PREVENTION OF LEPROSY USING RIFAMPICIN AS CHEMOPROPHYLAXIS

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Abstract. An intervention study was implemented on five Indonesian islands highly endemic for leprosy to determine whether rifampicin can be used as chemoprophylaxis to prevent leprosy. The population was actively screened before the intervention and subsequently once a year for three years. In the control group, no chemoprophylaxis was given. In the contact group, chemoprophylaxis was only given to contacts of leprosy patients and in the blanket group to all eligible persons. The cohort consisted of 3,965 persons. The yearly incidence rate in the control group was 39/10,000; the cumulative incidence after three years was significantly lower in the blanket group ($P = 0.031$). No difference was found between the contact and the control groups ($P = 0.93$). Whether this apparent reduced leprosy incidence in the first three years in the blanket group is due to a delayed development of leprosy or a complete clearance of infection needs to be determined.

INTRODUCTION

Leprosy is an infectious disease caused by *Mycobacterium leprae*. Multidrug treatment (MDT) was introduced by the World Health Organization (WHO) in 1982 and was seen as an instrument for the elimination of leprosy as a public health problem, defined as a national prevalence less than 1/10,000.[1] However, even after 20 years of MDT, case detection rates (CDRs) are not decreasing,[2] indicating that patients are probably not the only source of transmission; subclinically infected persons and contacts of patients have also been implicated.[3,4] Therefore, it is necessary to examine interventions which include these groups of potentially infectious persons.

Vaccination with bacillus Calmette-Guérin has been shown to have varying efficacy (20–80%) against leprosy.[5] In remote areas, chemoprophylaxis is operationally more feasible than vaccination, and among high risk groups it has been proposed as a strategy for lowering leprosy incidence.[6] Chemoprophylaxis is already successfully used in some countries to prevent the spread of tuberculosis.[7]

Contact with a leprosy patient is thought to be the main determinant in incident leprosy. Similar to tuberculosis transmission,[8] the "stone-in-the-pond" concept was suggested for describing leprosy transmission in concentric circles around a patient, whereby not only household contacts are at an increased risk of developing leprosy, but also neighbors and social contacts.[9] Application of this concept in leprosy control would shift control activities from the current population-based approach to a more targeted approach for high risk groups.

In their meta-analysis, Smith and Smith[6] have shown that chemoprophylaxis is an effective way to reduce the incidence of leprosy, and is more cost-effective when used in household contacts than in entire communities. Most chemoprophylaxis studies until now used dapsone and those few studies that did use rifampicin were non-controlled intervention studies.[6] Therefore, it remains unclear whether rifampicin is effective as a chemoprophylaxis.

The objective of this study was to evaluate rifampicin prophylaxis as a preventive measure in leprosy control. We investigated whether prophylaxis used in contacts compared with whole communities is equally effective in preventing leprosy. We report here, to our knowledge for the first time, on a controlled community-based intervention study to determine which categories of contacts need rifampicin prophylaxis to obtain a reduction of clinical leprosy as measured by leprosy incidence.

METHODS

Study population. From a 30-island archipelago in the Flores Sea in Indonesia, selected as the study area because of its geographic isolation and the absence of a routine leprosy control program, five islands were chosen by local health care officials based on their cooperation. A description of these islands was previously published.[10] Prior to the study, we received ethical clearance from the Ethical Research Committee of the Hasanuddin University and from the Ministry of Health of the Republic of Indonesia. The community leaders of each of the islands gave written communal consent each year.

Study design. To form similarly sized intervention groups, three islands were combined into one intervention group. Two types of chemoprophylactic intervention strategies were compared with a control group. The blanket group included three islands on which prophylaxis was given to all eligible persons. The contact group included an island on which prophylaxis was given to all eligible contacts of all known leprosy patients in 2000. The control group was an island on which no chemoprophylaxis was given.

Assignment of the intervention strategies to the islands was based on predetermined criteria: 1) only islands where ≤ 20% of the population was a contact of a leprosy patient were eligible for contact intervention to show a clear distinction between the contact and blanket interventions; and 2) island(s) with highest CDR received the blanket intervention.

In both interventions, we used two doses of 600 mg of rifampicin for adults and 300 mg for children (6–14 years old) with approximately 3.5 months between doses. Children < 6 years of age, pregnant women, and persons with clinically observed liver failure or suspected tuberculosis did not receive prophylaxis. All leprosy patients were treated with the standard MDT directly after diagnosis.

The baseline and intervention phase took place in June–July 2000 (first survey) and October–November 2000 (second survey). The first survey consisted of a population census, preparation of detailed maps of all islands including all houses, and an active door-to-door screening for leprosy.[10]

At the end of the first survey, the first dose of chemoprophylaxis was supplied. During the second survey persons, who were missed during the first survey were examined and the second dose of rifampicin was supplied. We recorded whether the prophylaxis was taken under supervision or given via a close relative when the person was absent. During three yearly follow-ups (June 2001, April 2002, and April 2003) active door-to-door screenings for leprosy were repeated on all islands by the same research team.

Outcome measure. Leprosy was clinically diagnosed based on detailed skin examination, including testing for anesthesia and examination for enlargement of nerves, and confirmed by an experienced doctor. Classification was based on the WHO system of lesion counting (paucibacillary [PB] patients = 1–5 lesions, multibacillary [MB] patients = > 5 lesions).[11] Classification of PB patients was afterwards adjusted to MB when the outcome of the skin smear microscopy was positive.[10]

Definition of contacts. Contacts comprised household and neighbor contacts.[9] Household contacts were persons who lived with a patient in the same household (house). Neighbor contacts were persons who lived either in a house adjacent to the patient's house (neighbor 1) or in a house adjacent to a neighbor 1 house, in both cases with a distance of less than 50 meters between the houses. For all contact types, the duration of contact should have been at least six months and the contact should not have ended longer than six months prior to the baseline survey. The contact status in 2000 was used in the analysis.

Data analysis. The outcome measure was leprosy incidence. Only persons who were at risk for leprosy in July 2000 (i.e., persons screened in 2000 without leprosy) and who had followed the protocol (Figure 1) were included in the survival analysis. Persons not following the protocol (62) were those who received only one dose of rifampicin because they died or moved away, were wrongly defined as contacts in the contact group during the first survey, or were only identified as a contact of a patient found during the second survey. Persons who received one or no dose for other reasons such as pregnancy, and thus followed the protocol, were included in the analysis.

Follow-up time in this study was measured in person-months to adjust for the various lengths of participation. The follow-up time for all persons in the cohort started July 1, 2000. This was also used for persons not screened in July 2000, but found to be leprosy free in November 2000. They were assumed to be also leprosy free in July 2000. Persons with a complete follow-up without developing leprosy had a follow-up time of 33.5 months. Persons who were found to be leprosy free during a follow-up and had missed screening during previous follow-ups were assumed to have been free of leprosy the year(s) before. The follow-up time of persons who had developed leprosy was set at the midpoint of the last follow-up in which they were found to be free of leprosy and the follow-up in which they were diagnosed with leprosy. The follow-up time of persons lost to follow-up was set to the midpoint of the last follow-up and the possible next follow-up. A sensitivity analysis showed that these assumptions had no effect on the results.

Kaplan-Meier cumulative incidence curves of each group were compared with the log-rank test. It should be noted that
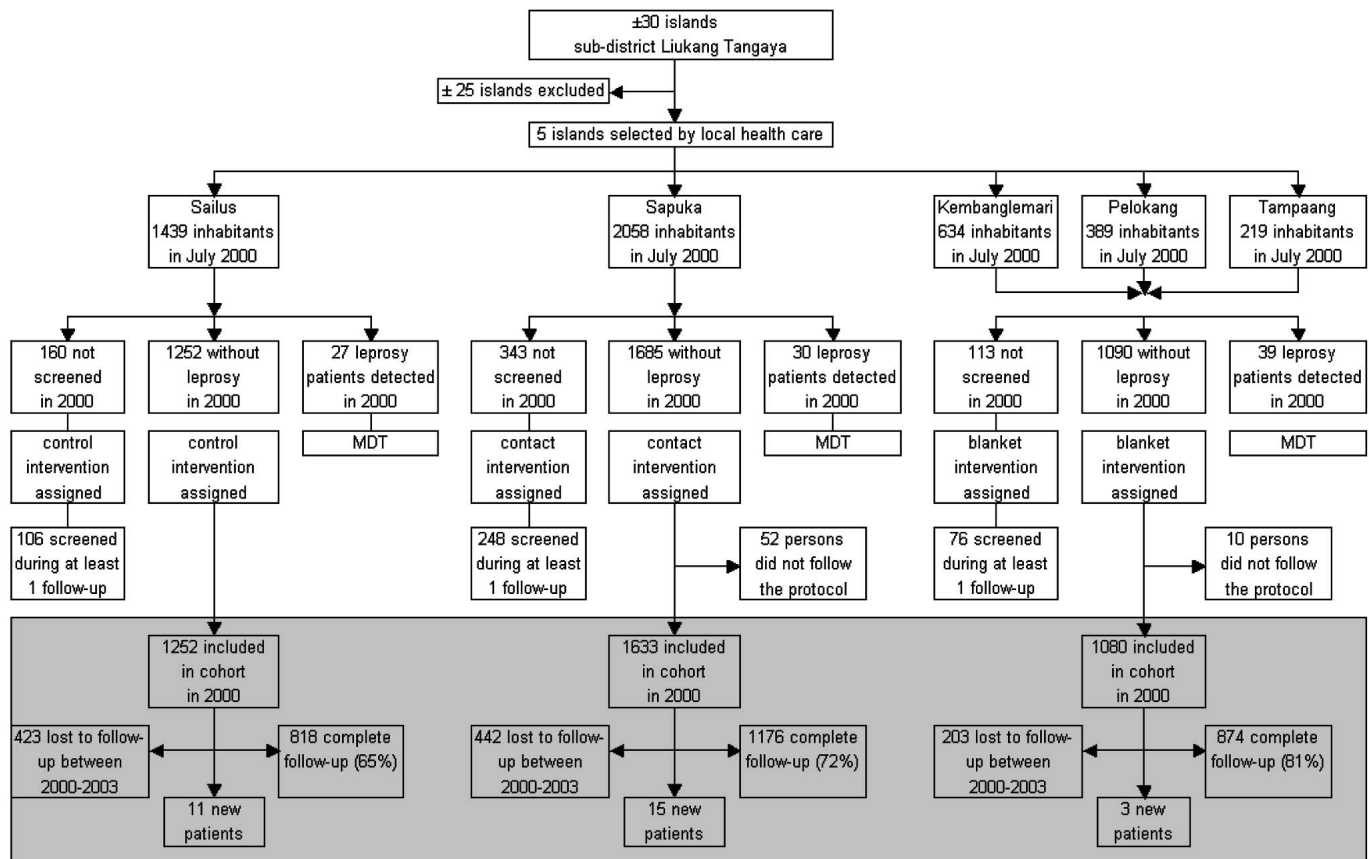

FIGURE 1. Trial profile. MDT = multidrug treatment.

TABLE 1
Baseline characteristics of the intervention groups*

	Control group	Contact group	Blanket group
Population in 2000	1,439	2,058	1,242
Screened in 2000	1,279 (88.9%)	1,715 (83.3%)	1,129 (90.9%)
Patients in 2000	27	30	39
MB:PB ratio of patients in 2000	0.69	1.00	0.77
Prevalence†	188	146	314
% contacts of population in 2000	28.1	19.0	58.8
Net migration rate‡	64.4	82.6	53.5
Cohort§	1,252	1,633	1,080
Median age (interquartile range)	20 (8–33)	21 (9–37)	18 (7–35)
Sex ratio (M/F)	0.86	0.74	0.90
BCG coverage in 2000	1.0%	7.5%	3.8%
Contacts (%)¶	348 (27.8)	339 (20.8)	661 (61.2)
Received prophylaxis (%)¶	0	291 (17.8)	880 (81.5)
At least 1 time supervised prophylaxis (%)#	0	263 (90.4)	790 (89.8)

* MB = multibacillary; PB = paucibacillary; BCG = bacille Calmette-Guérin.
† Prevalence = number of patients/population in 2000 per 10,000.
‡ Net migration rate = difference between the numbers of immigrants and emigrants divided by the average population of that area during follow-up per 1,000 population.
§ Cohort = persons at risk for leprosy in 2000 (screened persons minus leprosy patients in 2000 and those who did not follow the protocol).
¶ % of cohort.
# % of person who received prophylaxis.

the contact group consisted of both those who received prophylaxis (contacts) and those who did not receive prophylaxis (non-contacts). Cox proportional-hazards regression was used to independently estimate the effect of the different strategies and also the effect of prophylaxis regardless of the strategy calculating hazard ratios (HRs) and their 95% confidence intervals (CIs). In multivariate analysis sex, age (in categories), and contact status were added. We tested for interaction and confounding between covariates and performed stratified analysis for the different types of contacts. The proportionality assumption was satisfied for all covariates.

RESULTS

In June 2000, 4,739 persons were living on the five islands. During the baseline surveys, 4,123 inhabitants were screened. A total of 3,965 persons were included in the cohort (Figure 1). The male:female ratio was 0.82 in the cohort and 2.4 outside the cohort. This difference was seen in all three groups. Relevant differences between the three intervention groups during the baseline survey were screening coverage and leprosy prevalence (Table 1). Due to the differences in leprosy prevalence, the percentage of contacts differed between groups. The migration rate during the study period also differed between islands.

After 33.5 months, 2,868 (72%) persons were still under follow-up: 65% of the control group, 72% of the contact group, and 81% of the blanket group. Those people who were lost to follow-up were, in all three groups, more often men (male:female ratio = 1.31 versus 0.68 among those with complete follow-up) and were slightly older (median age = 23 compared with 19 for those with complete follow-up). The proportion of those who received at least one dose of rifampicin under supervision was the same for people with complete follow-up and those lost to follow-up. In the blanket group, the percentage of contacts was lower among those lost to follow-up (43.3%, 88 of 203) compared with those with complete follow-up (65.2%, 570 of 874). This did not differ in the other groups.

During follow-up, 29 new leprosy patients were detected in the cohort: 11 in the control group, 15 in the contact group, and 3 in the blanket group (Table 2). Figure 2 shows the cumulative incidence for the different groups. The cumulative incidence after 33.5 months was significantly lower in the blanket group compared with the control group ($P = 0.031$, by log-rank test). No difference was found between the contact and control groups ($P = 0.93$).

Of the 15 new patients in the contact group, three were a contact and had received prophylaxis (all at least one time supervised). All three new patients in the blanket group had received prophylaxis: one patient at least one time supervised and two patients only indirectly. The four new patients (three from the contact and one the from blanket group) who had received prophylaxis at least 1 time supervised were all PB.

Table 3 shows the adjusted HRs for developing leprosy in the blanket and contact groups compared with the control group. There were no interactions between the covariates and intervention strategy. The effectiveness of blanket supply of

TABLE 2
New patients during follow-up in cohort and outside cohort*

	Control group	Contact group	Blanket group
Cohort	1,252	1,633	1,080
Cohort after 33.5 months	818 (65%)	1,176 (72%)	874 (81%)
Observed new patients in cohort	11	15	3
MB	2 (18%)	1 (7%)	1 (33%)
PB 2–5	3 (27%)	8 (53%)	0
PB 1	6 (55%)	6 (40%)	2 (67%)
Patients outside cohort†			
MB	0	1	0
PB	2	3	0
Patients migrated to islands‡			
MB	2	2	0
PB	0	2	0

* MB = multibacillary; PB 2–5 = paucibacillary leprosy with 2–5 lesions; PB1 = single-lesion paucibacillary leprosy.
† Patients outside the cohort = number of patients found during follow-up who lived on the islands but were not screened in 2000.
‡ Patients migrated to islands = patients detected during follow-up who were not yet living on the islands in 2000.
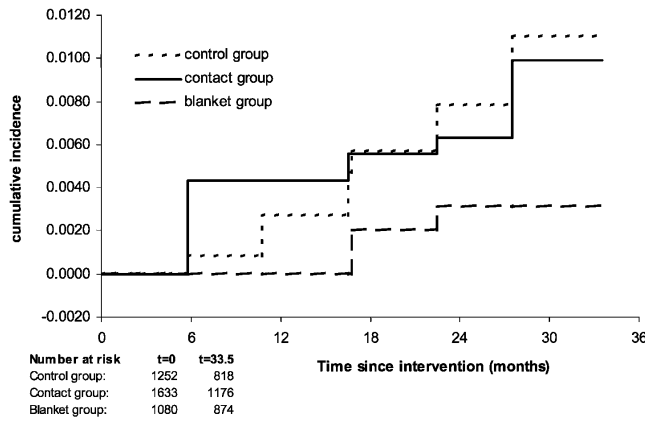
FIGURE 2. Kaplan-Meier curves for cumulative incidence of leprosy for three different intervention strategies.

prophylaxis based on the adjusted HR was 74.6% (95% CI = 5.4–93.2). The effectiveness increased to 90.9% (95% CI = 25.8–98.9) if only those persons in the blanket group who received at least one supervised dose of rifampicin were taken into account. The HRs were also calculated for the intake of prophylaxis regardless of intervention strategy. The adjusted HR in the population more than five years old for the intake of at least one supervised dose of rifampicin compared with no prophylaxis was 0.26 (95% CI = 0.078–0.86).

Although interaction of contact status and intake of prophylaxis was not significant in the Cox proportional hazards regression, differences were seen in the effect of the strategies between the different types of contacts and non-contacts. We calculated the expected number of patients for each type of contact for the contact and blanket group based on the cumulative incidence of each type of contact in the control group. No patients were observed among the non-contacts of the blanket group, while 4.1 were expected (95% CI = 1.2–7.0) (Table 4). No effect of chemoprophylaxis could be detected among the households contacts in the blanket group: two patients were observed in this group, which was as expected (95% CI = 0–9.1).

DISCUSSION

This first controlled intervention study of rifampicin prophylaxis against leprosy showed that prophylaxis given to the whole community was associated with a reduced incidence of leprosy. In contrast, prophylaxis given to only household and neighbor contacts did not have a detectable effect on leprosy incidence after 33.5 months in this highly endemic area.

Our findings are consistent with two previous blanket chemoprophylaxis studies that used dapsone rather than rifampicin. The studies were a large cluster randomized trial in India among persons less than 25 years old[12] and a controlled trial in Uganda among school children.[13] Both showed a 99% protective effect that was much higher compared with the levels of protection found in household trials.[6]

Only one trial (non-controlled) has been reported to have used rifampicin prophylaxis (single dose of 25 mg/kg) in a blanket strategy in the southern Marquesas and concluded after 10 years of follow-up that the prophylaxis was 35–40% effective. They used previous CDR as historical controls correcting for CDR trends in the population that was not administered chemoprophylaxis.[14–16]

The aim of chemoprophylaxis is to clear infection and interrupt transmission. The incubation period of leprosy lies in most instances between two and five years,[17] but may be as long as 21 years.[18] We therefore expect that the majority of the patients detected during the almost three years of follow-up were already infected before the intervention. Thus, chemoprophylaxis prevented the development of clinical signs in persons already infected with *M. leprae*. It is still uncertain whether this was a result of a lengthening of the incubation time or a complete clearance of infection. A longer follow-up time is needed to determine whether transmission was really interrupted in the blanket group.

We did not find a difference in the cumulative incidence after 33.5 months between the control and the contact groups. Based on our contact definition, 19% of the population in the contact group was defined as a contact of a leprosy patient and received prophylaxis. We defined contacts solely on spatial grounds; therefore, we may have missed important contacts such as social, work-related, and familial contacts. In the blanket group, all eligible persons received prophylaxis; thus, these other types of contacts were included in this intervention, which may be an explanation for the observed difference in effect of the two interventions. Another reason for not finding an effect of the contact intervention could be that within this area highly endemic for leprosy, everyone has contact with a leprosy patient. To measure the effect of prophylaxis in contacts, an intervention in an area with low disease endemicity may be needed with a much larger sample size since incidence rates will be low.

TABLE 3
Crude and adjusted hazard ratios for developing leprosy by intervention strategy and by intake of prophylaxis*

	No.	Cumulative number of events	HR (95% CI)	
			Crude	Adjusted†
Strategy				
Control group	1,252	11	1.0	1.0
Contact group	1,633	15	0.96 (0.44–2.10)	1.05 (0.48–2.30)
Blanket group	1,080	3	0.28 (0.078–1.00)	0.25 (0.068–0.95)
Intake of prophylaxis‡				
No rifampicin	2,147	23	1.0	1.0
Unsupervised rifampicin	117	2	1.55 (0.37–6.61)	0.81 (0.17–3.98)
At least 1 time supervised rifampicin	1,048	4	0.33 (0.11–0.95)	0.26 (0.078–0.86)

* HR = hazard ratio; CI = confidence interval.
† Adjusted for sex, age, and contact status in 2000.
‡ Only for the population greater than five years old.

Observed and expected number of patients for the different types of contacts and non-contacts in contact and blanket group based on the control group*

		Control group	Contact group	Blanket group
Non-contacts	Cohort in 2000	904 (72%)	1294 (79%)	419 (39%)
	Total person-months-at-risk	24,237	38,057	12,583
	Observed incidence† (95% CI)	39 (12–66)	35 (15–55)	0
	Observed new patients	8	12	0
	Expected new patients‡ (95% CI)		12.4 (3.7–21.1)	4.1 (1.2–7.0)
Neighbor contacts	Cohort in 2000	284 (23%)	273 (17%)	517 (48%)
	Total person-months-at-risk	7,745	8,111	16,061
	Observed incidence (95% CI)	32 (0–75)	29 (0–69)	8 (0–22)
	Observed new patient	2	2	1
	Expected new patients (95% CI)		2.1 (0–5.1)	4.2 (0–10.0)
Household contacts	Cohort in 2000	64 (5%)	66 (4%)	144 (13%)
	Total person-months-at-risk	1,571	1,631	4,550
	Observed incidence (95% CI)	81 (0–239)	81 (0–239)	53 (0–126)
	Observed new patients	1	1	2
	Expected new patients (95% CI)		1.1 (0–3.3)	3.1 (0–9.1)
Total	Cohort in 2000	1,252	1,633	1,080
	Total person-months-at-risk	33,553	47,800	33,193
	Observed incidence (95% CI)	39 (16–63)	35 (17–54)	11 (0–24)
	Observed new patients	11	15	3
	Expected new patients (95% CI)		15.7 (6.5–24.9)	10.9 (4.5–17.3)

* CI = confidence interval.
† Observed incidence = Kaplan-Meier cumulative incidence after 33.5 months re-calculated per 10,000 per year.
‡ Expected new patients = calculated using the corresponding cumulative incidence after 33.5 months of the control group.

Stratified analysis showed that a lower incidence of leprosy was observed mainly among the non-contacts in the blanket group. This could be an explanation for the absence of an effect of the intervention in the contact group. What are possible reasons that prophylaxis was not working as effectively as expected among contacts? First, new patients may have arisen due to ongoing transmission among contacts after the intervention. Even if this is the case, it is doubtful that it would have an effect on the outcome since new patients were most likely already infected before the intervention. Second, more subclinical patients may be expected among the contacts since they have a higher risk of developing leprosy than non-contacts.[9,19] For these subclinical patients, two doses of rifampicin may not be enough to stop the development of clinical disease.

It was not feasible to blind the study because of logistic constraints. Knowing the allocation of the intervention strategies, the research team may have been tempted to screen the control group more and/or the intervention group less thoroughly. In that case, one would expect more single lesion (PB1) patients in the control group compared with the other groups because single lesions are easier overlooked during a less-detailed examination. However, we did not find differences in the incidence of PB1 patients between the three groups.

Since this was a community-based intervention study in which whole communities (with their intrinsic differences) were compared, differences between the control and intervention groups could introduce a bias. We do not expect large differences with respect to socioeconomic and health status, since the islands have the same income generating activities and rudimentary health care system. We assigned the blanket intervention to the island group with the highest prevalence to ensure that a lower incidence during follow-up would not be caused by an already lower initial prevalence.

Selection bias due to persons lost to follow-up may have influenced the estimated incidence in the groups. In all three groups, men and older persons were more often lost to follow-up. Only in the blanket group contacts were less often lost to follow-up. Contacts have an increased risk of developing leprosy compared with non-contacts,[9,19] and thus a possible effect would be a lower incidence in the blanket group and consequently a stronger effect of blanket chemoprophylaxis.

There are three potential sources of continuing transmission: 1) prevalent patients outside the cohort who were not detected in 2000, 2) patients who migrated to the islands, and 3) incident patients among persons lost to follow-up. Prevalent patients as well as migrated patients were only detected on the control and contact islands. The influence of this on the outcome of the study is expected to be very small since the patients detected during follow-up were most likely already infected before the intervention.

A limitation of the study is that it has been performed in a setting with a very high incidence of 39/10,000 per year in the control group. Whether a blanket approach also gives high effectiveness in an area with lower endemicity needs to be explored.

In conclusion, population-based prophylaxis was associated with a reduced leprosy incidence in the first three years after implementation. Prolonged follow-up will show if the intervention only causes a delay in the development of leprosy or a complete clearance of infection and interruption of transmission. We showed that in this area of high endemicity rifampicin prophylaxis for spatially defined contacts only does not influence leprosy incidence. Further studies including social contacts are needed to investigate the effect of prophylaxis given to contacts in areas of low endemicity.

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