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Patient-related factors predicting the effectiveness of rifampicin chemoprophylaxis in contacts: 6 year follow up of the COLEP cohort in Bangladesh

SABIENA G. FEENSTRA*, DAVID PAHAN**, F. JOHANNES MOET*, LINDA OSKAM*** & JAN HENDRIK RICHARDUS*

**Erasmus MC, University Medical Center Rotterdam, The Netherlands*

***Rural Health Program Nilphamari, The Leprosy Mission Bangladesh, Dhaka, Bangladesh*

****KIT Biomedical Research, Amsterdam, The Netherlands*

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Summary

Objectives: The COLEP trial in Bangladesh showed a 57% reduction in leprosy incidence among contacts of newly diagnosed patients in the first 2 years after chemoprophylaxis with single dose rifampicin (SDR). We assessed the impact of this intervention after 6 years and identified characteristics of the leprosy index patients predicting the effectiveness of this intervention.

Design: The cohort of 1037 patients and their 28 092 contacts that participated in the randomised placebo controlled field trial with single dose rifampicin was followed for 6 years. The leprosy status of contacts was established at 2, 4 and 6 years after the intervention. We assessed the association between characteristics of the index leprosy patients and the development of clinical leprosy among their contacts using logistic regression.

Results: The protective effect of SDR was seen only in the first 2 years, with no additional effect after 4 and 6 years. However, the total impact of the intervention was still statistically significant ($P = 0{\cdot}025$) after 6 years and no excess cases were observed in the SDR arm at a later stage. The intervention prevented leprosy in contacts that actually received SDR, but did not offer protection to members of the same contact group who did not take chemoprophylaxis. The intervention was most effective in contact groups of female index patients, an enhanced effect was also observed in contact groups of patients belonging to a cluster of two or more leprosy patients at intake as well.

Correspondence to: Sabiena G. Feenstra, Researcher, Department of Public Health, Erasmus MC, University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, The Netherlands (e-mail: sgfeenstra@yahoo.com)

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Conclusion: These easy to recognise patient characteristics indicate a possible enhanced risk of transmission of *Mycobacterium leprae* to contacts in the vicinity of patients and are useful for deciding about preventive measures, such as early detection or chemoprophylaxis.

Keywords: leprosy; enhanced risk of transmission; chemoprophylaxis; Bangladesh

Introduction

Rifampicin is a strongly bactericidal antibiotic against *Mycobacterium leprae,* the causative agent of leprosy, and a single dose can prevent leprosy disease in contacts of leprosy patients. The COLEP trial in Bangladesh showed a 57% reduction in clinical leprosy incidence among contacts of newly diagnosed patients in the first 2 years after they received a single dose of rifampicin (SDR) as prophylactic treatment.[1] Chemoprophylaxis with rifampicin is a promising preventive intervention for contacts of leprosy patients, but before advocating this measure for routine application more information regarding the effects in field circumstances is required.[2–4]

Currently there is no appropriate and reliable test available to determine infection with *Mycobacterium leprae* before clinical signs of the disease develop. Consequently, prophylactic treatment can only be provided to people with a perceived high risk based on epidemiological risk assessment without knowing whether they are really infected. Deprived socio-economic circumstances and especially nutritional deficits are known risk factors for leprosy in general [5,6] and proximity to and blood relationship with an index patient, age of the contact, and bacterial load of the index patient are risk factors associated with clinical leprosy in contacts.[7,8]

However, the COLEP trial showed that chemoprophylaxis with SDR was most effective in contact groups with relatively low perceived *a priori* risks because the intervention was significantly more effective in contact groups of paucibacillary index patients, in contacts who were not living in the same household or had no close blood relationship to the index patient.[1] It was assumed that infected contacts in these groups had less exposure and therefore lower bacterial loads than those who are closer to an index patient, thus rendering treatment with SDR more successful. This finding poses a challenge for designing routine chemoprophylaxis interventions, because distant contacts are less approachable due to leprosy stigma related factors. It is important to establish more precisely, which contact groups benefit most from the intervention and how they can be reached best.

Three objectives were identified for this study. The first objective was to describe the 6-year follow up of the cohort of 1037 patients and their 28 092 contacts enrolled in the COLEP study in order to determine the long-term impact of SDR prophylaxis for contacts in more detail. The second objective was to establish if chemoprophylaxis with a SDR protected others in the same contact group who did not receive the intervention as they met exclusion criteria. The third objective was to identify patient related factors predicting the development of new cases among their contacts and effectiveness of SDR prophylaxis.

Methods

STUDY AREA AND POPULATION

In this prospective cohort study we assessed a cohort of 1037 leprosy patients and 28 092 contacts, participating in the COLEP study in northwest Bangladesh. A complete description of this prospective (sero-) epidemiological study on contact transmission and chemoprophylaxis in leprosy (COLEP) is given by Moet *et al.*[9]

As part of the COLEP study, a double blind placebo controlled trial was conducted, in which 21 711 contacts of the newly diagnosed leprosy patients received either a single dose of the prophylactic medicine rifampicin or a placebo. The remaining 6381 contacts in the study met an exclusion criterion and were excluded from the intervention. Exclusion criteria for contacts were refusal to participate, being a temporarily resident, aged under 5 years, pregnancy, liver disease or jaundice, under TB or leprosy treatment and suspect for leprosy at intake. However, all contacts were followed for 6 years to assess if any new leprosy cases developed, regardless of actual receiving chemoprophylaxis, placebo or nothing at all. When contacts were absent at one of the visits, they were not excluded but could participate again during the next follow up round.

After 4 years the study was un-blinded according to protocol and the first results were published.[1] The cohort of contacts of the index patients was followed for another 2 years to measure any long-term effects of the intervention. During the follow up visit after 6 years, all children born after the intake received a one-time check on symptoms and signs of leprosy as well.

The study was carried out in the districts Rangpur and Nilphamari in northwest Bangladesh, where The Leprosy Mission International Bangladesh conducts their Rural Health Programme. This mainly rural area had 4·4 million inhabitants at the start of the COLEP study in 2002. Of the 1037 patients included in the study, 400 had a single lesion paucibacillary (PB) leprosy, 342 PB leprosy (2–5 lesions), and 295 multibacillary (MB) leprosy. For each of these patients 20–30 contacts were registered. These contacts were either sharing the house or kitchen with the patient, were next door neighbours, neighbours of neighbours or social contacts that stayed in the same room with the patient for at least four hours a day during a minimum of 5 days a week.

DATA COLLECTION

Well-trained leprosy field staff of The Leprosy Mission International Bangladesh conducted home visits to collect the data. All participants were visited for an intake and the intervention in the period 2002/2003, 6 weeks after the index patient started with treatment. In the follow up period all contact groups were visited three times, respectively 2, 4 and 6 years after the intervention. During the follow up visits the contacts were examined for signs and symptoms of leprosy. Study participants who were registered as leprosy patients in between the follow up visits were recorded as well. The registers of the local health facilities were regularly reviewed to see if any of the study participants were registered as leprosy patients.

ANALYSIS

Data was entered in an Access database. After data cleaning analysis was performed with the statistical program STATA version 10.0. Contacts who actually participated in the trial and

who received chemoprophylaxis, either placebo or rifampicin, were analysed separately from those contacts that did not receive an intervention. The incidence rates per 10 000 person years at risk with confidence intervals were calculated for each group. Incidence rates for children below the age of 5 years, who were excluded for the intervention, were calculated separately.

Univariate and multivariate logistic regression with a backward elimination procedure was used to assess the association between characteristics of the original leprosy index patient and whether any of their contacts developed leprosy in the follow-up period. The characteristics age, sex, daily household income, household size, and education were used for this analysis as well as leprosy classification (MB or PB) and being part of a cluster of two or more leprosy patients. If among the contacts of an index patient another patient was found during the intake, the index patient was marked as being part of a cluster of two or more patients. Original index patients of the COLEP study were marked as having new leprosy cases among their contacts if there was at least one contact that received the intervention (rifampicin or placebo) and developed leprosy during the follow up period. Index patients who only had new cases among contacts who did not receive the intervention were excluded for this analysis.

Separate models were used for the placebo group and the rifampicin group. All characteristics of the index patients associated with new leprosy cases among contacts in the univariate analysis on a significance level $P < 0{\cdot}2$ were included in a multivariate analysis. Characteristics with a P value $> 0{\cdot}1$ in the multivariate analysis that did not contribute significantly to the model were eliminated one by one starting with the characteristic with the highest P-value to construct the final model. Characteristics of index patients significantly associated with the development of new cases among contacts in either the final model of the placebo or rifampicin group were tested for interaction to compare both groups. Besides univariate analysis, multivariate analysis was carried out to correct for confounding by one of the characteristics.

After getting the results of the previously mentioned analysis, further analysis was performed regarding the distance of new cases to and relation with the index patient. The mean number of new leprosy cases found in contact groups of solitary index patients was compared with the mean number of cases in contact groups of patients belonging to a cluster of one or more patients at intake as well.

ETHICS STATEMENT

Ethical clearance was obtained from the Ethical Review Committee of the Bangladesh Medical Research Council in Dhaka (ref. no. BMRC/ERC/2001–2004/799). All subjects were informed verbally in their own language (Bengali) about the study when they were invited to participate. Written consent was requested from each adult, while a parent or guardian had to sign the consent form for children who participated in the study.

Results

All 1037 contact groups participated in three 2-year rounds of follow up. Not all contacts participated in all follow up visits; some were absent during one of the visits but participated again in the next rounds, while others refused to participate in all rounds or passed away

during the follow up period. Of the 28 092 contacts identified, 90% participated in the first, 86% in the second, and 82% in the third follow up. These 28 092 contacts include those, not eligible to take SDR due to an exclusion criterion: 22% of all contacts in the rifampicin group and 21% in the placebo groups.

As reported previously, a 57% reduction in leprosy incidence was observed among contacts of newly diagnosed patients participating in the trial during the first two years after receiving SDR.[1] For the whole cohort, including members of the contact groups who had not been given SDR, a 39% reduction in leprosy incidence was observed in the SDR arm of the trial in the first 2 years after the intervention (Table 1).

The incidence rate per 10 000 person years at risk for the whole cohort was 31·9 [25·7–39·7] for the placebo arm of the trial and 19·6 [14·8–25·8] for the SDR arm. The incidence rate per 10 000 persons at risk among contacts within contact groups in the SDR arm who did not receive rifampicin themselves (37·1 [24·2–56·9]) was similar to that of the placebo arm of the study (33·6 [26·4–42·7]), indicating that SDR does not bring about group protection. The preventive effect of rifampicin was only seen in the first two years after

Table 1. New leprosy cases in contact groups of the index patients during the 6 years follow up by form of prophylaxis provided

Follow up (years)	Leprosy	No Leprosy	Total investigated	Incidence rate per 10 000 person years at risk (95% CI)
Placebo				
1–2	67	9939	10 006	33·6 (26·4–42·7)
3–4	24	9361	9385	12·8 (8·6–19·1)
5–6	17	8873	8890	9·6 (5·9–15·4)
Total	*108*		*10 006*	*18·0 (14·9–21·7)*
SDR				
1–2	29	9922	9951	14·6 (10·1–21·0)
3–4	30	9358	9388	16·0 (11·2–22·9)
5–6	18	8741	8759	10·3 (6·5–16·3)
Total	*77*		*9951*	*12·9 (10·3–16·1)*
No prophylaxis received, belongs to a placebo contact group				
1–2	14	2674	2688	26·0 (15·4–44·0)
3–4	6	2676	2682	11·2 (5·0–24·9)
5–6	3	2604	2607	5·8 (1·9–17·8)
Total	*23*			
No prophylaxis received, belongs to a SDR contact group				
1–2	21	2809	2830	37·1 (24·2–56·9)
3–4	5	2802	2807	8·9 (3·7–21·4)
5–6	5	2694	2699	9·3 (3·9–22·3)
Total	*31*			
Placebo contact group total				
1–2	81	12 613	12 694	31·9 (25·7–39·7)
3–4	30	12 037	12 067	12·4 (8·7–17·8)
5–6	20	11 477	11 497	8·7 (5·6–13·5)
Total	*131*			
SDR contact group total				
1–2	50	12 731	12 781	19·6 (14·8–25·8)
3–4	35	12 160	12 195	14·4 (10·3–20·0)
5–6	23	11 435	11 458	10·0 (6·7–15·1)
Total	*108*			

treatment. There was no additional effect after 4 and 6 years. However, the total difference in incidence between the placebo arm and the SDR arm remained statistically significant (5·1 [0·6–9·5], $P = 0{\cdot}025$) 6 years after the follow-up showing that no apparent access cases were observed in the SDR arm within 6 years after the intervention. For the total study period of 6 years the incidence rate per 10 000 persons at risk was 18·0 [14·9–21·7] in the placebo arm and 12·9 [10·3–16·1] in the SDR arm (Table 1).

The group not eligible for SDR included children in the contact groups who were under 5 years of age at the time of intake. Of these children, 14 developed leprosy in the 6 years follow up period, six in a rifampicin contact group (6·7 [3·0–14·9]) per 10 000 person years at risk) and eight in a placebo contact group (9·1 [4·5–18·1]) per 10 000 person years at risk). Although there were fewer cases in the rifampicin contact groups, the difference between the groups was not statistically significant (Table 2). There were no cases of leprosy recorded during the follow up period among children who were born after intake.

Index patients, whose contacts received placebo, had significantly more often a new case among their contacts if they were part of a cluster of two or more patients during intake (OR 5·97 [3·31–10·76], $P < 0{\cdot}001$). Significantly less new cases were observed among contacts of male index patients (OR 0·53 [0·32–0·87], $P = 0{\cdot}015$) and among contacts of index patients who were significantly older (0·98 [0·96–1·00], $P = 0{\cdot}30$) (Table 3).

For index patients whose contacts received SDR, it was significantly more likely to find new cases if they were part of a cluster of two or more patients found during intake (OR 2·80 [1·44–5·43], $P = 0{\cdot}002$), or if they had the multibacillary (MB) form of the disease (OR 1·80 [1·01–3·20], $P = 0{\cdot}045$) (Table 4).

The treatment groups were compared by analysis of interaction for all characteristics of the index patient that had a significant association with new cases among contacts in the placebo or SDR group. This analysis showed that chemoprophylaxis with SDR had significantly more effect when the index patients was female (*P*-value interaction $P = 0{\cdot}01$), while there was also an indication (although not statistically significant) that the intervention had a stronger effect when the index patient was part of a cluster of two or more patients at intake (*P*-value interaction $P = 0{\cdot}073$) (Table 5).

Table 2. New leprosy cases during 6 year follow up among children in the contact groups who were less than 5 years of age at intake

	Intervention at household level**					
	Placebo			Rifampicin		
Follow-up	Leprosy (N)	Total investigated (N)	Incidence per 10 000 person years at risk (95% CI)	Leprosy (N)	Total investigated (N)	Incidence per 10 000 person years at risk (95% CI)
1–2 years	5		17·0 (7·1–40·8)	5		16·8 (7·0–40·3)
3–4 years	3		10·2 (3·3–31·6)	0		0 (0–26·8)*
5–6 years	0		0 (0–27·1)*	1		3·4 (0·5–23·8)
Total	*8*	*1473*	*9·1 (4·5–18·1)*	*6*	*1492*	*6·7 (3·0–14·9)*

* 0·5 used as N to calculate the upper limit of the confidence interval

** Children <5 years at intake were excluded for the intervention and did not receive SDR themselves

Table 3. Logistic regression analysis of characteristics of the index patients and new leprosy cases among contacts during follow up: placebo group

Characteristic of original COLEP index patients belonging to the placebo group		Leprosy cases among contacts in 6 year follow up period				Univariate analysis			Multivariate analysis with backwards elimination		
		No		Yes		Crude Odds Ratio (95% CI)		*P*-value	Odds Ratio (95% CI)		*P*-value
		Mean (SD*)		Mean (SD*)							
Age (years)		32·3	(16·1)	27·6	(12·4)	0·98	(0·96–1·00)	$P = 0·013$	0·98	(0·96–1·00)	$P = 0·030$
Daily household income (BDT)		62·9	(69·6)	56·7	(36·6)	1·00	(0·99–1·00)	$P = 0·429$			
Household size		5·2	(2·4)	4·8	(1·4)	0·92	(0·82–1·03)	$P = 0·151$			
		N (%)		N (%)							
Part of a cluster of 2 or more patients at intake	No	392	(87·7)	55	(12·3)	1·00					
	Yes	33	(54·1)	28	(45·9)	6·05	(3·40–10·77)	$P < 0·001$	5·97	(3·31–10·76)	$P < 0·001$
Sex	Female	128	(77·1)	38	(22·9)	1·00					
	Male	297	(86·8)	45	(13·2)	0·51	(0·32–0·82)	$P = 0·006$	0·53	(0·32–0·87)	$P = 0·015$
Leprosy classification	PB**	294	(82·8)	61	(17·2)	1·00					
	MB**	131	(85·6)	22	(14·4)	0·81	(0·48–1·37)	$P = 0·433$			
Education	No	185	(82·2)	40	(17·8)	1·00					
	Yes	240	(84·8)	43	(15·2)	0·83	(0·52–1·33)	$P = 0·434$			
	Total	423		85							

* Standard deviation
** PB: paucibacillary; MB: multibacillary

Table 4. Logistic regression analysis of characteristics of the index patients and leprosy new cases among contacts during follow up: rifampicin group

Characteristic of original COLEP index patients belonging to the rifampicin group		Leprosy cases among contacts in 6 year follow up period				Univariate analysis			Multivariate analysis with backwards elimination		
		No		Yes		Crude Odds Ratio (95% CI)		*P*-value	Odds Ratio (95% CI)		*P*-value
		Mean (SD*)		Mean (SD*)							
Age (years)		33·0	(16·1)	30·0	(15·3)	0·99	(0·97–1·01)	$P = 0·173$			
Daily household income (BDT)		58·8	(49·1)	52·0	(34·9)	1·00	(0·99–1·00)	$P = 0·296$			
Household size		5·1	(2·3)	5·4	(2·7)	1·05	(0·94–1·17)	$P = 0·385$			
		N (%)		N (%)							
Part of a cluster of 2 or more patients at intake	No	386	(89·4)	46	(10·7)	1·00					
	Yes	47	(75·8)	15	(24·2)	2·68	(1·39–5·16)	$P = 0·003$	2·80	(1·44–5·43)	$P = 0·002$
Sex	Female	161	(91·0)	16	(9·0)	1·00					
	Male	272	(85·8)	45	(14·2)	1·67	(0·91–3·04)	$P = 0·098$			
Leprosy classification	PB**	325	(89·3)	39	(10·7)	1·00					
	MB**	108	(83·1)	22	(16·9)	1·69	(0·96–2·99)	$P = 0·067$	1·80	(1·01–3·20)	$P = 0·045$
Education	No	206	(87·7)	29	(12·3)	1·00					
	Yes	225	(87·6)	32	(12·4)	1·01	(0·59–1·73)	$P = 0·970$			
	Total	433		61							

* Standard deviation
** PB: paucibacillary; MB: multibacillary

Table 5. Univariate and multivariate ana7lysis of interaction between treatment group and patient characteristics

Characteristic of original COLEP index patients, with a significant association with new cases among contacts in one of the treatment groups	Univariate analysis of interaction			Multivariate analysis of interaction		
	OR for new leprosy cases among contacts in follow up			OR for new leprosy cases among contacts in follow up		
	Odds Ratio Placebo group (95% CI)	Odds Ratio Rifampicin group (95% CI)	*P*-value interaction	Odds Ratio Placebo group (95% CI)	Odds Ratio Rifampicin group (95% CI)	*P*-value interaction
Part of a cluster of 2 or more patients at intake	6·05 (3·40–10·77)	2·68 (1·39–5·16)	$P = 0·068$	5·98 (3·31–10·78)	2·64 (1·35–5·16)	$P = 0·073$
Age (years)	0·98 (0·96–1·00)	0·99 (0·97–1·01)	$P = 0·480$	0·98 (0·96–1·00)	0·99 (0·97–1·00)	$P = 0·725$
Sex	0·51 (0·32–0·82)	1·67 (0·91–3·04)	$P = 0·003$	0·54 (0·32–0·90)	1·55 (0·83–2·88)	$P = 0·010$
Leprosy classification	0·81 (0·48–1·37)	1·69 (0·96–2·99)	$P = 0·061$	0·99 (0·55–1·78)	1·84 (1·01–3·33)	$P = 0·148$

Table 6. Mean number of new leprosy cases in contact groups of solitary index patients versus those from a cluster

	Mean number of new cases in contact group (Std. Dev.)		Comparison of means (*t*-test)
	Placebo	Rifampicin	*P*-value
Index patients with at least one new case detected in their contact group during follow up ($N = 146$)	1·45 (0·79)	1·33 (0·70)	$P = 0·35$
Index patients solitary at intake ($N = 103$)	1·46 (0·76)	1·30 (0·76)	$P = 0·31$
Index patients belonging to a cluster of 2 or more at intake ($N = 43$)	1·43 (0·88)	1·40 (0·51)	$P = 0·91$

The mean number of new cases per index patient was slightly higher for patients belonging to a cluster of two or more cases compared to solitary patients (1·45 vs. 1·33), but this difference was not statistically significant (Table 6).

There was no difference between male and female index patients regarding the sex of new cases in their contact group. The highest number of new cases was observed among neighbours and social contacts without a blood relation of female index patients receiving placebo (24·7 new cases per 100 contact groups, Table 7). These contacts benefitted most from the protective effect of chemoprophylaxis with rifampicin as well, since the leprosy incidence was found 68% lower in neighbours and social contacts of female index patients receiving rifampicin (7·9 new cases per 100 contact groups, Table 7).

Discussion

Chemoprophylaxis with SDR was effective in preventing leprosy among contacts in the first 2 years after treatment, after which no additional effect was observed.[1] SDR prevented

Table 7. Number of new leprosy cases (6 year follow up) among contacts by sex of and distance to the original index patient and by prophylaxis received

		Distance of new case to original index patient*			
		Not close		Close	
		n	n per 100 contact groups (95% CI)	*n*	n per 100 contact groups (95% CI)
Placebo prophylaxis					
Sex index patient (n)	Female (166)	41	24·7 (18·2–33·5)	12	7·2 (4·1–12·7)
	Male (342)	28	8·2 (5·7–11·9)	27	7·9 (5·4–11·5)
Total		69	13·6 (10·7–17·2)	39	7·7 (5·6–10·5)
Rifampicin prophylaxis					
Sex index patient (n)	Female (177)	14	7·9 (4·7–13·4)	9	5·1 (2·6–9·8)
	Male (317)	29	9·1 (6·4–13·2)	25	7·9 (5·3–11·7)
Total		43	8·7 (6·5–11·7)	34	6·9 (4·9–9·6)

*Close: new case is genetically related to the index patient (child, parent or brother/sister) and/or lives in the same house (shares kitchen and/or roof)

leprosy in contacts that actually received the intervention, but did not offer protection to members of the same contact group who did not take chemoprophylaxis. The intervention was most effective in contact groups of female patients, especially in neighbours and social contacts, and there was an indication of enhanced effectiveness in contact groups of patients belonging to a cluster of two or more leprosy patients at intake.

Strengths of this study are its robust design as a prospective cohort study with a large number of participants, a relatively long follow up period of 6 years and a low loss to follow up of only 18% equally divided over case and control groups. It is therefore possible to assess the temporal relationship between the intervention and new cases of leprosy that develop afterwards. Although the incubation period of leprosy can be longer than 6 years, the majority of cases are known to occur before this time.[10] Another strength of the study is that all initially selected contacts in the cohort were followed, both those receiving the intervention and those who were not eligible, enabling prediction of the effectiveness of SDR chemoprophylaxis in an actual leprosy control programme where not all contacts will receive SDR. A limitation of the study is that it was carried out in a leprosy high endemic area and findings might not be generalised to areas where leprosy is less common.

The effect of chemoprophylaxis was only evident in the first 2 years and we considered initially that this early effect could be caused by a delayed outcome. Nevertheless, the difference in incidence rate remained statistically significant 6 years after the intervention without apparent excess cases in the SDR arm at a later stage, although we cannot exclude that there may be some in the longer term.

In the placebo arm of the study new cases of leprosy were observed significantly more often in contact groups in the vicinity of female index patients, indicating a possible enhanced risk of transmission. The protective effect of SDR was also significantly higher when the index patient was female. Especially contacts of female index patients with a low *a priori* risk like neighbours and social contacts without a blood relationship, benefitted from the intervention. In Bangladesh there are clear differences in the social positions of men and women. Due to cultural customs, the social contact pattern of females is concentrated in and around their homes, while males have more extensive contacts outside the house, inside and outside their own neighbourhood. In a study in the same region leprosy was found associated with social contacts within the village or urban ward, not limited to household contacts and nearby living neighbours.[11] In the COLEP study only contacts living nearby leprosy patients were included, household contacts, neighbours, neighbours of neighbours and social contacts living in the vicinity of the index patient. While most social contacts of women are thus included, the social circuit of men is reaching further and some of their social contacts at risk might not have been included in the study population. Since it can be assumed that the average number of transmissions is the same for male and female leprosy patients, differences between the sexes in this study might be explained by the fact that new cases of leprosy among social contacts of male index patients who do not live in the vicinity have been missed.

Enhanced transmission in contact groups of index patients who were part of a cluster of two or more patients at intake could be explained by the fact that there is proven transmission among contacts in these groups. In only 17% of the placebo contact groups (85 out of 508) new cases were observed during the follow up period as sign of transmission, while in 46% of the contact groups of index patients belonging to a cluster new cases were found (28 out of 61). Enhanced transmission can also explain the fact that SDR seems to be more effective in these contact groups. When there is transmission within a contact group it is likely that,

beside new cases with symptoms of disease, infected people without symptoms or signs of disease are present. These contacts can benefit from SDR. Although enhanced transmission is expected from MB patients as well this effect was not observed in this study.

An important issue with respect to the intervention is the preparedness of patients to reveal their leprosy diagnosis to contacts in order to provide them with chemoprophylaxis. Approximately 25% of the new leprosy cases registered in the area during the intake of the trial did not participate. Although there were several possible reasons for not participating (e.g. not present in the house at enrolment time, residing temporarily in the study area), the main reason was a refusal to take part in the study. When participating in the study patients had to give permission to disclose their diagnosis of leprosy to contacts in order to provide them with the intervention. Patients often accept disclosure of their diagnosis to household contacts (usually close family members) but regularly oppose disclosure to non-close contacts, such as neighbours or social contacts, because of stigma associated with the disease.[12] This ethical dilemma should be taken into account when designing a chemoprophylaxis intervention for routine implementation, and can differ considerably per country.

SDR has been shown most effective in non-close contacts that are not living in the same household or are not closely related to the index patient.[1] These contacts however, are more difficult to reach than close contacts belonging to the same household or family. An alternative to providing chemoprophylaxis to close (household) contacts during a contact survey is to reach the non-close contacts through mass campaigns without disclosure of the leprosy patients. During a study on five leprosy hyperendemic Indonesian islands it was shown that chemoprophylaxis with rifampicin for the whole population was more effective than an intervention for close contacts of patients only.[13] This approach could be considered in areas where leprosy is highly endemic with an increased risk of transmission and the intervention could be at neighbourhood, village or even at a district level. Chemoprophylaxis as routine practice in leprosy control programmes would be a socially acceptable option in Bangladesh, since people have a positive attitude towards taking medicines as prophylaxis.[12] Cost-effectiveness of SDR chemoprophylaxis for contacts of index patients has been established for the leprosy control situation in Bangladesh based on the findings of the COLEP study.[14] Cost effectiveness of SDR through mass campaigns for high risk populations needs to be addressed in future studies.

We found that chemoprophylaxis was most effective in contact groups of female patients and patients belonging to a cluster of two or more leprosy patients at intake. These easy to recognise patient characteristics indicate a possible enhanced risk of transmission of *Mycobacterium leprae* to contacts in the vicinity of patients and are useful for deciding about preventive measures for contacts, such as early detection or chemoprohylaxis.

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Contributors

JHR, LO, and FJM were involved in the design of the study, while DP was involved in implementing the study in the field. Analysis, interpretation, and writing were done by SGF

with input of all other authors. The corresponding author SGF had full access to all data in the study and had final responsibility to submit for publication.

Ethical approval

The Ethical Review Committee of the Bangladesh Medical Research Council in Dhaka approved this study (BMRC/ERC/2001-2004/799).

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