Lepr Rev (2014) **85,** 158–169

Leprosy incidence: six years follow-up of a population cohort in Bangladesh

PREM BASEL*, DAVID PAHAN**, FAKE J. MOET*, LINDA OSKAM*** & JAN HENDRIK RICHARDUS*
**Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands*
***Rural Health Program, The Leprosy Mission Bangladesh, Nilphamari, Bangladesh*
****KIT (Royal Tropical Institute), KIT Biomedical Research, Amsterdam, The Netherlands*

Accepted for publication 22 July 2014

Summary
Background: With approximately 250,000 new leprosy cases detected annually, transmission of *M. leprae* appears to be ongoing in many areas of the world. By studying prospectively the number of leprosy patients found in a population sample at the beginning of the study (prevalence) and the number of new patients found during the 6-year observation period (incidence), we aim to understand better the transmission of *M. leprae* and the burden of disease.
Methodology: To establish the prevalence and incidence rates of leprosy in the general population of a high endemic area in Bangladesh, we followed prospectively 20,218 individuals from a random cluster sample of the population and examined them at 2-yearly intervals for 6 years.
Results: At intake we found 27 new leprosy cases, indicating a prevalence of previously undiagnosed leprosy of 13·3/10,000. Follow-up at 2, 4 and 6 years revealed 17, 16, and eight new cases, respectively, representing incidence rates of 4.0, 4·5 and 2·3/10,000 PYAR, respectively. The incidence rate over 6 years was 3·7/10,000 PYAR. The observed incidence rate is three times higher than the new case detection rate in the same area. Of all 68 new leprosy cases, five (7%) had MB leprosy. The proportion of children under 15 years was 24%. The proportion of female patients was 60%, but the incidence rate of leprosy was the same for males and females.
Conclusions: The decline in incidence of leprosy in a general population sample is less pronounced than routine data from a control programme led us to expect.

Correspondence to: Jan Hendrik Richardus, Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands (e-mail: j.richardus@erasmusmc.nl)

 0305-7518/14/064053+12 $1.00

Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. The disease mainly affects the skin, peripheral nerves, mucosa of the upper respiratory tract, and the eyes. It can be progressive if left untreated, causing permanent damage to the skin, nerves, limbs, and eyes. However, leprosy is a curable disease and disability due to leprosy can be averted by early diagnosis and treatment.[1] Access to health services regarding information, diagnosis, and treatment of leprosy with multidrug therapy (MDT) are key components of the current strategy to control the disease.[2]

In 1991, the 44th World Health Assembly (WHA) adopted the objective to eliminate leprosy globally as a public health problem by the year 2000. Leprosy elimination is defined as reducing the prevalence rate to less than one case per 10,000 population. Although this was achieved at the global level by the end of 2000, in many countries a sizable leprosy problem persists. The global annual detection of new cases continued to decline, from 620,638 cases in 2002 to 232,857 in 2012.[3] In the Southeast Asia region of the World Health Organization (WHO), the number of newly detected patients has been remarkably stable over the last 5 years: from 174,118 in 2006 to 166,445 in 2012.[3] This indicates that transmission of *M. leprae* is ongoing, particularly in the Indian subcontinent, and further efforts are needed to control the disease.

Because there are as yet no reliable tests for the detection of sub-clinical *M. leprae* infection, assessing the results of leprosy control depends on information about disease, rather than infection. Disease statistics, such as those reported on the global leprosy situation by WHO, are expressed in terms of prevalence and new case detection. Disease prevalence in leprosy is measured by counting all patients receiving MDT at a given time and expressing this as a ratio, using the population as the denominator (per 10,000). Prevalence figures are therefore proportionally linked to length of treatment. Over the years, trends in prevalence have been strongly determined by shortening of treatment duration. New case detection is not affected by duration of treatment. Trends in new case detection rates reflect trends in incidence rates, provided that no significant changes occur in case detection efforts, self-reporting behaviour, or diagnostic procedures or criteria.[4] However, in the past 25 years case detection has been determined in many countries by operational factors such as expanding of control activities during the elimination drive leading up to 2000 and decreased activities thereafter.[5] Therefore, in-depth studies are necessary at the population level to understand better the occurrence of disease and the incidence of leprosy in the population. This information is useful for managers of leprosy control programmes to organise their activities effectively, but also provides epidemiological data for estimating disease burden, transmission of *M. leprae* in the population, and incubation periods, for instance through mathematical modelling.[6,7]

It is known that the actual number of leprosy patients in a community, region, or country can be much larger than the number registered for treatment, with the latter providing the basis for prevalence figures as reported by WHO. Many surveys have been performed to estimate the leprosy prevalence in the general population, but very few studies are available on the incidence of leprosy in a general population.[8–10] As part of a larger study of transmission of *M. leprae* and the efficacy of targeting contacts with preventive interventions such as chemoprophylaxis,[11] we estimated the background prevalence of leprosy in an endemic community in Bangladesh through a multistage random cluster sample of the general population. The number of newly found leprosy cases among 20,218 people from the cluster sample was 27, giving a prevalence of previously undiagnosed leprosy in the general

population of 13·3/10,000 people. This rate was six times higher than that of the registered cases (2·31 *vs*. 13·4/10,000) in the same area at the time of the survey (2002–2003). Details of this prevalence study were reported previously.[12]

We hypothesized that there is ongoing transmission of *M. leprae* in the general population of the study area and aimed to establish prospectively the incidence of leprosy in a general population sample. Here we report the incidence rate of leprosy in this multistage random cluster sample from the general population over a 6-year observation period and describe the main characteristics of the patients found.

Methods

ETHICS STATEMENT

The Ethical Review Committee of the Bangladesh Medical Research Council in Dhaka provided clearance for this study (ref. no. BMRC/ERC/2001–2004/799). All subjects were informed verbally in their own language (Bengali) about the study and invited to participate. Written consent was requested from each adult. For children, parents or guardians provided consent.

POPULATION

The study population consisted of the inhabitants of the Rangpur and Nilphamari districts in northwest Bangladesh, with a total population of over four million people (estimated population in 2000, based on the 1991 census). Of the total population, a multistage random cluster sample was taken to estimate the prevalence of previously undiagnosed leprosy (PPUL). The leprosy control staff of the Rural Health Program (formerly DBLM) of The Leprosy Mission International Bangladesh performed active door-to-door screening. As leprosy is known to occur in clusters, one large sample from a single area may not give a reliable approximation of the leprosy situation in the two districts, so multiple samples were taken from different areas. Therefore, a multistage cluster sampling procedure as described in the literature was followed.[13]

SAMPLING PROCEDURE

A total of 20 clusters of 1,000 people each were randomly sampled from the 13 sub-districts. One to three clusters were allocated to each sub-district proportional to the size of its population. A list of unions (in rural areas) and wards (in urban areas) per sub-district was drawn up. A union or ward has an average population of approximately 23,500. If the population of a large union was more than three times the size of the smallest union, the largest union was split. Then, one to three unions (the number of clusters allocated to that sub-district) were selected from the list by means of computerised randomization. Per selected union, a list of all sub-unions (mostly equivalent to villages) was prepared in such a way that the population of the largest village was maximally three times the population of the smallest. These sub-unions have an average population of 5,300. Grouping of small villages was sometimes needed, as the accepted minimum size was a population of 1,600 (estimation based on the 1991 census). The computer then randomly selected one sub-union per union. Three out of the 20 clusters were allocated to urban areas, which is a proper reflection of the population figures.

SURVEYS

Initial surveys of all clusters were performed between November 2002 and February 2003. The population of the village/area was informed in advance about the purpose and time the team would perform the survey. During the survey, participants were asked about symptoms of leprosy and a body check was performed. Genital areas, and for females also the buttocks and the breasts, were not examined. The survey included all people present, with female health workers examining the adult females. The survey started at the northern border of the selected area and stopped when approximately 1,000 people were examined. The local leprosy control programme criteria for diagnosis and classification, which generally follow the WHO guidelines, were used.[14,15] Leprosy was diagnosed 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 nerves, or a positive skin smear result for acid-fast bacilli. Patients with negative smear results at all sites and who had more than one but no more than five skin lesions were grouped as having paucibacillary leprosy (PB2-5) and those showing positive smear results at any site or who had more than five skin lesions, as having MB leprosy. Within the paucibacillary group we classified those with only one lesion as having single lesion paucibacillary disease (SLPB); patients with a single lesion with a satellite were also recorded as SLPB. All persons suspected of having leprosy were referred to a leprosy control officer on site. Final confirmation was made by a medical officer, who also made a digital photograph of the lesions for future reference. The health professionals confirming the diagnosis had a minimum of 5 years' experience in the diagnosis of leprosy at the referral centre level.

All suspected and confirmed cases were actively followed up and seen at one of the RHP clinics. If the disease was confirmed, participants were offered multidrug therapy (MDT) according to WHO guidelines.[15] All data were entered on registration cards, and entered into a database afterwards.

Follow-up surveys were performed on all people included during the initial survey after 2 (2004–2005), 4 (2006–2007), and 6 (2008–2009) years, during the same months (November to February) as the intake survey. Individuals who came into the households of the survey population after the initial survey were not taken into consideration.

STATISTICAL ANALYSIS

Person years at risk (PYAR) was calculated through log linear analysis by cluster for each follow-up and used to calculate the incidence rate at two, four, and six years, taking into account people lost to follow-up, diseased or deceased. With log linear analysis the numbers are assumed to follow a Poisson distribution. The numbers per year were large enough to get a reliable estimate of the rates, as is shown by the CI's.

We tested for heterogeneity by comparing the fitted numbers per cluster and the observed. If there would have been no clustering effect the observed numbers would not be different from the fitted, given the model. This was tested with a Chi-square distribution. The differences and thereby the heterogeneity was significant, so we corrected the standard errors by the over-dispersion parameter, based on this test.[16]

The trend of the incidence rate over the follow-up periods was calculated and the *p*-value estimated after correction for heterogeneity. Moreover, a calculation of the correlation between prevalence of previously undiagnosed leprosy (PPUL) among 20 clusters during intake and the incidence rate during first follow-up was carried out.

Data were analysed with descriptive statistics using the Statistical Package for the Social Sciences (SPSS for Windows, release 17·0·2, SPSS Inc., Chicago, IL, USA) and the R-package version 2·7·1, in which p-values were calculated through log linear regression with correction for heterogeneity. A p-value less than 0.05 was considered statistically significant.

Results

The total number of people enumerated on the registration cards was 20,303, of whom 85 were excluded due to missing data in the records. Fifty-two people were known to have completed leprosy treatment (RFT) before the survey. As cured leprosy patients presumably can become infected and diseased again, these known RFT cases were not excluded. Thus 20,218 people remained for analysis in this study. Participants were examined from 20 clusters in two districts, enrolling approximately 1,000 people from each cluster. At the first (2-year) follow-up, 18,626 participants were included; second (4-year) follow-up included 18,364 participants, and third (6-year) follow-up included 16,726 people. Loss to follow-up was thus approximately 8% at two and four years and 17% at six years, while the male-female ratio remained the same at 0·7 during all surveys. Mean age increased from 23 years at intake to 25, 27, and 29 years at two, four, and six-year follow-up, respectively. This indicates that with regard to sex and age there is no marked difference between those who remained in the study and those who were lost to follow-up during successive surveys.

In total, 68 people were diagnosed with leprosy from this cohort of 20,218 individuals during intake and 6-year follow-up (Table 1).

Of the 68 newly detected cases from intake to 6-year follow-up, five had MB leprosy, giving an overall proportion of MB cases of 7%. None of the patients diagnosed at intake and at 4-year follow-up were MB cases. The proportion of MB cases detected at first follow-up and third follow-up was 18% and 25%, respectively (Table 2).

Table 1 shows the PPUL by cluster. The number of cases detected at intake was 27, giving an overall PPUL of 13·3/10,000 (95% CI: 8·8–19·4). Females outnumbered males in nearly all clusters, with a male-female ratio of 0·7. Mean age was 23 years. Cluster number 2 had the highest burden of leprosy (6 cases; PPUL 59·5/10,000) among the 20 clusters.[12]

The number of cases detected at the 2-year follow-up was 17, giving an overall incidence rate of leprosy of 4·0/10,000 PYAR (95% CI: 2·1–7·5). Cluster 10 had the highest incidence rate of leprosy, with five cases giving an incidence rate of 22·2/10,000 PYAR. There was a statistically significant positive correlation between the prevalence rate at intake and incidence rate at first follow up ($P = 0.006$), after correction for heterogeneity. This correlation was not found for the next two follow-ups.

The number of cases detected at the 4-year follow-up was 16, giving an overall incidence rate of leprosy of 4·5/10,000 PYAR (95% CI: 2·4–8·6), which was not statistically significantly different from that of the 2-year follow-up. Urban cluster 6, however, had the highest incidence rate at second follow-up, with five cases giving an incidence rate of 28·2/10,000 PYAR compared to cluster 10 with five cases at the first follow-up.

The number of cases detected at the 6-year follow-up was eight, giving an overall incidence rate of leprosy of 2·3 /10,000 PYAR (95% CI: 0·9–5·8). Although this represents half of the number of new cases found during the previous follow-ups, the CI's overlap with those of follow-ups one and two, indicating that there is no statistically significant difference between the incidence rates of the three follow-ups. This was also demonstrated by

Table 1. Prevalence at intake of PPUL and incidence rate of leprosy during follow-up by sample cluster

	Intake				Follow-up 1		Follow-up 2		Follow-up 3	
Cluster	N	M/F ratio	Leprosy cases	PPUL (per 10,000)	Leprosy cases	IR (per 10,000 PYAR)	Leprosy cases	IR (per 10,000 PYAR)	Leprosy cases	IR (per 10,000 PYAR)
1	1008	0·7	0	0	1	4·6	1	5·9	1	5·1
2	1008	0·7	6	59·5	3	13·4	1	6	0	0
3	1000	1·0	0	0	0	0	0	0	0	0
4	1000	0·6	0	0	0	0	1	7·2	0	0
5	1008	0·8	0	0	0	0	1	5·6	1	5·8
6 (urban)	1054	0·6	2	19	2	9·0	5	28·2	1	5·7
7	1012	0·7	1	9·9	0	0	0	0	0	0
8	1000	0·7	5	50·0	1	4·6	0	0	0	0
9	1007	0·9	0	0	0	0	0	0	0	0
10	1017	0·6	3	29·5	5	22·2	0	0	0	0
11	1001	0·6	0	0	1	4·8	0	0	0	0
12 (urban)	1008	0·7	4	39·7	3	14·0	1	6·2	0	0
13 (urban)	1005	0·7	1	9·9	0	0	0	0	1	9·5
14	1004	0·9	0	0	1	5·2	0	0	1	6·0
15	999	0·7	0	0	0	0	0	0	0	0
16	1031	0·8	1	9·7	0	0	0	0	1	5·6
17	1007	0·6	1	9·9	0	0	0	0	1	5·4
18	1017	0·6	3	29·5	0	0	4	21·2	1	6·2
19	1007	0·7	0	0	0	0	2	10	0	0
20	1025	0·8	0	0	0	0	0	0	0	0
Total	20,218	0·7	27	13·3	17	4·0	16	4·5	8	2·3
				95% CI: 8·8–19·4		95% CI: 2·1–7·5		95% CI: 2·4–8·6		95% CI: 0·9–5·8

PPUL: prevalence of previously undiagnosed leprosy
IR: incidence rate

Table 2. Distribution of leprosy type by cluster from intake to third follow-up

	Intake			1st follow-up			2nd follow-up			3rd follow-up			
Cluster	MB	PB	PS	MB	PB	PS	MB	PB	PS	MB	PB	PS	Total
Nilphamari district													
1	–	–	–	1	–	–	–	1	–	–	–	1	3
2	–	1	5	–	1	2	–	–	1	–	–	–	10
3	–	–	–	–	–	–	–	–	–	–	–	–	0
4	–	–	–	–	–	–	–	–	1	–	–	–	1
5	–	–	–	–	–	–	–	1	–	1	–	–	2
6 (urban)	–	2	–	1	1	–	–	5	–	–	1	–	10
7	–	–	1	–	–	–	–	–	–	–	–	–	1
8	–	3	2	–	–	1	–	–	–	–	–	–	6
Rangpur district													
9	–	–	–	–	–	–	–	–	–	–	–	–	0
10	–	–	3	1	2	2	–	–	–	–	–	–	8
11	–	–	–	–	–	1	–	–	–	–	–	–	1
12 (urban)	–	1	3	–	2	1	–	1	–	–	–	–	8
13 (urban)	–	–	1	–	–	–	–	–	–	–	–	1	2
14	–	–	–	–	–	1	–	–	–	1	–	–	2
15	–	–	–	–	–	–	–	–	–	–	–	–	0
16	–	–	1	–	–	–	–	–	–	–	1	–	2
17	–	–	1	–	–	–	–	–	–	–	1	–	2
18	–	1	2	–	–	–	–	4	–	–	1	–	8
19	–	–	–	–	–	–	–	2	–	–	–	–	2
20	–	–	–	–	–	–	–	–	–	–	–	–	0
Total	0	8	19	3	6	8	0	14	2	2	4	2	68

MB: multibacillary leprosy
PB: paucibacillary leprosy, 2–5 lesions
PS: paucibacillary leprosy, single lesion

calculating the trend in incidence rate over the three follow-up periods, which was also not statistically significant ($P = 0{\cdot}385$) after correction for heterogeneity. In other words, there is no statistically significant downward trend in incidence rate over the full observation period of 6 years. Clusters with a low number (zero, one, or two) of newly found cases were scattered over every follow-up, as were clusters with higher numbers (Table 1). The test for heterogeneity among 20 clusters for all three follow-up periods combined was statistically significant ($P = 0{\cdot}005$).

The overall six-year incidence rate of leprosy was 3·7/10,000 PYAR (Table 3).

The highest incidence rates were in participants aged 15–19 years and 50 years and older at intake (9·3 and 7·0/10,000 PYAR, respectively), but the trend for age was not statistically significant with regard to the incidence of leprosy ($P = 0{\cdot}815$), after correction for heterogeneity. Of the total 68 newly detected cases from intake to the third follow-up, 16 (24%) were children younger than 15 years at intake, although some were actually older at the time of diagnosis. Of all newly detected cases, 41 were female (60%); the incidence rate was not statistically significantly different between sexes ($P = 0{\cdot}958$).

Discussion

In order to establish the incidence rate of leprosy in the general population of a high endemic area in Bangladesh, we followed prospectively 20,218 individuals from a random cluster

Table 3. Leprosy patients by age-group cohort and sex from first to third follow-up

Age group (years) at intake	PYAR		Leprosy cases						Total leprosy cases		6-year incidence		
			1st FU		2nd FU		3rd FU						
	M	F	M	F	M	F	M	F	M	F	M	F	M&F
≤4	8840·0	8454·8	0	0	0	2	0	0	0	2	0	2·4	1·1
5–9	8226·9	8479·9	0	1	3	0	0	1	3	2	3·6	2·3	3
10–14	6777·2	7535·3	1	0	1	1	1	0	3	1	4·4	1·3	2·8
15–19	3317·1	5315·7	2	1	1	0	1	3	4	4	12·0	7·5	9·3
20–24	2901·3	6002·1	1	1	0	2	0	0	1	3	3·4	5·0	4·5
25–29	2090·1	5917·2	0	0	1	0	0	0	1	0	4·8	0	1·2
30–34	2954·2	6888·1	0	1	0	2	1	0	1	3	3·4	4·3	4·1
35–39	2228·6	4131·7	0	0	1	0	0	1	1	1	4·5	2·4	3·1
40–44	2576·3	4672·0	0	3	0	0	0	0	0	3	0	6·4	4·1
45–49	1397·4	2268·7	0	1	0	0	0	0	0	1	0	4·4	2·7
≥50	4301·7	5688·0	1	4	1	1	0	0	2	5	4·6	8·8	7·0
Total	45,610·9	65,353·4	5	12	8	8	3	5	16	25	3·5	3·8	3·7

PYAR person year at risk
FU follow-up

sample of the population and examined them at 2-yearly intervals for 6 years. At intake we found 27 new leprosy cases, indicating a prevalence of previously undiagnosed leprosy of 13·3/10,000. Follow-up at 2, 4 and 6 years revealed 17, 16, and eight new cases, respectively, representing incidence rates of 4·0, 4·5 and 2·3/10,000 PYAR, respectively. The incidence rate over 6 years was 3·7/10,000 PYAR. Although the number of new cases had halved at 6 years compared to the 2 and 4 year follow-up, an overall downward trend in incidence rate could not be established due to small numbers. Of all 68 new leprosy cases, five (7%) had MB leprosy, reflecting the known MB:PB ratio among routinely detected cases in the area. The proportion of children under 15 years was 24%. The proportion of female patients was 60%, but the incidence rate of leprosy was the same for males and females, which is explained by overrepresentation of females in the population cohort. Loss to follow-up was 8% at 2 and 4 years and 17% at 6 years.

The strength of this study is that it is a prospective cohort study based on a random cluster survey of the general population in the two districts concerned. In this way it approaches an accurate representation of the leprosy situation in this particular population. At the intake survey, potential sources for selection bias were considered, especially as only those present during the survey were included. Selection bias on the cluster level is not likely, but on the individual level selection bias is possible as the survey is announced in advance and those afraid of the diagnosis may avoid participation, causing underestimation of prevalence and incidence rates. It is also possible that, due to stigma, those with leprosy have a higher chance of being unemployed or rejected at school, so they could be overrepresented. All patients found however, were in the early stage of the disease, so this does not seem to be a likely reason for the high number of cases found in our study. We assume that these possible sources of bias probably have had little or no effect. More important is the issue of males, who are generally less likely to be at home during the day; indeed, only 42% of those examined are

males and 60% of patients found at intake and during follow-up are females. Calculation of incidence rates in person years corrects statistically for this overrepresentation of females. Nevertheless, both prevalence and incidence rates of leprosy are slightly (but not significantly) higher in females than in males. This contrasts sharply with the percentage of females among newly diagnosed leprosy patients, which is reportedly around 40% in the districts during the same period as the study and even higher in the 1980's and 1990's.[17] Finally, loss to follow-up needs to be taken into account. Given the large population followed over many years, the numbers lost to follow-up are fairly limited: 8% at 4 years and 17% at 6 years. With regard to sex and age there is no marked difference between those who remained in the study and those lost to follow-up, indicating that this loss is unlikely to introduce significant bias.

It is very difficult to establish the transmission of *M. leprae* in the population. Many people are assumed to become infected, but only a small percentage of these (not more than 5%) ever develop clinical leprosy. As yet there is no reliable test for infection. Nasal carriage of *M. leprae* by healthy individuals has been established with polymerase chain reaction techniques in several endemic countries, but its relevance for the transmission of the microorganism remains unclear.[2,4,18] This leaves us with the incidence rate of clinical leprosy at the population level as the nearest proxy of *M. leprae* transmission. Our study provides unique information on the incidence rate of leprosy in the population, but the results should be interpreted with caution. There has been an ongoing leprosy control programme in the area for many years, which may influence the transmission of *M. leprae*. Moreover, conducting regular surveys among a population cohort as performed in our study represents an active intervention in itself. New leprosy patients identified during the surveys are put on treatment and thus removed as potential sources of infection from the population. New cases identified during follow-up are either those who were still in their incubation period or who were infected by an external source. *M. leprae* multiplies very slowly; the incubation period of the disease is about 5 years, but it can take as long as 20 years for symptoms to develop.[19] This relatively long incubation time of leprosy could explain why the incidence rate in our study only started to decline at 6 years. The average incubation time is necessarily shorter in children under 15 years of age and the high percentage of children with leprosy found during the observation period of our study indicates that at least some transmission of *M. leprae* has occurred during this time. Also, the occurrence of five MB cases during the observation period suggests that active transmission could have taken place during this period, as it is assumed that MB cases in particular spread *M. leprae* before diagnosis and can easily remain undetected for some time because of the initial absence of clearly recognizable symptoms. Whereas the high incidence rate of leprosy among young people reflects recent transmission, the high incidence rate in those aged 50 years and older is probably explained primarily by delayed diagnosis, long incubation periods and/or reactivation of latent infection, as also seen regularly with tuberculosis in the elderly.

There are only a few published studies of population-based incidence rates of leprosy. Most studies concern prevalence rates or incidence rates among risk groups, such as household contacts. In a study published in the early 1990's from Karonga District, northern Malawi, 489 new cases were identified among 83,500 individuals followed for an average of 5 years (11·2/10,000 PYAR).[10] In this study, 29 (6%) of the incident cases were MB and incidence rates were generally higher among females than males, and increased steadily with age. A more recent study on highly endemic islands in Indonesia reported 44 new cases out of 4,903 initially symptom free individuals after 4 years, giving an incidence rate of 29·8/10,000

PYAR.[9] In Agra district, India, an incidence rate of 6.2/10,000 PYAR was reported among 42,113 individuals observed,[8] but the study population was not randomly selected and therefore probably overestimates the incidence rate. Nevertheless, this figure is also much higher than the reported new case detection rate of 0·82/10,000 PYAR in that area. In the Agra study there was also no marked difference in incidence rates between males and females. All these studies demonstrate that transmission of *M. leprae* appears to be ongoing in the presence of a leprosy control programme and that cases found through these special population surveys yield much higher estimates of leprosy new case detection and prevalence rates than recorded in the official registries.

Our study also indicates that transmission of *M. leprae* had been ongoing in the population cohort during the observation period, although some people may have been infected before intake. Also, our observed overall incidence rate of 3·7/10,000 PYAR is nearly three times higher than the official registered new case detection rate (often used as a proxy for the incidence rate) of 1.45/10,000 population in the same area.[20] This difference is partly due to the fact that new cases are detected through self-reporting or referral, rather than through population-wide surveys. Also, it is known that a proportion of leprosy cases spontaneously resolve without further clinical consequences. These patients never present for diagnosis and treatment and it is unclear whether they contribute to ongoing transmission of *M. leprae*. It is therefore not necessarily bad that these patients are never registered and our 2-year follow-up periods may in fact represent an overestimation of the leprosy problem by identifying patients before they have had a chance for spontaneous remission. Nevertheless, a large proportion of leprosy cases in the community are not found, even in the presence of a long-standing and well-accepted leprosy control programme that has been ongoing in the area since the mid-1970s. New case detection more than halved in Rangpur and Nilphamari districts, from 1,776 in 2000 to 744 in 2009.[20] For the whole of Bangladesh, these figures were 12,135 and 5,239, respectively. Nonetheless, our study of the incidence rate of leprosy in the same population shows only a marginal decline in the same period, although this population was surveyed every 2 years for a 6-year period and all newly found leprosy patients were prescribed treatment immediately.

Another important factor that may influence the transmission of *M. leprae* in a population is the presence of an infant BCG vaccination programme. BCG is known to protect against leprosy.[21] In Bangladesh, including the study area, BCG vaccination is given routinely to new-born infants. Since the introduction of the BCG vaccination in 1974, the coverage had gradually expanded to 80% in 1990 and remained at that level in 2003.[22] Based on the current study, it is not possible to establish the effect of BCG vaccination on the transmission of *M. leprae* in the area, but the situation in the study area is not different from the country as a whole.

Because it is not feasible to intensify leprosy control work by doing regular population wide surveys in endemic areas, more effective intervention strategies that can be implemented widely must be developed. Such interventions are currently being developed and field-tested, such as new T-cell based assays for infection and preventive interventions aimed at contacts of leprosy patients such as chemoprophylaxis with single dose rifampicin and immunoprophylaxis with BCG vaccine. Such strategies will help to reduce transmission of *M. leprae* at the population level, while actual control activities can remain focused on newly diagnosed leprosy patients and their contacts.[7] In the meantime, maintenance of systematic leprosy control activities in endemic countries remains vital.

Funding

The COLEP study is supported financially by the American Leprosy Missions (ALM) and The Leprosy Mission International (TLMI). As ALM and TLMI are charities, there are no financial interests in the study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

This paper was written as part of an MSc programme in Public Health at the Netherlands Institute of Health Sciences (NIHES) in Rotterdam, the Netherlands.

Competing Interests

The authors have declared that no competing interests exist.

Acknowledgements

We thank the staff of the leprosy control unit and the statistical department of the Rural Health Program of the Leprosy Mission Bangladesh in Nilphamari and Rangpur for their dedicated work, often under difficult circumstances. We also acknowledge with gratitude the advice and scientific support of the Study Advisory Group of the COLEP study, consisting of Dr. W.H. van Brakel, Prof. P.R. Klatser, Dr. P.R. Saunderson, Prof. W.C.S. Smith, and Dr. S.G. Withington.

References

[1] Britton WJ, Lockwood DN. Leprosy. *Lancet*, 2004; **363**: 1209–1219.
[2] van Beers SM, Izumi S, Madjid B *et al.* An epidemiological study of leprosy infection by serology and polymerase chain reaction. *Int J Lepr Other Mycobact Dis*, 1994; **62**: 1–9.
[3] Anonymous. Global leprosy: update on the 2012 situation. *Wkly Epidemiol Rec*, 2013; **88**: 365–379.
[4] Beyene D, Aseffa A, Harboe M *et al.* Nasal carriage of *Mycobacterium leprae* DNA in healthy individuals in Lega Robi village, Ethiopia. *Epidemiology and Infection*, 2003; **131**: 841–848.
[5] Richardus JH, Habbema JD. The impact of leprosy control on the transmission of *M. leprae*: is elimination being attained? *Lepr Rev*, 2007; **78**: 330–337.
[6] Meima A, Smith WC, van Oortmarssen GJ *et al.* The future incidence of leprosy: a scenario analysis. *Bulletin of the World Health Organization*, 2004; **82**: 373–380.
[7] Fischer EA, de Vlas SJ, Habbema JD *et al.* The long-term effect of current and new interventions on the new case detection of leprosy: a modeling study. *PLoS NTD*, 2011; **5**: e1330.
[8] Kumar A, Girdhar A, Girdhar BK. Incidence of leprosy in Agra district. *Lepr Rev*, 2007; **78**: 131–136.
[9] Bakker MI, Hatta M, Kwenang A *et al.* Risk factors for developing leprosy-a population-based cohort study in Indonesia. *Lepr Rev*, 2006; **77**: 48–61.
[10] Ponnighaus JM, Fine PE, Sterne JA *et al.* Incidence rates of leprosy in Karonga District, northern Malawi: patterns by age, sex, BCG status and classification. *Int J Lepr Other Mycobact Dis*, 1994; **62**: 10–23.
[11] Moet FJ, Pahan D, Oskam L *et al.* Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ*, 2008; **336**: 761–764.
[12] Moet FJ, Schuring RP, Pahan D *et al.* The prevalence of previously undiagnosed leprosy in the general population of northwest Bangladesh. *PLoS NTD*, 2008; **2**: e198.
[13] Kish L. *Survey sampling*. Wiley, New York, 1965.
[14] Anonymous. *WHO Expert Committee on Leprosy. WHO Technical Report Series Seventh Report*. World Health Organization, Geneva, 1998.
[15] Feenstra SG, Nahar Q, Pahan D *et al.* Recent food shortage is associated with leprosy disease in Bangladesh: a case-control study. *PLoS NTD*, 2012; **5**: e1029.

[16] Overdispersion Collet D. *Modelling Binary Data*. Chapman & Hall, London, 2003.
[17] Richardus JH, Meima A, Croft RP *et al.* Case detection, gender and disability in leprosy in Bangladesh: a trend analysis. *Lepr Rev*, 1999; **70**: 160–173.
[18] Hatta M, van Beers SM, Madjid B *et al.* Distribution and persistence of *Mycobacterium leprae* nasal carriage among a population in which leprosy is endemic in Indonesia. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1995; **89**: 381–385.
[19] Anonymous. Leprosy fact sheet. *Wkly Epidemiol Rec*, 2010; **85**: 46–48.
[20] Anonymous. *Rural Health Program. Statistical summary report, 1977–2009*. The Leprosy Mission Bangladesh, Nilphamari, 2010.
[21] Merle CS, Cunha SS, Rodrigues LC. BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. *Expert Rev Vaccines*, 2010; **9**: 209–222.
[22] Anonymous. *WHO/UNICEF review of national immunization coverage, 1980–2006*. World Health Organization, Geneva, 2007.