] we found an incidence rate (IR) of leprosy among household contacts and direct neighbours of 40 per 10,000 per year in the untreated group over the first two years. We 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, we expected a 50% reduction through the SDR intervention (IR of 2 per 1000). Based on these figures (with $\alpha = 0.05$ two-sided, 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 two years was completed in January 2019.

Interim analyses and stopping guidelines. Because 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 literature.

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 BCG-vaccination (the timeframe before SDR was given)[21]. Since it was too early in the trial to draw definite conclusions about this finding, the study was continued according to protocol.

Randomisation. Each contact group was randomly allocated to one of the two study arms (Arm 1: BCG only, or Arm 2: BCG plus SDR) by means of computer generation 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 5 random numbers were assigned SDR, the lowest 5 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. A 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 (SDR+) arm of the trial. Contacts who developed leprosy after BCG-vaccination, but before FU1, were not included in the calculation of the primary outcome measure. Incidence rates per 10 000 person-years-at-risk 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 incidence rates assuming a constant hazard during the period (rate = -log (1-leprosy/total)/2). To obtain confidence intervals we applied the standard errors of the probability of developing leprosy (sqrt(1/leprosy + 1/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. Statistical analyses were done with SAS 9.4. We used techniques for the analysis of survey samples to account for clustering at the level of the index patient in the sample. Bivariate associations are investigated using proc surveyfreq and the Rao Scott $\chi 2$ instead of the Pearson $\chi 2$.

Additional analyses. The effectiveness of BCG alone and BCG with SDR were investigated in different subgroups and odds ratios were reported, which are comparable to relative risks due to the low prevalence of leprosy. Additionally, we reported the Number Needed to Treat (NNT) per subgroup of contacts. Clustering is accounted for through using proc survey logistic instead of ordinary logistic regression.

RESULTS

Participants flow

We included a total of 1,552 index patients, of whom 1,077 (70%) were PB patients and 475 (30%) MB patients. Intake of PB index patients was intentionally ended when around 1,000 had been included, to insure 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 tuberculosis (n=122), history of leprosy (n=462), leprosy patient or suspect at intake (n=228), refusal of informed consent (n=1,136), under 5 years old (n=1,900), residing temporarily in the area (n=1,314), or suffering from another serious illness (n=673). Some contacts were excluded because they had more than one exclusion criteria. HIV was not tested within the trial, but when reported was used as 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, 7,245 contacts in the SDR- arm were checked at FU1, 7,033 at FU2, and 6,898 at FU3 (Figure 1). A total of 7,322 contacts in the SDR+ arm received SDR at FU1, 7,042 were checked at FU2 and 6,906 at FU3. Of 7,322 contacts randomized to receive SDR, 283 did not receive it for various reasons. These contacts have not been 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 (Table 3). The incidence rate of leprosy per 10,000 person-years-at-risk (PYAR) was 44 PYAR in the SDR- arm, and 31 PYAR in the SDR+ arm at 1 year, and 34 PYAR in the SDR- arm and 41 PYAR 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% confidence interval -13% to 70%); Rao Scott $\chi 2=2.1$ (df=1), P=0.148; overall number needed to treat was 714 (95% confidence interval -2000 to 313)) for PB leprosy in the first year. The reduction of new PB cases in the BCG and SDR group occurred in the first year after treatment; in year 2 no statistically significant difference was found between the number of new PB cases in the groups.

Supplementary Table S1 and S2 (appendix) show the effect of BCG only and BCG with SDR prophylaxis by variable category one and two years after BCG-vaccination. No significant differences of interest were found. A negative NNT indicates a statistically non-significant difference.

Table 4 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%) occur within 3 months after receiving BCG. These are all (except one) PB cases; later in the trial more MB cases arise (8 MB cases after 1 year, and 6 after 2 years).

The rate of documented adverse events after BCG in the trial was low (0.34%) and comparable to studies in other countries[22-25]. These complications consisted primarily (80%) of skin ulcerations, which are known, common and benign adverse event after BCG-vaccination, which we have described previously[26]. Except for the orange urine discolouration caused by rifampicin, no adverse events were reported after SDR.

Figure 1. Flow of participants through the trial (MALTALEP study).

Figure 1

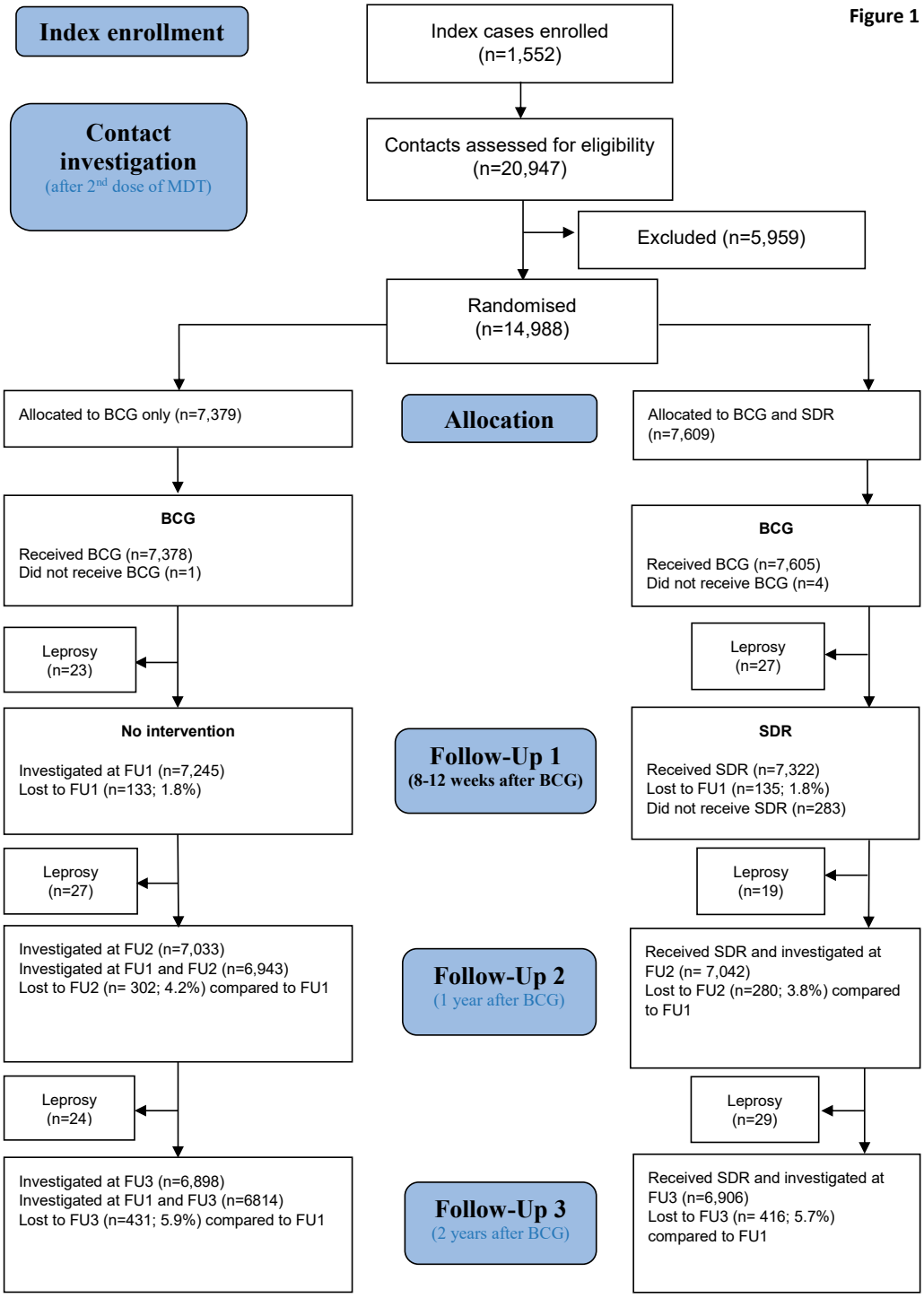
Index enrollment
Index cases enrolled (n=1,552)
Contact investigation (after 2nd dose of MDT)
Contacts assessed for eligibility (n=20,947)
Excluded (n=5,959)
Randomised (n=14,988)
Allocation
Allocated to BCG only (n=7,379)
Allocated to BCG and SDR (n=7,609)
BCG
Received BCG (n=7,378)
Did not receive BCG (n=1)
BCG
Received BCG (n=7,605)
Did not receive BCG (n=4)
Leprosy (n=23)
Leprosy (n=27)
No intervention
Investigated at FU1 (n=7,245)
Lost to FU1 (n=133; 1.8%)
Follow-Up 1 (8-12 weeks after BCG)
SDR
Received SDR (n=7,322)
Lost to FU1 (n=135; 1.8%)
Did not receive SDR (n=283)
Leprosy (n=27)
Leprosy (n=19)
Investigated at FU2 (n=7,033)
Investigated at FU1 and FU2 (n=6,943)
Lost to FU2 (n= 302; 4.2%) compared to FU1
Follow-Up 2 (1 year after BCG)
Received SDR and investigated at FU2 (n= 7,042)
Lost to FU2 (n=280; 3.8%) compared to FU1
Leprosy (n=24)
Leprosy (n=29)
Investigated at FU3 (n=6,898)
Investigated at FU1 and FU3 (n=6814)
Lost to FU3 (n=431; 5.9%) compared to FU1
Follow-Up 3 (2 years after BCG)
Received SDR and investigated at FU3 (n=6,906)
Lost to FU3 (n= 416; 5.7%) compared to FU1

Table 2. Baseline characteristics at intake of contacts of newly diagnosed leprosy patients (n=14,988) by treatment allocation.

Variable	BCG (n=7,379)*	%*	BCG and SDR (n=7,609)	%	p-value
Age at intake (in years)					
5-14	2,203	29.85	2,302	30.25	
15-29	2,051	27.80	2,113	27.77	
30-44	1,586	21.49	1,610	21.16	
≥45	1,539	20.86	1,584	20.82	0.68
Gender					
Male	3,358	45.51	3,407	44.78	
Female	4,021	54.49	4,202	55.22	0.27
Genetic distance to index patient					
Blood-related	1,662	22.52	1,647	21.65	
Not blood-related (or unclear)	5,717	77.48	5,962	78.35	0.34
Type of leprosy in index patient					
Paucibacillary	5,009	67.88	5,367	70.53	
Multibacillary	2,370	32.12	2,242	29.47	0.31
BCG scar					
Present	4,201	56.93	4,369	57.42	
Absent	3,172	42.99	3,236	42.53	
Unknown	6	0.08	4	0.05	0.67
Physical distance to index patient					
Household contact	2,192	29.71	2,117	27.82	
Neighbour	5,187	70.29	5,492	72.18	0.09

*Values are numbers and percentages of total numbers of contacts

Table 3A. Analysis of all cases of leprosy in contacts of patients with newly diagnosed leprosy*

Treatment	Leprosy	No leprosy	Total no. at risk	Incidence Rates per 10,000 PYAR	95% CI
BCG					
1 year FU	27	7,250	7,277	44	30-64
2 year FU	24	7,118	7,142	34	23-50
1-2 years FU	51				
BCG and SDR					
1 year FU	19	7,228	7,247	31	20-48
2 year FU	29	7,087	7,116	41	28-59
1-2 years FU	48				

Table 3B. Analysis of PB leprosy in contacts of patients with newly diagnosed leprosy*

Treatment	PB	No leprosy	Total no. at risk	Incidence Rates per 10,000 PYAR	95% CI
BCG					
1 year FU	24	7,253	7,277	39**	26-58
2 year FU	24	7,118	7,142	34	23-50
1-2 years FU	48				
BCG and SDR					
1 year FU	14	7,233	7,247	23**	13-38
2 year FU	23	7,093	7,116	32	22-49
1-2 years FU	37				

Table 3C. Analysis of MB leprosy in contacts of patients with newly diagnosed leprosy*

Treatment	MB	No leprosy	Total no. at risk	Incidence Rates per 10,000 PYAR	95% CI
BCG					
1 year FU	3	7,274	7,277	4.9	1.6-15
2 year FU	0	7,142	7,142	0.00	-
1-2 years FU	3				
BCG and SDR					
1 year FU	5	7,242	7,247	8.1	3.4-20
2 year FU	6	7,110	7,116	8.4	3.8-19
1-2 years FU	11				

*Numbers are provided by treatment arm at one and two years' follow-up, with incidence rates per 10,000 person-years at risk (95% confidence interval); **Overall reduction in incidence of PB leprosy in SDR+ group in year 1: 42% (95% confidence interval -13% to 70%); Rao Scott $\chi 2=2.1$ (df=1), P=0.148; overall number needed to treat 714 (95% confidence interval -2000 to 313).

Table 4. 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*	0	3
BCG and SDR				
PB	26	14	23	63
MB	1	5	6	12
Total	50	46	53	149

*Only 1 new MB leprosy case had a BI of 2+ (BL), the rest of the MB cases were smear negative (MB BT).

Supplementary Table S1. Protective efficacy of BCG versus BCG and SDR prophylaxis in contacts of newly diagnosed leprosy patients by variable category at one year follow-up.

	BCG		BCG and SDR					
Age group (years)	**No leprosy**	**Leprosy (n)**	**No leprosy (n)**	**Leprosy (n)**	**OR (95% CI)***	**p-value**	**p-value interaction**	**NNT****
5-14	2,171	5	2,212	5	0.98 (0.28, 3.40)	0.98	0.85	23,425.62
15-29	2,005	10	1,958	5	0.51 (0.18, 1.50)	0.22		410.86
30-44	1,561	7	1,527	6	0.88 (0.29, 2.61)	0.81		1,801.70
≥45	1,513	5	1,531	3	0.59 (0.14, 2.48)	0.47		743.39
Gender								
Female	3,952	15	4,013	6	0.39 (0.15, 1.03)	0.06	0.10	434.71
Male	3,928	12	3,215	13	1.11 (0.48, 2.58)	0.81		-1,011.58
Blood relative								
Yes	1,623	13	1,562	7	0.56 (0.22, 1.40)	0.22	0.47	283.41
No	5,627	14	5,666	12	0.85 (0.38, 1.93)	0.70		2,701.91
Type of leprosy index patient								
PB	4,927	12	5,099	9	0.73 (0.28, 1.87)	0.51	1.00	1,491.41
MB	2,323	15	2,129	10	0.73 (0.30, 1.75)	0.48		568.14
Physical distance								
Household	2,130	19	2,005	10	0.56 (0.24, 1.31)	0.18	0.28	254.28
Neighbour	5,120	8	5,223	9	1.10 (0.43, 2.86)	0.84		-6,224.80
BCG scar								
Present	4,314	15	4,154	8	0.53 (0.22, 1.28)	0.16	0.34	644.66
Absent	3,110	12	3,072	11	0.93 (0.40, 2.18)	0.86		3,599.82

*Odds Ratio (with 95% confidence interval), ** Numbers Needed to Treat

Supplementary Table S2. Protective efficacy of BCG versus BCG and SDR prophylaxis in contacts of newly diagnosed leprosy patients by variable category at two years' follow-up.

	BCG		BCG and SDR					
Age group	**No leprosy**	**Leprosy**	**No leprosy**	**Leprosy**	**OR (95% CI)***	**p-value**	**p-value interaction**	**NNT****
5-14	2,135	10	2,182	6	0.59 (0.21, 1.61)	0.30	0.12	517.04
15-29	1,960	5	1,900	8	1.65 (0.54, 5.03)	0.38		-602.59
30-44	1,541	2	1,506	9	4.61 (0.99, 21.4)	0.05		-213.76
≥45	1,482	7	1,499	6	0.85 (0.26, 2.70)	0.78		1,387.58
Gender								
Female	3,889	12	3,940	15	1.23 (0.53, 2.90)	0.63	0.96	-1,386.04
Male	3,229	12	3,147	14	1.20 (0.54, 2.65)	0.66		-1,365.45
Blood relative								
Yes	1,591	8	1,529	10	1.30 (0.51, 3.30)	0.58	0.87	-661.40
No	5,527	16	5,558	19	1.18 (0.56, 2.48)	0.66		-1,909.80
Type of leprosy index patient								
PB	4,832	11	4,995	25	2.20 (0.86, 5.64)	0.10	0.01	-366.50
MB	2,286	13	2,092	4	0.34 (0.11, 1.02)	0.06		264.92
Physical distance								
Household	2,084	14	1,967	13	0.98 (0.46, 2.09)	0.97	0.42	9,191.09
Neighbour	5,034	10	5,120	16	1.57 (0.62, 4.02)	0.34		-878.34
BCG scar								
Present	4,057	15	4,066	17	1.13 (0.54, 2.36)	0.74	0.75	-2,067.40
Absent	3,056	9	3,019	12	1.35 (0.54, 3.38)	0.52		-971.06

*Odds Ratio (with 95% confidence interval), ** Numbers Needed to Treat

DISCUSSION

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

By providing rifampicin (a bactericidal drug) 8-12 weeks after BCG-vaccination, we envisaged preventing new leprosy cases among contacts in the first year after the BCG. This was described in Brazil by Duppre *et al.*[12], 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 cases following BCG-vaccination; however, this phenomenon already occurred in the period between BCG-vaccination and SDR provision. We had designed this time interval to ensure that rifampicin would not affect the efficacy of BCG, which is a live vaccine. At the time of the conceptualisation of the trial, we had no indication to expect this would occur this early after BCG. Most trials only include long-term follow-up, often starting 1 year after vaccination. The Brazilian trial[12] diagnosed the new leprosy cases 2-10 months after BCG-vaccination, which was also later than what we found in our trial. In previous studies the number of cases were either too low to confirm early 'induction' of leprosy after BCG[27 28] or did not specify when exactly leprosy occurred after vaccination[29 30]. 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 was 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 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 could have been preferable to first provide SDR, and this should be explored in a future study.

The level of protection offered by SDR in our study is 42%, which is less that the COLEP study (57%) conducted 10 years previously in the same population[13]. 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 the effect of SDR is 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[13 31]. Immunological screening of the effect of SDR on *M. leprae* infection in contacts can provide insight to what extent, how fast and how durable *M. leprae* infection is reduced by this single dose of antibiotics.

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. Possibly 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 nonspecifically activates protective innate responses[32 33]. In a previous study[26] we showed that BCG-vaccination induced significant Th1-type immunity (higher levels of IFN-γ) in those who presented with high local inflammation responses, implicating that efficient protection against *M. leprae* is dependent on an adequate Th1 response[34], although the concomitant inflammation may result in collateral tissue damage[35].

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 world-wide)[36-38], a low socioeconomic 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[39 40].

Our trial was not designed to establish the protective effect of BCG against leprosy. We assumed this is a given based on literature[5 27 41] and had therefore not included an arm in the trial without BCG. However, we doubt that the protective effect of BCG alone was large in our study. The incidence rate 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[13]. The incidence rate is 33.72 per

10,000 PYAR in the BCG only arm at 2 years of the MALTALEP trial. This implies a 14.3% reduction of leprosy incidence by BCG vaccination compared to no intervention. A Brazilian trial[12] 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 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[1].

In a subgroup analysis (supplementary data), we found no significant difference between the development of leprosy in revaccinated (BCG-scar positive) versus primarily vaccinated (BCG-scar naïve) contacts. In their meta-analysis, Merle et al.[5] also found no statistical difference in BCG-protection against leprosy between studies where individuals are vaccinated once and studies where individuals receive 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[10] and LepVax[42 9 10]. The MIP vaccine has only been evaluated in Uttar Pradesh, India, when both patients and contacts were vaccinated. The protective efficacy was 68%, 60%, and 28% after three, six, and nine years, respectively[10]. For LepVax, post-exposure prophylaxis tested in nine-banded armadillos appears safe and, unlike BCG, diminishes the neurologic disruptions caused by *M. leprae* infection[42]. Further trials are needed to investigate these vaccines before they can be introduced in the field.

Strengths of our trial is that it is randomized-controlled and field-based. An extensive number of leprosy contacts (14,988) were included. Also, because it is based in a leprosy-endemic area, implementation lies close to clinical field practice. Our loss to follow-up was less than 6%, which was less than expected. A limitation is that it was not possible to make it double-blind (placebo was not available), which may bias 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 know the difference. For instance, the field staff may expect and look more closely for signs and symptoms of leprosy in those that 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.

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 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 as guideline in their leprosy elimination strategy[15]. Implementation studies on the effectiveness of SDR as leprosy post-exposure prophylaxis (LPEP) are currently ongoing [43 44].

Ethical approval

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

Competing interests

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

Authors' contributions

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

Funding

This work is supported by the Order of Malta-Grants-for-Leprosy-Research (MALTALEP), the Q.M. Gastmann-Wichers Foundation (to AG and JHR), the Netherlands Leprosy Relief Foundation (NLR; ILEP#: 702.02.73) and the Leprosy Research Initiative (LRI; ILEP#: 703.15.07) both together with the Turing Foundation.

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