LEPROSY and SOCIAL ENVIRONMENT

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CHAPTER 1

General introduction

Age-old Lepers Act Repealed

Parliament yesterday passed a private member's bill to repeal the Lepers Act 1898 that segregated leprosy patients from society and their families. This is the first time a private bill has got through the House during the tenure of the present Awami League-led government. Ruling party lawmaker Saber Hossain Chowdhury, who piloted the bill in parliament in June last year, proposed its passage yesterday. With the passage of the bill, all cases filed under this act will cease to have any effect. Leper asylums will be turned into hospitals where people suffering from leprosy will receive treatment, according to a provision of the bill. In a brief statement attached to copies of the bill, Saber said the Lepers Act goes against people's fundamental rights guaranteed by the constitution. He said the law was enacted during the period of British rule in order to segregate leprosy patients from society. They were not allowed to take up any public job or profession. But leprosy is now curable.....

Dhaka, Bangladesh, 25-11-2011: The Daily Star

This short article in newspaper "The Daily Star" of 25th November 2011 was very important news for leprosy patients in Bangladesh, who officially saw their rights restored. The article reveals something of the profound history of leprosy and makes clear that interference in the social environment of leprosy patients had enormous impact on patients' lives. It also shows that for more than a century control measures have been applied in the Indian subcontinent.

Although the number of new cases of leprosy declined worldwide and the disease is eliminated from the developed world, active transmission is still going on in many low-income countries, including India and Bangladesh. In the year 2010 there were 228,474 new cases of leprosy reported globally [1], indicating that this ancient infectious disease is still an actual problem. Control measures seem insufficient to eliminate the disease, especially in the poorest areas of the world. This implies that the social environment plays an important role in the spread and also the control of the disease, the subject of this thesis.

The history of leprosy

Leprosy is one of oldest known diseases of mankind, but also one of the most feared and misunderstood diseases. It was already recognized in the ancient civilisations of China, Egypt and India. The first written record is from 600 BC, while the causative agent and for leprosy characteristic malformations are found in skeletal material dating back as far as two centuries BC [2-5]. Historically, leprosy is often associated with uncleanliness or seen as a curse due to physical disfigurement and mutilation, causing fear and leaving patients isolated and disgraced. The colonial British government in India enacted The Lepers Act in 1898 as an attempt to control

leprosy. When Armauer Hansen identified the causative agent *Mycobacterium leprae* in 1873, defining leprosy as a infectious disease, there was high pressure by the population to segregate 'lepers' (sufferers of leprosy) to contain the disease. The fear for this disfiguring disease was high and although it was already realised that the disease was not very contagious, people with leprosy were institutionalised in colonies and segregated from society by law. Segregation by gender was used as well to avoid reproduction, since the disease was also thought to have a genetic component. Sufferers from leprosy were restricted in the use of public transport and water facilities and, had limited employment opportunities. This had an enormous impact on sufferers of the disease, causing stigma still affecting people with leprosy today [6].

Treatment and prevalence of leprosy

Effective treatment for leprosy became available in the early 1940s following the discovery of dapsone. Other effective drugs such as rifampicin and clofazimine were developed in the early 1960s. Bacterial resistance became a problem with monotherapy and a combination of the before mentioned drugs was recommended from 1981. The prevalence of the disease has fallen tremendously since the World Health Organization (WHO) supported multidrug treatment (MDT) and intensive control programmes from 1995 [7-9]. Elimination of leprosy as a public health problem, defined by the WHO as less than one registered case per 10,000 population, was reached globally in the year 2000. A case of leprosy was defined as a person with clinical signs of leprosy who requires chemotherapy. Achieving elimination of leprosy as public health problem was impressive, although it is understood that prevalence as indicator is highly influenced by changes in disease definition and duration of therapy over time. In addition, other factors such as increasing coverage of BCG vaccination and increasing socioeconomic circumstances worldwide have very likely also contributed to the decline of leprosy in many areas of the world. The new case detection rate, as proxy for incidence of the disease, is a more stable indicator [7]. The new case detection rate has also decreased, but seems to have stabilised over the last decade, especially in some of the poorest areas in the world. In many of the same areas a high child detection rate is seen, indicating continuing transmission of *M. leprae*, the causative agent of leprosy. This indicates that the disease is still active and further research is necessary to find innovative ways to improve leprosy control programmes and reduce the burden of leprosy [10].

Causative agent and clinical symptoms

Leprosy is caused by the intracellular, acid fast rod *Mycobacterium leprae*. The bacterium has mainly a human reservoir, although *M. leprae* is found regularly in the armadillo as well. The most likely route of transmission is airborne person-to-person infection by small droplets. This hypothesis is never conclusively demonstrated, but supported by the observation of *M. leprae* in nasal secretions of many patients [11]. Direct skin-to-skin contact may also play a role in

transmission, with some patients having large numbers of bacteria in skin lesions [12,13], while transmission through the environment is possible as well, as *M. leprae* has been identified in soil samples in endemic areas [14].

M. leprae causes a chronic granulomatous inflammation of the peripheral nerves. Clinical leprosy can be differentiated in several forms, ranging from a single skin lesion to a generalized response with extensive nerve damage leading to the classical leprosy deformities that often cause severe disability. The diversity in clinical symptoms is determined by the host immunity towards the causative agent. Although not completely understood, genetic differences between individuals as well as other factors influencing the immune status, like age, nutritional status, health status and previous exposure to mycobacteria (e.g. BCG vaccination), appear to influence the host reaction to *M. leprae* [15]. When a strong cellular immune response towards *M. leprae* is present, a person clears the infection quickly or develops a limited clinical response. However, when cellular response is low or absent, extensive clinical symptoms can appear. Leprosy can be classified based on the type of skin lesion and the bacterial load, according to the Ridley-Joping classification [16]. This classification, already in use from the 1960s, divides patients into five categories with increasing severity of symptoms, ranging from the mild tuberculoid form (TT), to the most severe lepromatous (LL) form of leprosy, with borderline forms (BT, BB, BL) in between. Tuberculoid patients have a good cell mediated immune response to *M. leprae*, but not enough to clear the infection completely. Some skin patches are visible, but only a small number of bacteria are detected through a slit skin smear or biopsy. In lepromatous leprosy the cell mediated immune response is almost absent and *M. leprae* can spread throughout the body, giving multiple lesions or generalised symptoms with high bacterial loads. The borderline forms are in between these poles and patients show some and often changing degree of cell mediated immunity towards *M. leprae*. Lepromatous leprosy is the most infective form of the disease because of the high bacterial load often found in these patients.

For the purpose of simplicity in field circumstances, the WHO developed a classification with only two categories based on easy recognizable symptoms. When a person has five or less skin lesions and *M. leprae* is not seen in a slit skin smear, the disease is classified as paucibacillary (PB) leprosy. When there are more than five lesions or when *M. leprae* is seen in a smear, the disease is classified as multibacillary (MB) leprosy. Sometimes this classification is further simplified to the counting of skin lesions only. PB patients receive MDT with dapsone and rifampicin for 6 months and MB patients receive MDT with dapsone, rifampicin and clofazimine for 12 months [17]. Although useful for clinical decision-making, this classification is not very specific [18].

Leprosy in Bangladesh

Bangladesh is one of the countries where leprosy is still endemic. The new case detection rate of the disease initially decreased quickly after adoption of the WHO strategy of early detection and treatment with MDT. The WHO elimination target of less than one registered case per 10,000 population was officially reached for the whole country in 1998 [19]. However, the new case detection rate of leprosy is still above target in some high endemic areas in the country [20]. These areas, the northwest, southeast (refugee camps and tribal areas) and slums of the two largest cities Chittagong and Dhaka, all have very high poverty rates [21-23]. In the leprosy endemic northwest part of the country, the Leprosy Mission Bangladesh (TLMB) has operated a leprosy control programme for many years. They assist government clinics in passive case finding and do active surveillance, diagnosis and treatment. In this poverty stricken area the new case detection rate was 1.2 per 10.000 population in 2010. Of the newly diagnosed patients 8.7% had grade 2 disability, defined by the WHO as having visible impairments, indicating late detection of the disease. It also indicates a high chance that *M. leprae* has been transmitted to others already. Child cases of leprosy were also reported frequently (10.7% children under 15 years in 2010), which is a sign of recent infection and an indication that active transmission is ongoing. Although the new case detection rate has been declining slowly in northwest Bangladesh over the past years, it now seems that a steady state has been reached.

The COLEP study

To generate more knowledge about risk factors of leprosy and to trial new interventions with prophylactic measures a research project was initiated in northwest Bangladesh: the COLEP study, a prospective (sero-) epidemiological study on contact transmission and chemoprophylaxis in leprosy [24]. The aims of this study that started in 2002 were to perform a randomised controlled trial with a single dose of rifampicin as chemoprophylaxis to prevent leprosy in contacts of leprosy patients, and to identify and evaluate risk factors and transmission patterns of leprosy. With the generated knowledge, leprosy control programmes can timely identify individuals at high risk of leprosy and prevent new leprosy cases by improved surveillance activities and chemoprophylactic treatment of contacts. The first results of the study indicated that prophylactic treatment is able to prevent leprosy in contacts of patients [25]. Physical distance to a patient and the severity of the disease were identified as risk factors associated with transmission of *M. leprae* to contacts of a patient [15]. The host characteristics of blood relationship to the patient and age were also identified as risk factors for development of leprosy among contacts, while a previous vaccination with BCG had a preventive effect.

Control of leprosy

The potential for a communicable disease to spread in a population is called the effective reproductive rate (R). The effective reproductive rate is the average number of individuals directly infected by an infectious case during his entire infectious period. The R of a disease depends on the number of susceptible contacts in the population, the risk of transmission and the duration of infectivity. A disease is endemic in a population when R=1. When R>1 the disease becomes epidemic, while the disease will eventually disappear when R<1. Control of a disease is successful when R of the disease is reduced to a value below 1. Thorough understanding of characteristics of the causative agent and transmission pattern is important to reduce R. Control measures should be directed to one or more factors that influence R. These factors are specific for each causative agent, but also for the social environment in which a given population resides. The number of susceptible people depends for example on the actual number of people in a population as well as on environmental, social and cultural factors (e.g. climate, living circumstances, poverty, and access to healthcare) and on host factors (e.g. general health status, inherited immunity, malnutrition and pregnancy rate). The risk of transmission is influenced by factors related to the causative agent, but also by intensity and duration of contacts between susceptible and infectious people. The duration of infectivity depends not only on characteristics of the causative agent, but also on treatment options and diagnostic methods, as well as socioeconomic and cultural context influencing access to health services and health seeking behavior [26].

Early detection and treatment with MDT is the mainstay of leprosy control. The WHO supports leprosy control in endemic areas and distributes the drugs free of charge. With early detection and treatment both the risk of transmission and the duration of infectiveness is reduced. Another control measure is childhood vaccination with BCG. This vaccine, introduced to control tuberculosis, induces immunity against *M. leprae* as well [27]. Increased coverage of BCG vaccination in many leprosy endemic areas reduced the number of susceptible people in the population and very likely contributed to the decreasing prevalence of leprosy [28]. A control measure used in the past was separation of patients with leprosy in colonies to reduce the risk of infection. Since effective treatment with anti-leprosy drugs is already available from the 1940s, this measure is no longer advocated as it unnecessary and contributes to stigma of leprosy sufferers. Although these control measures have been applied for decades, leprosy is still endemic in many areas of the world, including Bangladesh.

Why is leprosy control complicated?

Clinical leprosy occurs most probably in only 1-5% of persons exposed to *M. leprae* after a long incubation period of several years, ranging from 1 to 20 years with an estimated average of 5 years [2,29]. Diagnosis of leprosy is generally made on clinical signs of disease; the causative

agent can be identified in split skin smears or skin biopsies in a limited number of cases only. Exact information regarding incubation period and the number of infected individuals without clinical signs of disease is not available, since there is no reliable test to measure infection in individuals without symptoms of disease. Nevertheless, it is suspected that individuals with a subclinical infection play a role in transmitting *M. leprae* [30]. Another complicating factor is that patients often only come to a clinic when they experience severe symptoms in the later stages of the disease or in periods of inflammation (leprosy reactions). This is particularly the case in areas were the educational level is low and access to healthcare limited. These patients have often been infective for a long time and therefore have very likely transmitted *M. leprae* to many others before starting treatment. Although stigma has declined due to health education programmes in many countries, there is still reluctance to seek care out of fear for isolation and discrimination. This causes patient delay and hampers successful disease control [31].

Another challenge in leprosy control is that people are not solitary individuals, but part of complex social networks with specific values and norms, operating in a continuously changing environment in which they are exposed to a variety of risks, threats and opportunities [32]. Choices have to be made continuously, resulting in decisions that are not always in line with ideal circumstances for disease control. These decisions are not only individual, but also political. The prevalence of leprosy is relatively low compared to other diseases, and scarce resources for healthcare are often directed to other problems, especially in the low-income countries were leprosy is endemic. Therefore leprosy has recently been referred to as a 'neglected tropical disease' or NTD.

Interestingly the incidence of leprosy, similar to tuberculosis, declined in most parts of the world before effective treatment became available and even before any control measures were applied. Although the exact cause is unknown, increasing wealth and cooler temperatures are suspected to play a role, while also cross immunity to tuberculosis is thought to be of importance [33-35]. This implies an important role of the social environment in leprosy in endemic areas. The influence of the social environment on population health has received increasing attention over recent years, because inequalities in the social environment are seen as important determinants for health [36,37]. Some infectious diseases seem to be influenced more by the social environment than others. Leprosy is an example in which the role of social determinants is well recognised, although not fully understood [38].

Social environment and leprosy

The social environment is defined as the immediate physical surrounding, social relationships, and cultural milieu in which a group of people function and interact [39]. This includes infrastructure and physical environment, but also social and economic processes, wealth, power relations, social inequality and cultural believes and practices.

This thesis focuses on social contact patterns and socioeconomic determinants as risk factors for leprosy, since these factors in the social environment of leprosy patients are thought to have a major influence on the disease. *M. leprae* is transmitted from person-to-person most likely by droplet infection or direct skin-to-skin contact. Therefore interaction between people through social contacts plays an essential role in transmission of the disease. Social contact patterns and the social contact network in which people operate are highly influenced by socioeconomic and cultural factors and are very specific for a certain area. Leprosy is seen as a disease of poverty. It is still endemic in the poorest countries of the world (Figure 1) and within these countries leprosy is found in the poorest regions or urban slums. Although a causal relationship between poverty and leprosy is difficult to demonstrate, socioeconomic determinants have been suggested to be of major influence on the continuing transmission of this infectious disease [40,41].

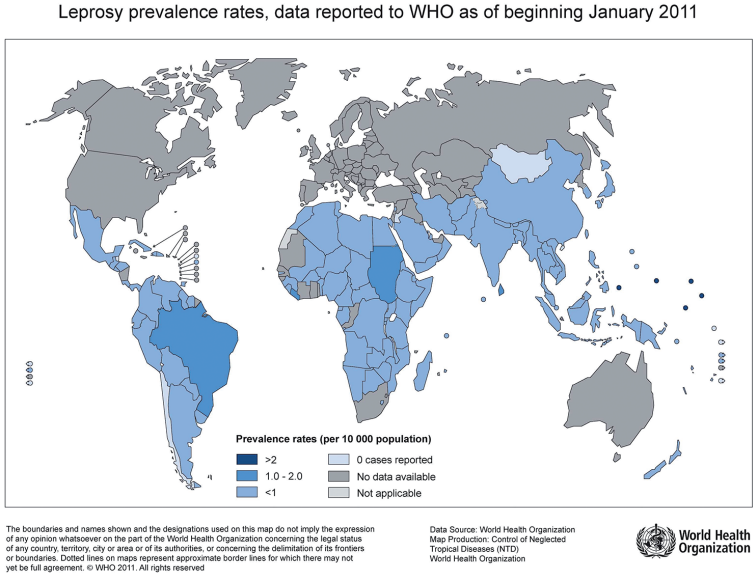

Figure 1 | WHO: Leprosy prevalence rates, 2011 (http://www.who.int/lep/situation/Leprosy_PR_2010.pdf)

Social contact patterns

Data on social contact patterns were limited for northwest Bangladesh, especially in relation to the transmission of infectious diseases. We therefore decided to follow a two-step approach. In the first step social contacts in this region were explored with focus group discussions and

ordered regarding their relevance for the transmission of leprosy. In the next step the information gathered was used to construct a questionnaire for a case-control study. Information regarding social contacts of newly diagnosed leprosy patients and healthy controls from the same geographical area was gathered at one moment in time.

In Bangladesh, the family is the most important functional unit through which social and cultural norms operate. A functional unit of importance is the household, defined as a group of people living under a common "head" and eat food prepared from a common hearth. A household lives in a house or "ghor", consisting of one or more rooms, sometimes within a large house, which may be divided into several rooms. Members of a "ghor" usually belong to the same family, but not always. While economic production of a household is limited to the members of the household, social networks of its members extend beyond its physical boundary to the community and outside [42,43].

In infectious disease epidemiology intensity and duration of social contacts are important to establish the risk of infection of a social contact pattern [26]. We assumed that social contact with household and family members was most intensive in the home. Therefore social contacts were studied in three different distance levels, taking the household as core functional unit in the Bangladeshi society as centre of the social contact structure and assuming that the intensity of social contacts decreased with distance from the core unit (Figure 2).

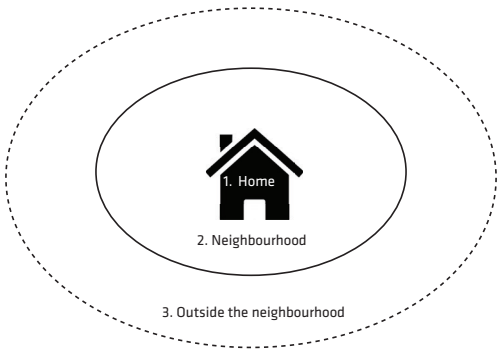

Figure 2 | Distance levels of social contacts

Socioeconomic determinants

The socioeconomic determinants educational level, profession and household income were collected from the COLEP cohort. We used these determinants to study the effects of socio-economic status on leprosy in this cohort. Northwest Bangladesh is a poverty-stricken and mainly agricultural area and data on income should be accompanied by data on expenditure

for an accurate picture of the socioeconomic status. Collecting this data however, is difficult and time consuming, while the value is doubtful in a developing country where income changes seasonally and self-subsistence agriculture and non-monetary trade is important [44]. We therefore used an asset index as a proxy to measure the economic status in our case-control study. An index based on assets is an easy instrument to measure differences in wealth in a population without collecting data on income and expenditure [45,46]. A set of assets was chosen based on the Bangladesh Demographic and Health Survey, the local version of the Demographic and Health Surveys (DHS) for Bangladesh [20]. Based on field visits and discussions with staff of TLMB with experience in the region, we made some changes to adapt this basic set to the local situation in the study area and to make it easy to use for our study. We changed, for example, the item *'boat with a motor'* to *'tractor or motorized farm equipment'*, as this was more appropriate for the rural area far away from major waterways where the study was carried out. Since only minor differences in assets were expected between people of different socioeconomic status in this poor area, we added the items *'computer'*, *'fan'*, *'air conditioner'* and *'local rice husking equipment'* to make a better distinction between the highest and poorest categories in our study population. The questionnaire was simplified compared to the Bangladesh DHS for observations about the house, as we only included locally used materials.

A single, consolidated asset index as method to measure wealth was constructed by using factor analysis, principal components factor (pcf) as used by Filmer and Pritchett [45]. With this method a weight was generated for each asset variable. An asset score was calculated for each household, by weighing the response for each asset of that household by the coefficient of the first factor as determined by application of the factor analysis, and summing the results (Box 1).

Box 1 | Formula to construct the asset index as used by Filmer and Pritchett [45]

$$A_k = f_1 \times (a_{k1}-a_1) / (s_1) + \ldots\ldots\ldots\ldots + f_N \times (a_{kN}-a_N) / (s_N)$$

A_k	= asset score of household k,
f_1	= weighing factor for the first asset, coefficient of first factor as determined by the procedure
ak_1	= value for the first asset of household k
a_1	= mean of the first asset value over all households
s_1	= standard deviation of the first asset variable over all households
N	= total number of assets included in the procedure

In addition to the asset index, data on income, educational level, household composition, crowding and food shortage were collected. By collecting data on different aspects of the socioeconomic situation of the study population it was possible to determine which of these aspects are most strongly associated with clinical leprosy.

Research questions

The objective of this thesis is to study the association between determinants in the social environment and acquiring clinical leprosy in an endemic area. By addressing relevant social determinants, leprosy control programmes can be improved to decrease the burden of disease in endemic areas. Socioeconomic factors and social contacts are chosen as the main determinants of study.

The research questions of this thesis are:

1. Is there a relation between social contact patterns and acquiring clinical leprosy?
2. How are socioeconomic determinants associated with the risk of acquiring clinical leprosy?
3. Which patient related factors and social determinants are associated with increased risk of leprosy among contacts?
4. How can social determinants be used effectively to improve leprosy control programmes?

We conducted qualitative and quantitative studies of different nature in the leprosy endemic area of northwest Bangladesh to study the problem and to answer the research questions. In chapter 2 the results of a qualitative study with focus group discussions is presented, exploring social contact patterns that could potentially play a role in transmission of infectious diseases like leprosy. The results of a case-control study, comparing social contact patterns and socioeconomic factors of a group of new leprosy patients with these of a representative population control group are presented in chapter 3 and 4. Results of a cohort study are presented in chapter 5, following for 6 years the group of 1037 patients and their 28,092 contacts participating in the randomized placebo controlled trial with single dose rifampicin (SDR) as prophylaxis in contacts: the COLEP study. Analysis focused on patient related factors and easy to measure social determinants predicting enhanced transmission or increased impact of interventions. In chapter 6 we present the results of a qualitative study regarding the acceptability of interventions like SDR for contacts of patients. In the final chapter of this thesis (chapter 7) we discuss the results and answer the research questions, and formulate conclusions and recommendations for practice and further research.

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CHAPTER 2

A qualitative exploration of social contact patterns relevant for airborne transmitted infectious diseases in northwest Bangladesh

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CHAPTER 3

Social contact patterns and leprosy disease: a case-control study in Bangladesh

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SUMMARY

Socioeconomic and cultural defined social contact patterns are expected to be an important determinant in the continuing transmission of *Mycobacterium leprae* in leprosy endemic areas. In a case-control study in two districts in Bangladesh, we assessed the association between social contact patterns and the risk of acquiring clinical leprosy. Social contacts of 90 recently diagnosed patients were compared with that of 199 controls. Leprosy was associated with a more intensive social contact pattern in the home [odds ratio (OR) 1.09, 95% confidence interval (CI) 1.00-1.19, *P*=0.043] and in the nearby neighbourhood (OR 1.07, 95% CI 1.03-1.11, *P*=0.001). Although it is known that *Mycobacterium leprae* spreads most easily within households of infected persons, in endemic areas social contacts within the neighbourhood, village or urban ward, are apparently also important for transmission. We advise that disease control measures in leprosy endemic areas should not be limited to households, but include high-risk groups in the nearby neighbourhood of patients.

INTRODUCTION

Despite effective treatment options and intensive control programmes, leprosy is still endemic in several of the poorest areas of the world. Since the route of transmission of *Mycobacterium leprae*, the causative agent of leprosy, is thought to be mainly airborne from person to person, socioeconomic and culturally defined social interaction patterns are considered to be an important determinant in the continuing transmission of this infectious disease.

Bangladesh is one of the countries where the disease remains endemic. Despite reaching the target of eliminating leprosy as a public health problem, defined as less than one registered case/10000 inhabitants for the whole country in 1998, the prevalence is still above target in some of the poorest areas of Bangladesh [1,2]. In the poverty stricken northwest part of the country, the new case detection rate was still 1.25 /10000 inhabitants in 2008.

Studies in this densely populated area showed that physical distance to a patient and severity of the disease (leprosy classification) are risk factors associated with transmission of *M. leprae.* The host characteristics 'blood relationship to the patient' and 'age' are risk factors for the development of clinical signs of disease [3]. A qualitative exploration with focus group discussions revealed that the most intensive social contacts in this area occur within the home and take place across different sex and age groups. Outside the home interaction patterns are assortative for age and sex. Most women and girls have social contacts limited to their home and nearby neighbourhood, while men and boys also report regular contacts outside their neighbourhood. Adult males have the most intensive social contacts both within and outside their neighbourhood (see Chapter 2).

In this study we assessed the association between different social contact patterns and the risk of acquiring clinical leprosy disease in the same leprosy endemic area in northwest Bangladesh. The objective of the case-control study was to identify social contact patterns that contribute to the transmission of *M. leprae*, with the aim to improve leprosy control activities as a result of this knowledge.

METHODS

Study area and population

A case-control study was carried out in August 2009 in the districts of Nilphamari and Rangpur in northwest Bangladesh. This large (3951 km^2), mainly rural area has approximately 4.5 million inhabitants and is one of the poorest parts of Bangladesh [4,5].

The first 110 new leprosy patients registered in 2009 in the study area were selected as cases. The Leprosy Mission International Bangladesh (TLMB) or government primary-care facilities

diagnosed the patients according to WHO guidelines [6]. Only one patient per household was interviewed to avoid bias due to clustering. From the initially selected group, 10 people could not been reached, while one was excluded because he was living in the same household as another selected patient.

Controls without leprosy were randomly selected from a referent group representative for the general population in the area. This group was selected by a multi-cluster sampling procedure at the start of the COLEP project, a prospective (sero-) epidemiological study on Contact transmission and chemoprophylaxis in leprosy [7]. The study was initiated in 2001 to generate knowledge about risk factors for leprosy and to assess the effect of new interventions. For the current study, which is part of the COLEP project, 15 people were randomly selected from each of the 20 previously assigned clusters by computerized sampling. The 15 selected candidates of each cluster were numbered 1 to 15. Interviewers started to contact the first person and continued following the numbering until 10 people were interviewed or everyone was contacted. Controls were excluded when they were ever diagnosed as leprosy patient or if they came from the same household as another participant in the study.

Data collection

Research staff of TLMB carried out home visits to conduct interviews with a pre-tested structured questionnaire (annex 1). Participants were questioned 6-7 months after they were diagnosed as leprosy patient, on personal data, disease status, living circumstances and economic situation (including assets, educational level and periods of food shortage) and social contacts. Any changes in living circumstances or economic situation due to the disease leprosy were specifically enquired about, while changes in economic situation of the household due to other reasons over the last 3 years were also recorded.

The home of the participant was identified as the most important structure from where social contacts take place in the Bangladeshi society [8,9]. Therefore, social contacts were assessed on three different levels representing the distance of the contact from the home of the participant:

- Level 1: social contacts that take place inside the home
- Level 2: social contacts that take place outside the home but within the own neighbourhood, village or urban ward
- Level 3: social contacts outside the neighbourhood, ranging from the next village or city to contacts outside the country

Based on a qualitative exploration with focus group discussions carried out before the start of the study, the most common social contact patterns for each level were pre-listed in the questionnaire. Participants were asked to report the frequency of occurrence of the listed

social contact patterns, but could also report contacts not pre-listed. For each contact pattern mentioned, they could report how often they usually had this type of contact. They were asked to keep the last year in mind while reporting. Participants were also asked if leprosy had changed their social contact pattern.

Ethical approval

All participants received verbal information about the study in their own language and were asked to sign a consent form. Ethical approval for this study was obtained from the Bangladesh Medical Research Council (under reference: BMRC/NREC/2007-2010/2107).

ANALYSIS

Data from the questionnaires was entered into an Access database. After data cleaning, analysis was performed using the statistical package STATA version 10.0 (StataCorp., USA).

A scoring system for the different contact patterns was developed based on the knowledge that both intensity and the duration of contact with a patient is of influence on transmission [10,11]. The following assumptions were made:

- Contacts inside a room or building were assumed to be more intensive than contacts in an open outside area.
- An overnight stay was assumed to be of longer duration and more intensive than a social contact in a room during daytime.
- Regular short contacts were assumed to be as important for the transmission of disease as a contact of long duration.

Each of the contact patterns in the questionnaire was assigned an intensity score between 1 and 3, based on the findings of the qualitative exploration of social contacts carried out in the preparation stage of the study (Chapter 2). This intensity score was multiplied by a frequency score, based on the frequency of occurrence of the particular social contact pattern as reported by the participant (Table 1).

A total score per social contact level was calculated for each participant by adding the results for each contact pattern within the level concerned. Each participant thus received three final scores; one for each of the social contact levels. The higher the score, the more intensive or frequent contacts the participant reported at the particular level. For the first level, inside the home, a measure of crowding was also included. A value for crowding was calculated by dividing the number of household members by the number of sleeping rooms.

Table 1. Scoring system for social contact patterns in Bangladesh

Frequency score:	
3= this type of contact occurs daily	
2= this type of contact occurs weekly	
1= this type of contact occurs monthly or less	
0= this type of contact occurs never	
Level 1: Social contact in the home	
Crowding: number of household members / number of sleeping rooms	Crowding score (min=1, max=9)
Visitors to the house at daytime: **intensity score = 2**	
Neighbours	2 x frequency score
People from village	2 x frequency score
Relatives from outside village	2 x frequency score
Others from outside village	2 x frequency score
Visitors stay overnight: **intensity score = 3**	
Visitors stay overnight	3 x frequency score
	---------- +
	Total level 1 (min=0, max=42)
Level 2: Social contacts within the neighbourhood	
Outdoor meetings at: **intensity score = 1**	
Workplace	1x frequency score
Market	1x frequency score
Yard of neighbours /friends	1x frequency score
Outdoor gathering /religious festival / fair	1x frequency score
Outdoor wedding ceremony	1x frequency score
Indoor meetings: **intensity score = 2**	
Inside house or shop	2x frequency score
Inside building for work	2x frequency score
Inside mosque or temple	2x frequency score
Inside building for regular meeting	2x frequency score
Special occasions in someone's house	2x frequency score
Indoor wedding, gathering or fair	2x frequency score
Indoor religious festival	2x frequency score
	---------- +
	Total level 2 (min=0, max=57)
Level 3: Social contacts outside the neighbourhood	
Social contacts outside neighbourhood: **intensity score = 1**	
In nearby villages	1x frequency score
In nearest city	1x frequency score
In other cities in Bangladesh	1x frequency score
In other countries	1x frequency score
Stay overnight in another area: **intensity score = 3**	
Staying overnight	3x frequency score
Share room with more than 10 people	yes=5, no=0
	---------- +
	Total level 3 (min=0, max=26)

Socioeconomic status of the participants was estimated by an asset index. Factor analysis, principal components factor (PCF), was used to construct an asset index to assign a wealth score to all participants [12]. Data on ownership of different assets in their household was used to calculate a wealth score by weighing the response for each asset of their household by the coefficient of the first factors determined by application of the factor analysis (PCF), and summing the results (see Chapter 4). The first factor accounted for 19.95% of the variance in the data. The control group was assigned to five wealth quintiles according to their final score. Cases were assigned to these quintiles according to the threshold values set by the control group.

To identify possible confounders on the association between social contacts and leprosy, the mean social contact scores for groups of different socioeconomic background, educational level, age and sex were assessed within the control population. Since the social contact scores were normally distributed, the means for variables with two levels were compared with a *t* test, while an ANOVA test was used for variables with more than two levels.

Univariate and multivariate logistic regression was used to assess the association between clinical leprosy and social contacts. All potential confounding variables with a *P* value >0.2 in the univariate analysis, were incorporated in a multivariable model. A backwards elimination procedure ($P>0.1$) was performed, in which variables without a significant effect on the odds ratio of the main outcome variables were excluded from the final model since they were not confounders. A likelihood ratio test was performed to test whether the variables had a significant effect.

RESULTS

Initially 99 patients (cases) and 199 controls were included in the study population. A deterioration of social contacts, economic situation or living condition due to the disease was mentioned by nine (8.9%) of the cases. Because the objective of this study was to assess social contact patterns as a risk factor for developing clinical signs of leprosy disease, it was important to establish the situation just before symptoms of the disease became apparent. We therefore excluded for further analysis the nine cases, which mentioned that their situation had changed due to the disease, to avoid confusion about cause and effect. Change in economic situation of the household over the last 3 years due to other reasons was similar for case and control group (16% experienced an deterioration and 22% an improvement) and therefore no reason for exclusion.

Of the 90 patients included for analysis, the sex ratio (M/F) was 1.2; 21.1% had the multibacillary (MB) form of the disease, while 6.6% was diagnosed with a grade II disability,

according to the WHO classification (Table 2). The proportion of children <15 years of age was 15.6%. At the time of the interview, 58.9% of the cases were still on multidrug therapy (MDT), while the other 41.1% had just completed their therapy and were released from treatment.

Table 2. General characteristics for male and female cases of leprosy in the study population, by age group (n=90)

	Male			Female			
Age group (years)	**Cases n (%)**	**Multibacillary n (%)**	**Disability grade II n (%)**	**Cases n (%)**	**Multibacillary n (%)**	**Disability grade II n (%)**	**Total no. of cases n (%)**
5-14	5 (10.2)	0/5 (0)	0/5 (0)	9 (22.0)	0/9 (0)	0/9 (0)	14 (15.6)
15-39	28 (57.1)	5/28 (17.9)	1/28 (3.6)	20 (48.8)	4/20 (20)	0/20 (0)	48 (53.3)
≥40	16 (32.6)	5/16 (31.3)	4/16 (25.0)	12 (29.3)	5/12 (41.7)	1/12 (8.3)	28 (31.1)
Total	49 (100)	10/49 (20.4)	5/49 (10.2)	41 (100)	9/41 (22.0)	1/41 (2.4)	90 (100)

Both the case and control populations were distributed randomly throughout the study area. The control group was representative for the general population in the area with respect to the household characteristics religion, household composition, educational level, and neighbourhood (urban/rural), as compared to the national statistics, but males in the working age (20-39 years) were slightly underrepresented in the control group [4,5].

The mean social contact score for leprosy cases was higher than the score for the control group at the first and second levels (Table 3). On the first level, inside the home, both cases and controls had relatively the highest scores. To create a better understanding of social contact patterns in the region and to identify possible confounders on the association between social contacts and leprosy, social contact scores for groups of different socioeconomic background, educational level, age and sex were assessed within the control population (Table 4). By comparing the means with a *t* test, it was observed that on the first level (in the household) there was a significant difference in mean score by household size, age (adult/child) and educational level ($P<0.05$). The mean score was higher for people from large households, aged <20 years and with a higher educational level. Within the neighbourhood (level 2), males and people aged <20 years had a significantly higher mean score than females and older people ($P<0.05$). Social contacts outside the neighbourhood were limited and the scores were relatively low. However, the mean score was significantly higher in males compared to females ($P<0.05$).

Table 3. Summary of the social contact scores for each distance level for cases and controls

Social contacts	Group	n	Mean	S.D.*	Min	Max	OR* (95% CI)	p value
In the home: level 1	Control	199	19.5	3.5	6	30		
(max. possible score = 42)	Case	90	20.5	3.1	14	31	1.09 (1.01-1.18)	p=0.024
Within the neighbourhood: level 2	Control	199	20.6	7.3	0	39		
(max. possible score = 57)	Case	90	24.1	6.8	8	37	1.07 (1.03-1.11)	p<0.001
Outside the neighbourhood: level 3	Control	199	7.1	3.1	0	16		
(max. possible score = 26)	Case	90	7.6	3.1	1	15	1.05 (0.97-1.16)	p=0.266

OR, Odds ratio,; CI, confidence interval; S.D., standard deviation
*Univariate logistic regression

Table 4. Mean social contact scores per level for subgroups of the control population

	n	Mean score Level 1	Mean score Level 2	Mean score Level 3
Wealth quintile (asset index)				
1	40	18.0	21.4	7.4
2	40	19.7	22.8	6.4
3	40	20.0	19.6	7.0
4	40	19.7	22.7	7.4
5	39	20.0	21.9	7.5
Educational level †				
High	113	20.1	21.1	7.3
Low	86	18.7*	19.9	6.9
Household size				
1-4 members	72	18.7	20.1	6.8
≥5 members	127	19.9*	20.9	7.3
Food shortage ‡				
No	128	19.7	21.3	7.2
Yes	71	19.1	19.4	7.0
Sex				
Female	116	19.5	18.3	6.9
Male	83	19.5	23.8*	7.7*
Age				
<20 years	87	20.3	21.8	7.2
≥20 years	112	18.9*	19.6*	7.1
Total	199	19.5	20.6	7.1

† Educational level low: highest educated person in the household had less than 6 years of schooling, high: highest educated person in the household had 6 years or more schooling
‡ There was a recent period of food shortage reported (in the year before the interview)
* *t* test for the difference between means: p<0.05

Table 5. Results of univariate and multivariate logistic regression analysis with a backwards elimination procedure.

					Univariate			Multivariate		
Variables	Control Mean (S.D.)		Cases Mean (SD)		Crude OR (95% CI)		p value	OR (95% CI)		p value
Social contact score level 1	19.5	(3.5)	20.5	(3.0)	1.09	(1.01-1.18)	p=0.024	1.09	(1.00-1.19)	p=0.043
Social contact score level 2	20.6	(7.3)	24.1	(6.7)	1.07	(1.03-1.11)	p<0.001	1.07	(1.03-1.11)	p=0.001
Social contact score level 3	7.1	(3.1)	7.6	(3.1)	1.05	(0.97-1.14)	p=0.266			
Household size	5.3	(2.3)	5.0	(2.0)	0.93	(0.82-1.05)	p=0.253			
Other Variables	**Control, n (%)**		**Cases, n (%)**							
Wealth quintile (asset index)										
1	40	(20.1)	25	(27.8)	1.00					
2	40	(20.1)	20	(22.2)	0.80	(0.38-1.67)				
3	40	(20.1)	16	(17.8)	0.64	(0.30-1.38)				
4	40	(20.1)	17	(18.9)	0.68	(0.32-1.45)				
5	39	(19.6)	12	(13.3)	0.49	(0.22-1.12)				
Wealth score continuous					0.75	(0.57-0.97)	p=0.029			
Educational level*										
High	113	(56.8)	49	(54.4)	1.00					
Low	86	(43.2)	41	(45.6)	1.10	(0.67-1.81)	p=0.711			
Food shortage†										
No	128	(64.3)	47	(52.2)	1.00			1.00		
Yes	71	(35.7)	43	(47.8)	1.65	(1.00-2.73)	p=0.052	2.03	(1.17-3.52)	p=0.012
Sex										
Female	116	(58.3)	41	(45.6)	1.00					
Male	83	(41.7)	49	(54.4)	1.67	(1.01-2.76)	p=0.045			

Table 5. Results of univariate and multivariate logistic regression analysis with a backwards elimination procedure *(continued)*.

Variables	Control Mean (S.D.)		Cases Mean (SD)		Univariate Crude OR (95% CI)		p value	Multivariate OR (95% CI)		p value
Age										
<10	22	(11.1)	6	(6.7)	1.00					
10-19	65	(32.7)	20	(22.2)	1.13	(0.40-3.17)	p=0.819	1.38	(0.48-4.00)	p=0.554
20-29	27	(13.6)	21	(23.3)	2.85	(0.98-8.30)	p=0.054	4.07	(1.33-12.47)	p=0.014
30-39	32	(16.1)	15	(16.7)	1.72	(0.58-5.12)	p=0.331	2.41	(0.77-7.57)	p=0.132
40-49	35	(17.6)	11	(12.2)	1.15	0.37-3.56)	p=0.805	1.50	(0.47-4.87)	p=0.491
50+	18	(9.1)	17	(18.9)	3.46	(1.13-10.61)	p=0.030	5.17	(1.56-17.11)	p=0.007
Total	**199**	**(100)**	**90**	**(100)**						

OR, Odds ratio,; CI, confidence interval; S.D., standard deviation

* Educational level low: highest educated person in the household had less than 6 years of schooling, high: highest educated person in the household had 6 years or more schooling

† There was a recent period of food shortage reported (in the year before the interview)

Leprosy was associated with a higher score for social contacts in the home (OR 1.09, 95% CI 1.00-1.19, *P*=0.043) and in the nearby neighbourhood (OR 1.07, 95% CI 1.03-1.11, *P*=0.001), even after correction for age in the multivariate analysis (Table 5). The variables sex and socioeconomic status as measured with the wealth index did not change the odds ratio of the main outcome variables in the multivariate analysis, therefore these variables were not confounders and dropped in the final model. A significant association between leprosy and a period of food shortage in the last year (OR 2.03, 95% CI 1.17-3.52, *P*=0.012), the 20-29 years age group (OR 4.07, 95% CI 1.33-12.47, *P*=0.014) and the >50 years age group (OR 5.17, 95% CI1.56-17.11, *P*=0.007) was observed in the final model. We have reported the issue of food shortage in relation to leprosy disease in detail elsewhere [13].

DISCUSSION

Clinical leprosy in the endemic area of northwest Bangladesh is associated with a more intensive social contact pattern within the home and nearby neighbourhood.

The strength of this case-control study is that it takes into account recently diagnosed leprosy cases while patients who reported deterioration in social contacts, living situation or economic status due to their disease were excluded. Since 70% of the participating patients mentioned that their symptoms appeared recently (less than 6 months before the diagnosis) we could assume that the situation around the time of diagnosis represented the situation before any symptoms of disease appeared, allowing assessment of social contact patterns as risk factor for acquiring leprosy disease. Only one patient mentioned improved social contacts due to the disease, therefore this was not used as exclusion criterion for analysis. Positive changes however might be underreported and more patients may have improved social lives due to the disease.

We emphasize that we could only study the association between social contact patterns and clinical leprosy disease. Individuals infected with *M. leprae* without clinical signs of disease are difficult to identify. They do not present themselves at a health facility and there is no reliable test for infection with *M. leprae*. The average incubation time of leprosy is estimated to be 2-5 years, but it can take 20 years or longer before clinical disease becomes apparent after a person is infected. Changes in social contact patterns are possible during such long period. However, common alterations due to, e.g. ageing or changing environment are expected to be similar for cases and controls and therefore accounted for by the study design. Such alterations are not expected to be caused or influenced by subclinical infection with *M. leprae*.

A limitation of the study is the use of self-reported data on social contacts as measured by a questionnaire, which is by definition subjective. Although we tried to compose simple questions

with categories of social contacts that are familiar to the people in the study area, there may be differences in interpretation and valuing of social contacts due to the knowledge level of people with different educational background or age. People were asked to report on their regular pattern of social contacts at the time of interview, but recall bias will be of influence on social contacts patterns that do not occur regularly (e.g. only a few times a year). By asking cases and controls exactly the same questions, we attempted to reduce the effect of the above forms of bias. Another possible source of bias was the slight underrepresentation of males in the working age (20-39 years) within the control group, because they were not always available during household visits. In the multivariate analysis age group and sex were taken into account to correct for this underrepresentation.

We developed a scoring system specifically for this study based on a one-time measurement of social contact patterns, because no method was available that could be adapted to our situation. A diary method was used in Europe and Vietnam to study contact patterns relevant for the spread of infectious diseases [11,14]. However, a diary method requires either registration over a long period or a very large study population. Because leprosy has a relatively low prevalence and keeping a diary for a long time is difficult in a developing country with high levels of illiteracy, using such method was not feasible. An advantage of a newly developed method is that it could be designed for the study area and that intensity as well as duration and frequency of social contacts could be included. A disadvantage is that the results are not completely applicable to other areas and that it is difficult to compare the results of this study with other studies. The validity of the method was assessed by comparing the score results of the control population with the expected pattern of social contacts for the area [8,9 and Chapter 2] and by a detailed analysis of the variables within each level (annex 2). As expected, social contacts on the first level, inside the home, were the most intensive for both cases and controls in our study, while males had higher scores for social contacts outside the home than females.

Because we used general categories and a simple scoring system, the overall pattern found in this study could be compared with other studies on airborne infectious diseases and social contact patterns. Most of the studies identified were carried out in developed countries with different cultural practices. However, contact profiles and implications for infectious disease transmission of these studies have similarities with our results. In a European study on airborne infectious diseases, households were also identified as an important connective place for people of different age and sex groups [15]. The authors conclude that households play a bridging role in the transmission of airborne infectious diseases between sub-groups. In two other studies social contacts outside the home were found to be highly associated with age and sex [11,16]. The conclusion of these studies was that contact patterns were highly assortative for age and sex, which has major implications for disease transmission patterns. In our study we found significant differences in social contact scores for age and sex groups, indicating differences in behaviour between age and sex groups.

Social contact scores outside the home (level 2 and 3) were significantly higher for males. Since a higher social contact score in the neighbourhood (level 2) was strongly associated with clinical leprosy, we conclude that males have potentially a higher risk to become infected with *M. leprae* due to their social contact patterns.

A higher risk for males in Bangladesh is reflected in the male/female distribution of leprosy in this region, which has always been in favour of males [17]. The male/female ratio of newly detected cases for the study area was 1.35 in 2008. Similar sex ratios are observed in other Asian countries, but the new case detection rate of leprosy is the same for both sexes in Africa and South America. Although suggested in literature, there is not a hard evidence for a biological reason to explain the difference in case detection rate between males and females [18]. Therefore differences in social contact patterns between the sexes in Bangladesh could be an important factor that contributes to the higher risk of males to acquire leprosy in this area.

To measure economic status of households, we used an asset index as proxy measurement of wealth. Although this index measurement is objective, a limitation is that the score of the index depends highly on the set of assets used [19,20]. We measured socioeconomic status with an asset index similar to the index used in the USAID-sponsored Demographic and Health Survey, carried out in 84 developing countries, because this is a method with proven value for public health purposes [21]. We used a set of assets based on the local version of the Demographic and health Survey for Bangladesh. Beside wealth index we also took a recent period of food shortage, educational level and household size into account. Although none of these socioeconomic parameters had a confounding effect on the association between social contacts and leprosy in our analysis, we need to point out that measuring the socioeconomic status of households is an issue of debate and controversy and using a different method might yield different results [22].

Existing control measures are mostly targeted at household contacts of leprosy cases. These interventions are very effective, because household contacts of leprosy patients have the highest risk of being infected and are an easy-to-reach target for disease control measures. However, control measures in an endemic area should not be limited to the households of patients. Social contacts between leprosy patients and susceptible individuals inside their neighbourhood are very important for continuing disease transmission, since these contacts cause infections to spread from household to household over a larger area. We therefore advise to extend disease control measures in endemic areas to high-risk groups within the neighbourhood (villages or urban wards) of leprosy patients. Social contact profiles can be used to identify people at risk, while meeting places in the neighbourhood can be used to get in touch with people at high risk.

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ANNEX 1: Questionnaire

COLEP

Questionnaire case-control study

Socio-economic circumstances and social contacts

Study ID number		□ case □ control
Name:	Year of birth:	Sex: M / F
Village: Union: Is this family living in the same village for 6 years or more?		□ yes □ no
date visit 1: ...../...../2009 signature : _____ date visit 2: ...../...../2009 signature : _____ date visit 3: ...../...../2009 signature : _____		
If the person above could not be interviewed give the reason here: Name:_____ Date:_____		

Date of the interview: _____/_____/_____

Name interviewer: _____

Can the selected person answer the questions themselves: □ yes □ no
If no, (for example in case of a child),
Name of person who answers questions: _____
Relation of this person to study participant: _____

Consent was given: □ yes □ no

a. Personal data

personal data

a1. Sex: M / F
a2. Age: _____ years
a3. Ethnicity : □ Bengali □ Bihari □ Shantali □ Other, _____
a4. Religion: □ Hindu □ Muslim □ Christian □ Other, _____
a5. Who is the head of this household: _____ M / F

Remarks:_____
_____
_____
_____

b. Health

b1. Case of Leprosy in 2009: □ yes □ no

If yes, continue with b2. If no, go to question b10

Leprosy

b2. Type of Leprosy: □ PB □ MB
b3. Disability grade: □ 0 □ 1 □ 2
b4. How long ago did you observe the first symptoms? _____ months
b5. When was the disease diagnosed? date: ___/___/____
b6. Do you still use the medicines for leprosy (MDT)? □ yes □ no
b7. Has leprosy changed your living conditions? □ yes □ no

If yes, explain: □ worse / □ better, because _____
_____
_____

b8. Has this disease changed the household income? □ yes □ no

If yes, explain: □ worse / □ better, because _____
_____
_____

b9. Has this disease changed your social contacts? □ yes □ no

If yes, explain: □ worse / □ better, because _____
_____
_____

b10. Has anyone (else) in your household ever had leprosy? □ yes □ no □ don't know
b11. Has any of your neighbours (N1,N2) ever had leprosy? □ yes □ no □ don't know
b12. Has anyone in your village or living area (S) ever had leprosy? □ yes □ no □ don't know
b13. Has any of your social contacts (S) outside the village ever had leprosy? □ yes □ no □ don't know

If yes, where did this person come from?_____ Explain relation: _____
_____
_____
_____

Tuberculosis and BCG vaccination

b14. Did you ever have TB? □ yes □ no
b15. Did you receive a BCG vaccination? (check scar) □ yes □ no

c. Living circumstances and economic situation

c1. Living area:
□ rural □ urban □ urban slum / camp
c2. The village or living area has approximately _____ inhabitants
c3.
Remarks:_____
_____
_____
_____

Observe the house and cross the materials the floor, walls and roof are made off

c4. **Floor**
□ Earth / mud / clay
□ Bamboo / wood planks
□ Cement / tiles / carpet
□ Other: _____

c5. **Roof**
□ Bamboo / thatch
□ Tin
□ Cement /concrete /tiled
□ Other: _____

c6. **Walls**
□ Mud / bamboo / palm
□ Tin
□ Cement / bricks
□ Other: _____

one answer in every block!

Questions on assets

c7. Does your household have:			
	electricity	□ yes	□ no
	a radio	□ yes	□ no
	a television	□ yes	□ no
	a computer	□ yes	□ no
	a mobile phone	□ yes	□ no
	a refrigerator	□ yes	□ no
	a fan	□ yes	□ no
	an air conditioner	□ yes	□ no
	an almirah or wardrobe	□ yes	□ no
	a table	□ yes	□ no
	a chair	□ yes	□ no
	a watch	□ yes	□ no
	a bicycle	□ yes	□ no
	a van or rickshaw	□ yes	□ no
	an animal drawn cart	□ yes	□ no
	a motorcycle or scooter	□ yes	□ no
	a tractor or other motorized farm equipment	□ yes	□ no
	local rice hasking equipment	□ yes	□ no
	a car or truck	□ yes	□ no

c8. Does your household own livestock	□ yes	□ no	Number
	□ cows/ bulls / buffalos:		_____
	□ goats/sheep		_____
	□ chickens / duck		_____
	□ other,_____		_____

c9. Does your household own the house	□ yes	□ no
c10. Does your household own the land of the house (homestead)	□ yes	□ no
c11. Does your household own land other than land of the house (farmland)?	□ yes	□ no
How much land does your household own	_____ decimals	

c12. What kind of drink water supply does your household use	□ Piped water □ Tube well / bore hole □ Open well □ Surface water □ Other: _____

c13. What kind of toilet facility does your household use normally	□ Flush toilet/septic tank □ Latrine □ No facility / bush / field □ Other: _____
c14 Do you share this toilet facility with other households	□ yes □ no

c15. Who generates most income for this household?	□ I generate most income □ _____ generates most income
What is the occupation of the person who generates most income for this household?	□ farmer □ fishing man □ labourer □ shopkeeper □ business □ teacher □ government official □ no job □ other:.....
c16. Employment status:	□ employer □ employee □ self employed

c17. Who has the **highest level of education in this household?**	□ I have □ _____ has the highest level
What is the highest level of school attended?	□ primary □ secondary □ college and higher
Which class was completed? _____	
c18. Can the **person who has the highest level of education** read and write?	□ can read and write easily □ can read and / or write a little bit □ can not read and write □ other: _____

c19. What is **your** occupation?

- □ student
- □ housewife
- □ farmer
- □ labourer
- □ shopkeeper
- □ business
- □ teacher
- □ government official
- □ no job
- □ other:.....

c20 Employment status: □ employer □ employee □ self employed

c21 What is the highest level of school **you** attended?

- □ primary
- □ secondary
- □ college and higher

Which class was reached? _____

c22. Can **you** read and write?

- □ I can read and write easily
- □ I can read and / or write a little bit
- □ I can not read and write
- □ other: _____

c23. What is the average monthly income of your household? _____Tk.

c24. Are there variations in the monthly household income? □ yes □ no

If yes: maximum income: _____Tk. Minimum income: _____Tk.

c25. How do you classify your household:

very poor	poor	low middle income	middle income	rich	very rich
1 □	2 □	3 □	4 □	5 □	6 □

c26. Were you able to buy some new cloths and/or gifts with the last Ramadan, Durga Puja or other large festival? □ yes □ no

c27. Have there been any changes in the economic situation of your household over the last three years? □ yes □ no

If yes, explain _____

_____

_____

c28. Has your household ever experienced food shortage? □ yes □ no

c29. Has your household experienced food shortage during the last year? □ yes □ no

d. Social contacts

d1. Social contacts inside the house

d1a. How many people are living in your house?

	Number
Number of male adults (>18 years of age)	_____
Number of female adults (>18 years of age)	_____
Number of male children (0-18 years of age)	_____
Number of female children (0-18 years of age)	_____
Total number of household members	_____

d1b. How many rooms used for sleeping are there in your house? _____

d1c. With how many people are you sharing your sleeping room (including yourself) ? _____

d1d. With how many people do you share your bed normally (incl. yourself)? _____

d1e. Are you sharing clothes with other household members? **Often** ☐ **Sometimes** ☐ **Never** ☐

Visitors to the house	day	week	month	three months	½ year	> ½ year	never
d1f. We have people coming to our house at least every:	☐	☐	☐	☐	☐	☐	☐
d1g. Neighbours come at least every	☐	☐	☐	☐	☐	☐	☐
d1h. Nearby living friends / villagers, at least every:	☐	☐	☐	☐	☐	☐	☐
d1i. Relatives from outside living area, at least every:	☐	☐	☐	☐	☐	☐	☐
d1j. Other people from outside village / living area, every:	☐	☐	☐	☐	☐	☐	☐
d1k. Other visitors come every	☐	☐	☐	☐	☐	☐	☐
d1l. We invite people inside the house / rooms, every	☐	☐	☐	☐	☐	☐	☐
d1m.We receive visitors in the yard of our house, every	☐	☐	☐	☐	☐	☐	☐
d1n. How often are visitors staying overnight? In your house? Every,	☐	☐	☐	☐	☐	☐	☐

When visitors stay overnight:	**Often**	**Sometimes**	**Never**	**N.A.**
d1o. They stay with me in the same room	☐	☐	☐	☐
d1p. I share my bed or the floor with them	☐	☐	☐	☐
d1q. I share clothes and / or towels with them	☐	☐	☐	☐

Remarks:_____

d2. Social contacts in the village or neighbourhood

Outdoor meetings in the neighbourhood:

I meet people:	day	week	month	three months	½ year	> ½ year	never
d2a. At outdoor meeting places in my village, every:	□	□	□	□	□	□	□
d2b. In the field or outdoor working place, every:	□	□	□	□	□	□	□
d2c. At the market or outdoor place at the school, every:	□	□	□	□	□	□	□
d2d. In the yard of people in my neighbourhood, every:	□	□	□	□	□	□	□
d2e. At outdoor gathering, religious festival or fair	□	□	□	□	□	□	□
d2f. At an outdoor wedding ceremony, every	□	□	□	□	□	□	□
d2g. At other outdoor place	□	□	□	□	□	□	□

Indoor meetings in the neighbourhood:

I meet people:	day	week	month	three months	½ year	> ½ year	never
d2h. Inside houses of neighbours, at least every:	□	□	□	□	□	□	□
d2i. Inside a house / building or shop (to watch TV, tea shop, beauty parlour etc.), at least every:	□	□	□	□	□	□	□
d2j. At an inside working place or school, at least every:	□	□	□	□	□	□	□
d2k. Inside a mosque or temple, at least every:	□	□	□	□	□	□	□
d2l. Inside a building / meeting hall for a regular meeting (micro credit meeting, association meeting, etc.)	□	□	□	□	□	□	□
d2m.At special occasions in someone's house, every:	□	□	□	□	□	□	□
d2n. At a wedding, gathering or fair in a community hall,	□	□	□	□	□	□	□
d2o. Indoor religious festival, every:	□	□	□	□	□	□	□
d2p. Other place	□	□	□	□	□	□	□

Remarks:_____
_____
_____
_____

d3. Social contacts outside the living area, in other villages, cities or countries

I meet people:	day	week	month	three months	½ year	> ½ year	never
d3a. In villages outside my living area every:	□	□	□	□	□	□	□
d3b. In the nearest city at least every:	□	□	□	□	□	□	□
d3c. In other cities in Bangladesh every:	□	□	□	□	□	□	□
d3d. In other countries every:	□	□	□	□	□	□	□
I travel to areas outside my living area for:							
d3e. For business / work	□	□	□	□	□	□	□
d3f. For special occasions like fairs or a wedding	□	□	□	□	□	□	□
d3g. For religious festivals, other religious occasions	□	□	□	□	□	□	□
d3h. To visit my relatives	□	□	□	□	□	□	□
d3i. Other reason:_____	□	□	□	□	□	□	□

	day	week	month	three months	½ year	> ½ year	never
d3j. I stay overnight in other areas, every	□	□	□	□	□	□	□
d3k. I stay there on average	_____ days / months						
d3l. I share a room with more than 10 people	□ yes	□ no					
d3m. I share a bed with other people	□ yes	□ no					
d3n. I share clothes and / or towels with other people	□ yes	□ no					

Remarks:_____
_____
_____
_____

ANNEX 2: Correlation between the value of the original variable and the score on the three different levels

Variable	Correlation with score level 1	Correlation with score level 2	Correlation with score level 3
Social contacts in the home: level 1			
Crowding score	0.36	0.15	0.08
With neighbours	0.43	0.17	0.15
With people from village	0.65	0.11	0.08
With relatives from outside village	0.44	0.03	0.15
With others from outside village	0.54	0.23	0.07
Visitors staying overnight	0.43	0.08	0.10
Social contacts within the neighbourhood: level 2			
At the outdoor workplace	0.18	0.65	0.17
At the market	0.28	0.65	0.20
In yard of neighbours/ friends	0.23	0.47	-0.02
At outdoor gathering, religious festival or fair	0.18	0.36	0.10
At outdoor wedding ceremony	0.11	0.25	0.14
Inside a building (school, other house or shop)	0.20	0.59	0.25
Inside building for work	0.11	0.63	0.21
Inside mosque or temple	0.001	0.54	0.10
Inside building for regular meeting	0.03	0.32	0.11
Special occasion at someone's house	0.08	0.30	-0.06
Indoor wedding, gathering or fair	0.22	0.25	-0.02
Indoor religious festival	0.09	0.30	-0.02
Social contacts outside the neighbourhood: level 3			
In nearby villages	0.12	0.34	0.43
In nearest city	0.13	0.47	0.42
In other cities in Bangladesh	0.01	0.25	0.41
In other countries	-0.02	0.13	0.17
Staying overnight	0.29	0.12	0.38
Share room with >10 people	0.07	-0.03	0.78

CHAPTER 4

Recent food shortage is associated with leprosy disease in Bangladesh: a case-control study

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ABSTRACT

Background

Leprosy is remaining prevalent in the poorest areas of the world. Intensive control programmes with multidrug therapy (MDT) reduced the number of registered cases in these areas, but transmission of *Mycobacterium leprae* continues in most endemic countries. Socio-economic circumstances are considered to be a major determinant, but uncertainty exists regarding the association between leprosy and poverty. We assessed the association between different socio-economic factors and the risk of acquiring clinical signs of leprosy.

Methods and findings

We performed a case-control study in two leprosy endemic districts in northwest Bangladesh. Using interviews with structured questionnaires we compared the socio-economic circumstances of recently diagnosed leprosy patients with a control population from a random cluster sample in the same area. Logistic regression was used to compare cases and controls for their wealth score as calculated with an asset index and other socio-economic factors. The study included 90 patients and 199 controls.

A recent period of food shortage and not poverty *per se* was identified as the only socio-economic factor significantly associated with clinical manifestation of leprosy disease (OR 1.79 (1.06-3.02); p=0.030). A decreasing trend in leprosy prevalence with an increasing socio-economic status as measured with an asset index is apparent, but not statistically significant (test for a trend: OR 0.85 (0.71-1.02); p=0.083).

Conclusions

Recent food shortage is an important poverty related predictor for the clinical manifestation of leprosy disease. Food shortage is seasonal and poverty related in northwest Bangladesh. Targeted nutritional support for high risk groups should be included in leprosy control programmes in endemic areas to reduce risk of disease.

AUTHOR SUMMARY

Although intensive control programs reduced the prevalence of leprosy worldwide, new cases of this infectious disease are still detected in several of the poorest areas of the world. Therefore the disease is known as a disease of poverty. To be able to control the disease it is important to know which aspects of poverty play a role in transmission and acquiring clinical signs of disease. In this study socio-economic circumstances of recently diagnosed leprosy patients were compared with these of a control population in the poverty stricken northwest area of Bangladesh were leprosy is common. A recent period of food shortage was the only socio-economic factor that was found related to leprosy disease in this study and not poverty as such. Food shortage is seasonal and poverty related in northwest Bangladesh, while malnutrition is known to lower immunity and make people more vulnerable for infectious diseases. Therefore it was concluded that malnutrition as aspect of poverty played an important role the development of clinical signs of leprosy. We therefore recommend that nutritional support for high risk groups should be included in leprosy control programmes to reduce risk of disease in areas were leprosy is common.

INTRODUCTION

Leprosy is known as a disease of poverty. Only in the poorest areas of the world the infectious disease caused by *Mycobacterium leprae* is still endemic. A causal relationship between poverty and leprosy is difficult to demonstrate, and uncertainty exists about how leprosy and poverty are associated [1,2].

Bangladesh is one of the countries where the disease is still endemic. Despite reaching the 'elimination' target of less than one registered case per 10,000 inhabitants for the whole country in 1998, the prevalence is still above target in some of the poorest areas of Bangladesh [3,4]. In the poverty stricken northwest part of the country, where The Leprosy Mission Bangladesh is operating a leprosy control programme, the new case detection rate was still 1.25 per 10,000 inhabitants in 2008.

To generate more knowledge about risk factors for leprosy and to assess the effect of new interventions, a research project was initiated in northwest Bangladesh in 2001: the COLEP study, a prospective (sero-) epidemiological study on contact transmission and chemoprophylaxis in leprosy [5]. The first results of the study indicated that prophylactic treatment with rifampicin is a promising way to prevent leprosy in contacts of patients [6]. Physical distance to a patient and the severity of the disease (leprosy classification) were identified as risk factors associated with transmission of *Mycobacterium leprae* to contacts of a patient. Furthermore, the host characteristics "blood relationship to the patient" and "age" were identified as risk factors for the development of clinically apparent disease, while a previous vaccination with BCG had a preventive effect [7]. These findings indicate that innate and acquired immunity affects the development of clinical signs of leprosy. Clinical disease occurs most probably in only 1-5% of persons infected with *Mycobacterium leprae*, after an incubation period of several years.
The objective of this study, which is part of the COLEP project, was to assess the association between poverty and leprosy more closely, by measuring the effects of different socio-economic factors on acquiring clinical signs of leprosy disease.

METHODS

Study area and population

A case-control study was carried out in August 2009 in the districts of Nilphamari and Rangpur in northwest Bangladesh. This large (3951 km^2) – mainly rural – area has app. 4.5 million inhabitants and is one of the poorest parts of Bangladesh [8,9].

The first 110 new leprosy patients registered in 2009 in the study area were selected as cases. These patients were diagnosed by The Leprosy Mission Bangladesh or government facilities

according to the national guidelines [10]. Only one patient per household was interviewed to avoid bias due to clustering. From the initially selected group, 10 people could not been reached, while one was excluded because he was living in the same household as another selected patient.

Controls without leprosy were randomly selected from a referent group, representative for the general population in the area. This group was selected at the start of the COLEP study in 2002 by a multi-cluster sampling procedure [11]. Twenty clusters of 1000 people each were randomly selected from the 13 sub-districts in this area. In each of the sub-districts one to three clusters were allocated proportional to the population size. Within the sub-districts first unions and thereafter sub-unions were selected randomly by computerized sampling. In each of the thus created clusters, everyone willing to participate and available on the day of registration was included. Registration started at the northern border of the selected village or urban ward and continued until 1000 people were included in the cluster.

For this study, 15 people were randomly selected from each of the 20 clusters by computerized sampling. The 15 selected candidates of each cluster were numbered one to fifteen. Interviewers started to contact the first person and continued following the numbering until 10 people were interviewed or everyone was contacted. Controls were excluded when they were ever diagnosed as leprosy patient or if they came from the same household as another participant in the study.

Data collection

Research staff of The Leprosy Mission Bangladesh carried out home visits to conduct interviews with pre-tested structured questionnaires. Besides questions on personal data and some details about their disease (for patients only), participants were asked about their living circumstances and economic situation. They were asked about ownership of assets, including housing, drink water supply, sanitary facilities, livestock and land, while they were also questioned about educational level, job status, monthly household income, seasonal income variations, changes in economic and living situation due to the disease leprosy as well as over the last three years in general, and periods of food shortage in the previous year and ever in life. Food shortage was defined as a period in which a family had to reduce the number of meals a day or had to reduce the intake of foods other than rice, like vegetables, fruits, meat or fish.

Analysis

Data from the questionnaires were entered into an Access database. After data cleaning, analysis was performed using the statistical package STATA version 10.0.

Table 1. Variables in the asset index with weighing value as obtained by factor analysis (first factor).

Description of assets	Number and % possessing the asset	Weighing value in the final formula
Floor of house: earth, mud or clay	254 (87.9%)	-0.5990
Floor of house: bamboo or wood	10 (3.5%)	0.1100
Floor of house: cement, tiles or carpet	25 (8.7%)	0.6237
Roof of house: bamboo, thatch	22 (7.6%)	-0.2038
Roof of house: tin	267 (92.4%)	0.2038
Walls of house: mud, bamboo or palm	209 (72.3%)	-0.5467
Walls of house: tin	39 (13.5%)	0.1328
Walls of house: cement or bricks	41 (14.2%)	0.5710
Electricity	102 (35.3%)	0.6874
Radio	36 (12.5%)	0.1877
Television	81 (28.0%)	0.7294
Computer	5 (1.7%)	0.2094
Mobile phone	110 (38.1%)	0.6272
Refrigerator	6 (2.1%)	0.1696
Fan	87 (30.1%)	0.7295
Air conditioner	3 (1.0%)	0.1586
Almirah or wardrobe	126 (43.6%)	0.6567
Table	240 (83.0%)	0.5185
Chair	210 (72.7%)	0.6167
Watch or clock	167 (57.8%)	0.6183
Bicycle	133 (46.0%)	0.5943
Van or rickshaw	31 (10.7%)	x
Animal drawn cart	10 (3.5%)	x
Motorcycle or scooter	11 (3.8%)	0.4073
Tractor or motorized farm equipment	29 (10.0%)	0.2934
Local rice husking equipment	77 (26.6%)	0.2661
Car or truck	2 (0.7%)	x
Owns livestock	251 (86.9%)	0.2189
Owns the house	281 (97.2%)	0.1879
Owns the land of the house	253 (87.5%)	0.4170
Owns farmland	164 (56.8%)	0.4187
Drink water from tube well / bore hole	280 (96.9%)	x
Flush toilet or septic tank	3 (1.0%)	0.2606
Latrine	222 (76.8%)	0.3632
No toilet facility (bush / field)	64 (22.2%)	-0.4327
Shares toilet	48 (16.6%)	-0.1281
Total number of participants	289	

Socio-economic status of the participants was estimated by an asset index. Factor analysis, principal components factor, as described by Filmer and Pritchett was used to construct an asset index to assign a wealth score to all participants [12]. Data on ownership of different assets in their household was used to calculate a wealth score by weighing the response for each asset of their household by the coefficient of the first factor as determined by application of the factor analysis, and summing the results (Table 1). Data regarding possession of a car, rickshaw, animal cart, and drink-water supply were not correlated with the wealth scores as calculated and therefore excluded from the final model. The control group was assigned to five wealth quintiles according to their final score. Cases were assigned to these quintiles according to the threshold values set by the control group.

Logistic regression was used to compare cases and controls for the wealth score quintile and the other factors measuring aspects of socio-economic situation: income level, educational level of the highest educated person in the household, household size, crowding (defined for this study as more than three people per sleeping room on average), food shortage ever and a period of food shortage in the last year. Univariate and multivariate logistic regression with a backwards elimination procedure was used to assess the association between these factors as well as the potential confounding factors age and sex.

Ethics statement

All participants received verbal information about the study and were asked to sign a consent form. Ethical approval for this study was obtained from the Bangladesh Medical Research Council (under reference: BMRC/NREC/2007-2010/2107).

RESULTS

Initially 99 patients (cases) and 199 controls were included in the study population. A deterioration of socio-economic or living condition due to the disease was mentioned by 9 (8.9%) of the cases. All these patients had severe forms of leprosy; 6 had grade II disabilities, while the other 3 had the more severe MB form of leprosy. Because the objective of this study was to assess the socio-economic condition as a risk factor for developing clinical signs of leprosy disease, it was important to establish the situation around the time the disease became apparent. We therefore excluded for further analysis the 9 cases in which the economic situation had changed due to the disease, to avoid confusion about cause and effect.

Of the 90 patients included for analysis, the sex ratio (M/F) of the was 1.2; 21.1% had the multibacillary (MB) form of the disease, while 6.6% was diagnosed with a grade II disability, according to the WHO classification (Table 2). The child rate (<15 years of age) was 15.6%. At the

time of the interview, 58.9% of the cases were still on multidrug therapy (MDT), while the other 41.1% had just completed their therapy and were released from treatment.

Table 2. General characteristics of the leprosy cases in the analysis population.

	Male			Female			
Age group (in years)	**Case N (%)**	**MB (% of cases)**	**Disability grade II (% of cases)**	**Case N (%)**	**MB (% of cases)**	**Disability grade II (% of cases)**	**Total N (%)**
5 - 14	5 (10.2%)	0 (0%)	0 (0%)	9 (22.0%)	0 (0%)	0 (0%)	14 (15.6%)
15-39	28 (57.1%)	5 (17.9%)	1 (3.6%)	20 (48.8%)	4 (20.0%)	0 (0%)	48 (53.3%)
≥40	16 (32.6%)	5 (31.3%)	4 (25.0%)	12 (29.3%)	5 (41.7%)	1 (8.3%)	28 (31.1%)
Total	49 (100%)	10 (20.4%)	5 (10.2%)	41 (100%)	9 (22.0%)	1 (2.4%)	90 (100%)

Both the case and control populations were distributed randomly throughout the study area. The control group was representative for the general population in the area with respect to the household characteristics religion, household composition, educational level, and living area (urban/rural), as compared to the national statistics, but males in the working age (20-39 years) were slightly underrepresented in the control group [8,9].

The prevalence of leprosy decreased with an increased level of economic status, measured by the wealth score quintile (test for a trend: OR 0.85 (0.71-1.02); p=0·083, Table 3). Uni- and multivariate logistic regression analysis revealed only a statistically significant association of the socio-economic factor "a self reported period of food shortage in the last year" with leprosy disease (OR 1.79 (1.06-3.02); p=0.030, Table 3). None of the other socio-economic factors were associated with leprosy disease.

DISCUSSION

A recent period of food shortage and not poverty *per se* was identified as the only socio-economic risk factor significantly associated with clinical manifestation of leprosy disease in northwest Bangladesh. A decreasing trend in leprosy prevalence with an increasing socio-economic status as measured with an asset index is apparent, but not statistically significant.

The strength of this case control study is that it takes into account recently diagnosed leprosy cases, while patients who reported changes in economic or living situation due to their disease were excluded. In this way the actual situation at the time of diagnosis could be measured, making it possible to draw conclusions about the association of leprosy and socio-economic situation as risk factor for acquiring clinical signs of leprosy disease.

A limitation of the study is the use of self-reported data on income, educational level and food shortage as measured by a questionnaire, which is by definition subjective. The effect of this form of bias was reduced by asking cases and controls the same questions. Furthermore also an asset index as proxy to measure wealth was constructed, which is a more objective measure for socio-economic status of the household.

Although objective, a limitation of the use of a wealth index is that the score of the index depends highly on the set of assets used [13]. Since the asset index used in the USAID sponsored Demographic and Health Survey, carried out in 84 developing countries, has a proven valuable for public health purposes we used a set of assets based the local version of the Demographic and health Survey for Bangladesh [14], [15]. Another limitation of this method is that the index is relative and based on the assets of others in the group. The whole assessed group is divided into five equal quintiles based on their wealth score. Since the majority of people are very poor in the study area in northwest Bangladesh, people assigned to the higher quintiles have more assets and are somewhat better off than the households included in lower quintiles, but can not be considered as rich by any means in this poverty stricken area.

It is likely that most people who reported "food shortage in the last year" in our study observed shortage of food in the yearly period of seasonal income shortage in rural Bangladesh which lasts from the end of September until November, just after the rainy season and before the main rice harvest in November/December. In this period there are few work opportunities, low household food stocks, and increased rice prices. The yearly period of food shortage roughly coincides with the start of symptoms of leprosy in the selected cases, as 70% of the patients reported start of their symptoms less than six months before they were registered (between seven to twelve months before the interview, between September to December 2008).

In poor rural communities in Bangladesh seasonal income changes are common. In our study the reported income changed from a monthly average of 3000 BDT (43 US$) to 9000 BDT (130 US$) per household. Seasonal income changes are closely related to daily expenditure on food and influences the nutritional status of the people in rural Bangladesh [16]. In rural Bangladesh, chronic energy deficiency (CED) based on body mass index (BMI) is high (between 60-70%) in all age and sex groups, while seasonal differences in energy intake are substantial in all age and sex group as well [17]. The amount of rice consumed is quite stable, but expenditure on high nutritious and more expensive food decreases in months of low income in rural communities, likely causing micronutrient deficiencies. Studies in Bangladesh revealed an association

Table 3. Results of univariate and multivariate logistic regression analysis with a backwards elimination procedure.

Variable		Control N (%)	Case N (%)	Univariate Crude Odds Ratio (95% CI)	p-value	Multivariate Odds ratio (95% CI)	p-value
Wealth quintile (asset index)	1	40 (20.1%)	25 (27.8%)	1.00			
	2	40 (20.1%)	20 (22.2%)	0.80 (0.38-1.67)			
	3	40 (20.1%)	16 (17.8%)	0.64 (0.30-1.38)			
	4	40 (20.1%)	17 (18.9%)	0.68 (0.32-1.45)			
	5	39 (19.6%)	12 (13.3%)	0.49 (0.22-1.12)			
	Assuming a linear trend			0.85 (0.71-1.02)	p=0.083		
Income level (BDT)	Mean	4108	4853				
	Std. Dev.	3978	3991	1.00 (1.00-1.00)	p=0.148		
Educational level*	High	113 (56.8%)	49 (54.4%)	1.00			
	Low	86 (43.2%)	41 (45.6%)	1.10 (0.67-1.81)	p=0.711		
Household size	Mean	5.28	4.96				
	Std. Dev.	2.30	1.97	0.93 (0.82-1.05)	p=0.248		
Crowding‡	No	129 (64.8%)	55 (61.1%)	1.00			
	Yes	70 (35.2%)	35 (38.9%)	1.17 (0.70-1.96)	p=0.544		
Ever food shortage	No	76 (38.2%)	30 (33.3%)	1.00			
	Yes	123 (61.8%)	60 (66.7%)	1.24 (0.73-2.09)	p=0.428		
Food shortage in the last year	No	128 (64.3%)	47 (52.2%)	1.00		1.00	
	Yes	71 (35.7%)	43 (47.8%)	1.65 (1..00-2.74)	p=0.052	1.79 (1.06-3.02)	p=0.030
Sex	Female	116 (58.3%)	41 (45.6%)	1.00			
	Male	83 (41.7%)	49 (54.4%)	1.67 (1.01-2.76)	p=0.045		

Table 3. Results of univariate and multivariate logistic regression analysis with a backwards elimination procedure *(continued)*.

Variable		Control N (%)	Case N (%)	Univariate Crude Odds Ratio (95% CI)	Univariate p-value	Multivariate Odds ratio (95% CI)	Multivariate p-value
Age (years)	<10	22 (11.1%)	6 (6.7%)	1.00		1.00	
	10-19	65 (32.7%)	20 (22.2%)	1.13 (0.42-3.17)	p=0.819	1.17 (0.41-3.32)	p=0.762
	20-29	27 (13.6%)	21 (23.3%)	2.85 (0.98-8.30)	p=0.054	3.22 (1.09-9.51)	p=0.034
	30-39	32 (16.1%)	15 (16.7%)	1.72 (0.58-5.12)	p=0.331	1.84 (0.61-5.55)	p=0.277
	40-49	35 (17.6%)	11 (12.2%)	1.15 0.37-3.56)	p=0.805	1.28 (0.38-3.67)	p=0.781
	50+	18 (9.1%)	17 (18.9%)	3.46 (1.13-10.61)	p=0.030	3.56 (1.15-11.02)	p=0.028
	Total	199 (100%)	90 (100%)				

*Educational level: Low: highest educated person in the household had 0-5 years of schooling; High: highest educated person had more than 5 years of schooling
‡Crowding: for this study defined as more than three people per sleeping room (average)

between the proportion of expenditure on non-rice food and maternal underweight as well as child stunting [18], and an association between a low BMI and increased mortality in adults [19].

The hypothesis that seasonal food deficiencies might be associated with leprosy is strengthened by the seasonal pattern in number of new leprosy cases registered per month over the last nine years (2002-2010) in the districts where the study was carried out. The number of newly registered cases is rising from February, about four months after the start of the seasonal low-income period, and reaches a maximum in June at the beginning of the monsoon period in Bangladesh and six months after the end of the low-income period (figure 1).

However alternative explanations are possible. A study in a leprosy endemic area in India showed a strong seasonal pattern in *Mycobacterium leprae* bacteria detectable in the general population by nasal PCR and salivary ML-IgA positivity. The rates of PCR positive nasal swabs were high in the period immediately after the monsoon rains from July to November, while salivary ML-IgA titres were high in November at the end of the wet period. This indicates a seasonal pattern in exposure to *Mycobacterium leprae* [20].

"Food shortage in the last year" as assessed in this study represents a recent (short) period of poverty with limited expenditure on high nutritious food, likely causing nutritional deficit. In contrast, an asset index as a proxy to measure wealth gives an indication of the long-term economic status of a household, since people tend not to sell their assets in seasonal short periods of low income, but only in longer term poverty [12,21].

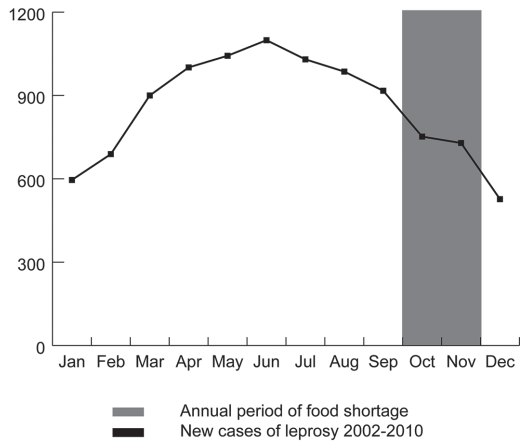

Figure 1. Seasonal pattern of leprosy cases in the study area (2002-2010) in relation to the annual period of food shortage.

Although the general population sample (referent group) of the COLEP trial was selected almost seven years before this study, a selection of this group is still suitable to use as control group. Only three of the selected leprosy cases were born less than seven years before the start of the study, from which you can conclude that leprosy below this age is rare. Furthermore 80% of the selected people of the control group participated in the study, which indicates that the population in this area is not very mobile. However, due to the original selection method used for this referent group, men in the working age are underrepresented, since many of them were absent from their house at the time of registration. Therefore age and sex were included as potential confounders in the analysis.

The actual association between poverty and leprosy might be stronger than indicated by this study, because only registered cases were included in the study. Registered cases receive leprosy treatment and have access to health services. Although the area has a long running active disease control programme in which treatment is given free of charge, there are still people who have no access to these services. In a study carried out in 2002 in northwest Bangladesh, the population prevalence of leprosy was found to be six times higher than the registered prevalence [11]. The fact that 11% of the original selected cases in our study had grade II disability, indicating late detection of the disease, suggests that there may be undetected leprosy cases in the area. Poverty is one of the reasons for limited access to leprosy care. Stigma, although less common due to the active control and health education activities in the area, and cultural defined limited access to health care for women might be of importance as well [22].

An association between food shortage and leprosy was also observed in Brazil [1]. However, in Brazil a period of food shortage at any time in life, as indicator of poverty in general, was found associated with leprosy, while in our study only a recent period of food shortage was associated with the disease. Although a higher percentage of leprosy cases also reported food shortage at any time of life in Bangladesh, this association was not statistically significant. Different case definitions of food shortage or differences in social norms regarding nutritional requirements between the countries could be an explanation for this difference. Food shortage however, may also be a less strong indicator of poverty in general in Bangladesh than in Brazil, since the percentage of people who reported food shortage ever was much higher in Bangladesh (66.7% of the cases and 61.8% of the controls) than in Brazil (28% of the cases and 19% of the controls).

Nutritional status is known to influence the development of other infectious diseases such as respiratory infections, infectious diarrhoea, measles and malaria. These diseases are observed more commonly in malnourished children. Malnutrition affects the immune system negatively, causing infected individuals to be more vulnerable for developing a clinically apparent infection [23]. In tuberculosis, which has similarities to leprosy since it is also caused by a mycobacterium, nutritional deficit has been identified as an important risk factor in the

development of clinical symptoms of disease. This is based on historical reports of outbreaks during famines and wars, and on animal studies in which cell mediated immunity was diminished in malnourished guinea pigs. Cell mediated immunity, which is affected by both protein energy malnutrition and micronutrient deficiencies, plays an important role in host defense against tuberculosis and leprosy [24]. A recent period of food shortage as identified in our study as most important poverty-related factor associated with leprosy, very likely has reduced the cell mediated immunity of individuals incubating *Mycobacterium leprae*, causing the development of clinical leprosy disease.

Targeted nutritional support to high-risk groups should therefore be included in leprosy control programmes in endemic areas to reduce risk of disease. It would be useful to give contacts of leprosy patients, who are at high risk of developing leprosy themselves, dietary advices to prevent malnutrition. Because food shortage is seasonal and poverty related in northwest Bangladesh, extra attention and support should be given to the poorest families with leprosy patients. It is important to prevent malnutrition in these families to prevent clinical leprosy among contacts of patients.

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CHAPTER 5

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

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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 two 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 randomized 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 ($p=0.025$) 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.

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.

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 two 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 six-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, age 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 six 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 four years the study was unblinded according to protocol and the first results were published [1]. The cohort of contacts of the index patients was followed for another two 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 Program. 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 five 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, six weeks after the index patient started with treatment. In the follow up period all contact groups were visited three times, respectively two, four and six 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 patient 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 patient.

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 2 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 $p<0.2$ were included in a multivariate analysis. Characteristics with a p-value >0.1 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 two 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 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=0.025) 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 five years of age at the time of intake. Of these children, 14 developed leprosy in the six years follow up period, 6 in a rifampicin contact group (6.7 [3.0-14.9]) per 10,000 person years at risk) and 8 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.

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	10006	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*		*10006*	*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	12613	12694	31.9 (25.7 – 39.7)
3-4	30	12037	12067	12.4 (8.7 – 17.8)
5-6	20	11477	11497	8.7 (5.6 – 13.5)
Total	*131*			
SDR contact group total				
1-2	50	12731	12781	19.6 (14.8 – 25.8)
3-4	35	12160	12195	14.4 (10.3 – 20.0)
5-6	23	11435	11458	10.0 (6.7 – 15.1)
Total	*108*			

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

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<0.001). Significantly less new cases were observed among contacts of male index patients (OR 0.53 [0.32-0.87], p=0.015) and among contacts of index patients who were significantly older (0.98 [0.96-1.00], p=0.30) (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=0.002), or if they had the multibacillary (MB) form of the disease (OR 1.80 [1.01-3.20], p=0.045) (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=0.01), 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 2 or more patients at intake (p-value interaction p=0.073) (Table 5). 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).

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	No	392	(87.7)	55	(12.3)	1.00					
patients at intake	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	No	386	(89.4)	46	(10.7)	1.00					
patients at intake	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 analysis of interaction between treatment group and patient characteristics

	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		
Characteristic of original COLEP index patients, with a significant association with new cases among contacts in one of the treatment groups	**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

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).

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 two years after treatment, after which no additional effect was observed [1]. SDR prevented 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 program 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 generalized to areas where leprosy is less common.

The effect of chemoprophylaxis was only evident in the first two 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 group 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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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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CHAPTER 6

Acceptability of chemoprophylaxis for household contacts of leprosy patients in Bangladesh: a qualitative study

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SUMMARY

Objectives

Chemoprophylaxis with single dose rifampicin is a promising intervention to prevent leprosy in close contacts of patients. However, application in control programmes often requires disclosure of the leprosy diagnosis, which is still a stigmatised disease in many countries. Promoting control and treatment of stigmatised diseases without contributing towards stigma of the individuals involved can be very difficult. The objective of this study was to assess the social acceptability of disclosure of the diagnosis and the attitude towards taking prophylactic medicines in a leprosy endemic area in Bangladesh.

Design

Qualitative study through focus group discussions with 136 healthy men and women from different age groups and religions, coming from two rural villages and an urban area in northwest Bangladesh, and 14 health workers with extensive experience with leprosy patients.

Results

The participants would not object to disclosure of the diagnosis to household members and nearby family if they were diagnosed with leprosy. However, many participants were not willing to share this information with their neighbours and other social contacts due to stigma of the disease. All healthy participants were willing to take chemoprophylaxis if any of their close contacts were diagnosed with leprosy, even after explaining that full protection against leprosy was not guaranteed.

Conclusion

It can be concluded that chemoprophylaxis for household contacts of leprosy patients is an effective and socially acceptable addition to the current leprosy control programme. Chemoprophylaxis for other categories of contacts likely to benefit would only be feasible, without disclosure of patient information, if given in the form of mass campaigns for the whole population in the area.

INTRODUCTION

Chemoprophylaxis in chronic infectious diseases such as tuberculosis, is of established benefit when given to people who are known to be at an increased risk of the disease. Trials with rifampicin used as chemoprophylaxis for contacts of leprosy patients have shown it to be effective. In a large trial in northwest Bangladesh (COLEP study), a 57% reduction in incidence among contacts was reached in the first 2 years after prophylactic treatment with a single dose of rifampicin [1]. Rifampicin was provided to household contacts, neighbours and close social contacts after the leprosy patient had taken the second dose of multidrug therapy and could be expected to be non-contagious. People not closely related to the leprosy patient or not living in the same household, benefited relatively more from this prophylactic treatment with a single dose of rifampicin. However, household members of patients are at highest risk of being infected with *Mycobacterium leprae*. Physical distance to a patient and severity of the disease (leprosy classification) were identified as risk factors associated with transmission of *Mycobacterium leprae* while the contact characteristics 'blood relationship to the patient' and 'age' were identified as risk factors for the development of clinically apparent disease [2].

The WHO recently suggested in their 'Enhanced Global Strategy for Further Reducing the Disease Burden due to Leprosy, 2011–2015' that the use of chemoprophylaxis as a tool to prevent the occurrence of new leprosy cases among household contacts should be explored further [3]. One important issue for further study is the acceptance of chemoprophylactic measures by leprosy patients and their potentially benefiting contacts [4]. Although many will appreciate the preventive effects of this kind of treatment, leprosy patients could object to disclosure of their diagnosis to others. Disclosure of the stigmatised diagnosis of leprosy to community members may have a major impact on the social life of people affected by the disease [5,6]. Although mass distribution of rifampicin in a whole village without identifying the index case would be possible, disclosure of the diagnosis is a necessary step in the provision of targeted chemoprophylaxis to household members or close contacts of a patient, who have the highest risk of getting infected. This aspect was not addressed in the COLEP study, since only patients who did not object to disclosure of their diagnosis were included in the study. However, about 25% of those new leprosy cases registered in the period the COLEP cohort was being enrolled did not participate in the trial and were also not related to any of the cases included in the study. Although there were several possible reasons for not participating in the study (e.g. not present in the house at enrolment time, only temporarily in the study area, living less them 100 metres from a COLEP patient), the main reason was a refusal to participate. Another possible issue may be the difficulty of motivating healthy contacts of patients to take prophylactic medication.

In this qualitative study by means of focus group discussions, we assessed the social acceptability of disclosure of the leprosy diagnosis and the attitude towards taking prophylactic

medicines in a group of healthy individuals in the same leprosy endemic area in northwest Bangladesh where the COLEP study was carried out. A focus group discussion on the same subject was conducted with a group of 14 staff members of the Leprosy Mission Bangladesh (TLMB) who all had extensive experience with leprosy patients in the hospital, rehabilitation projects or leprosy control programmes in the same area.

METHODS

Study area and population

The study was carried out in March 2009 in the leprosy endemic districts of Nilphamari and Rangpur. The large (3951km^2), mainly rural area has approximately 4.5 million inhabitants and is one of the poorest parts of Bangladesh [7,8]. The new case detection rate for leprosy was 1.3 per 10,000 inhabitants in 2008, with a child rate of 10.5% which indicates an active transmission of *Mycobacterium leprae*. The new case detection rate in this area dropped remarkably over the last decade, from around 4.0 to 1.3 per 10,000 inhabitants. However, a study based on active case finding in 2002–2003 showed a prevalence of previously undiagnosed leprosy of 15.1 per 10,000 inhabitants, which was about six times higher than the reported prevalence rate [9]. Therefore, the disease is still quite common in this region and many people are familiar with it.

Focus group discussions were conducted in two rural villages and one urban ward. In collaboration with field staff of the rural health program (RHP) of TLMB, locations were selected where there was a trained RHP volunteer available. The local RHP volunteer facilitated in the logistic management of the discussions, obtaining consent from the village leader, recruiting participants and organising an appropriate venue.

Participants from poor as well as better-off families were invited for the discussions to ensure representatives from different socio-economic backgrounds. The two main religions in the region (Muslim and Hindu) were represented in all groups. In each location separate group discussions were held for adult women, adolescent girls, adult men and adolescent boys (adult: above 20 years of age and adolescent: between 12 and 20 years of age).

Data collection

Staff members from RHP facilitated the focus group discussions. Before the start of the study they received training and instruction from an experienced local social scientist from the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) in Dhaka, and the international researcher; besides written guidelines in Bengali and English were provided. For good rapport a female staff member facilitated the female discussion groups, while a male one conducted the male discussions. The Bangladeshi social scientist and the international

researcher were present in the different discussions to observe and to assist the facilitator when necessary. The discussions were held in the local language (Bengali) and recorded with one or two tape recorders. Additional notes were taken on observations and the context under which the discussions took place.

The group started with a general introduction and discussion about social contact structures. Thereafter the facilitator gave some brief information about leprosy and confirmed that everyone was familiar with the disease. The facilitator explained that a study with chemoprophylaxis showed promising effects in the prevention of leprosy, but that these medicines do not give full protection against disease.

A topic list was used to structure the discussion. However, the facilitators were instructed to give participants the opportunity to raise new issues as well.

Ethical approval and consent

At the start of the focus group discussion the subject, purpose and procedures of the meeting were explained to the participants. After this explanation participants gave their verbal consent for the discussion. Ethical approval for this study was obtained from the Bangladesh Medical Research Council under reference: BMRC/NREC/2007-2010/2107.

Analysis

The staff members who facilitated the interviews transcribed the recorded interviews in Bengali. Afterwards these transcriptions were translated into English by a researcher from ICDDR,B in Dhaka, supervised by the social scientist and the international researcher. The software programme N-vivo (version 8, QSR International), was used to conduct a thematic analysis.

RESULTS

Demographic information

In total 150 people participated in the study, 136 participants from the villages and urban ward and 14 staff members (Table 1). There was an almost equal representation of Muslims and Hindus among the participants. The adult male and female participants had an average age of 41 and 38 years respectively, while the adolescent boys and girls were on average 18 and 16 years old. Adolescent participants in the study had a higher educational level than adult participants. Most of them, both male and female, had received secondary education. Only half of the male adult participants in rural as well as urban areas had secondary education, while the majority of the female adult participants in urban areas had only primary education and in rural areas no education at all. Most rural male adults as well as adolescents were involved in

farming, whereas urban participants were involved in a variety of jobs ranging from day labourer to running a small business. Almost all female participants who were not going to school were housewives; in rural areas however, all females were also involved in farming.

Two main themes were extracted for analysis: the attitude towards taking prophylactic medication and the attitude towards disclosure of a leprosy diagnosis to household members, neighbours and others.

Table 1. Number and age characteristics of participants of the focus group discussions.

Group	Site	Number of participants	Minimum Age	Maximum Age	Average Age
Adult male	Urban	11	30	70	44
	Rural	24	30	70	40
Adult female	Urban	11	25	60	38
	Rural	23	25	65	38
Adolescent boys	Urban	11	17	20	19
	Rural	23	11	20	17
Adolescent girls	Urban	12	15	20	18
	Rural	21	12	17	15
Staff TLMB	Male	7			
	Female	7			
Total		**150**	**11**	**70**	

Attitude towards chemoprophylaxis

All participants were positive about taking a prophylactic drug in the event of someone in their household, family or neighbourhood having leprosy, even when they were told that the medicine could not give 100% protection. There were no differences between male and female or adult and adolescent participants. Many people were already familiar with taking medicines as a precaution against other diseases; several people mentioned the example of prophylaxis for lymphatic filariasis.

Rural male adult:

– "It is good to take a medicine. We don't have any problem with that"

Rural female adult:

– *"Of course we will take the medicine. We are also taking the medicine for filariasis, because we know we will be protected from the disease when we take the medicine"*

Urban female adolescent:

– *"Health workers in our area give medicine for different diseases. Our parents are taking these medicines and allow us to take them also. They do not have any objection for that"*

The participants of the discussion groups anticipated that their household members, other family and nearby neighbours would have no problem with taking a prophylactic medicine as well. Taking medicines for all kind of problems and complaints is well accepted in the area and everyone regularly uses medicines.

Also staff of TLMB with extensive experience with leprosy patients think that everyone will agree to take prophylactic medication.

TLMB staff:

– *"Yes, people in this area will support this and take the medicine"*

– *"Most of the people in this area also come to take medicines to protect them from filariasis"*

– *"In the COLEP study many people came to us to ask for the medicine spontaneously"*

Attitude towards disclosure of a leprosy diagnosis to others

Participants were asked to imagine whether they would have any problem with informing household members, neighbours and other social contacts about their diagnosis if they were to be affected by leprosy (Table 2).

Rural female adult:

– *" It can be told to our household members, but not to other relatives"*

– *"In our family, all family members help each other. So we will do what is the best for all of our family members"*

Rural male adolescent:

– *"I have to tell my parents about my problem for my own good. They will help me"*

Rural male adult:

– *"It will create problems if my household members don't know anything about it. For example: if we dine together, my son or grandson may eat my leftover food. If I have a disease, I will not let them eat my food. But it will look odd if I don't offer food to my grandson who stays with me. I have to tell my family about the disease, so they will know why I am doing this"*

Urban male adult:

– *"If I have any problem, my family should know about it. It is important that our family knows about the disease so that they can be aware and take precautions"*

The urban groups were also happy to have their neighbours or other nearby contacts informed about their disease if they had leprosy.

Urban male adult:

– *"First of all, my family needs to know. Then I will tell my neighbours that I have this disease and that there is a medicine for them to take as prevention. If anyone of them also has leprosy, it is important that they get treatment too"*

Urban male adolescent:

– *"We don't have any objection to tell others about this disease. We can't hide this disease; the disease will spread if we hide it"*

In rural areas people were more reluctant, and only some of them agreed that their neighbours or other nearby contacts should be informed. In the rural adult female groups the participants unanimously objected to informing their neighbours and other contacts, while in the rural adult male and adolescent boys groups there were objections as well. The reasons for not informing neighbours or other social contacts all had to do with the stigma of the disease. Participants mentioned that they were afraid of embarrassment, humiliation, social isolation and problems in finding a marriage partner.

Rural male adult

– *"Maybe it is not good to inform the neighbours, they should not know in detail. It is a matter of embarrassment"*
– *"It will be a problem for our children, they will not get married"*
– *"It is common that people say: 'Do not go to that house because he or she has leprosy'. That person will be hurt by hearing this, but other people will be protected"*

Rural male adolescents;

– *"I don't want to tell my neighbours about the disease, because they might hate us. It will be good if they don't know"*

Rural female adult participants:

– *"We will not let other people hear about it, but there is no problem if our family knows it"*
– *"There are many people who will not talk to a person who has leprosy, will not walk beside her, will not touch her"*

The more educated adolescent participants had fewer objections to disclosure of information than the older generation. Only rural adolescent boys were reluctant to disclose information. Some girls mentioned that they themselves were happy to give information about their diagnosis, but that they thought their parents would not agree.

Urban female adolescent participant:

– *"What we are trying to say is that we want to tell everyone, but our family might not agree to that. Other people will be aware of the disease if we tell them. This is good for the society. We are educated and therefore we have this way of thinking. People who are illiterate will not tell anyone about the disease. They think that telling other people will cause damage and problems in their marriage"*

The group of experienced TLMB staff members said that most patients would not object to disclosure of the diagnosis to their household members, but would object to disclosure to others. However, they also have experience with patients who have problems with telling household members about their disease.

TLMB staff:

– *"Sometimes the family doesn't love them anymore the way they used to do if they tell about the disease. This happens to many people. We have learned from our patients that family members don't eat with him anymore or don't want to share their clothes. Sometimes the family don't want to spend money on this member anymore"*
– *"I think this is not a common picture. They will not face any problems in their household unless they become disabled. Then it will create some problems, but this is the minority. However, the majority of patients will not like to tell their neighbours or other contacts about their disease"*

– *"At present we have two female patients who do not want us to go to their home places, because they don't want their husband and other family members to know about their disease"*
– *"I have another female patient who doesn't want us to go her house, because she thinks it will create problems for her marriage"*

Table 2. Attitude towards disclosure of information about the leprosy diagnosis towards others.

Group	Site	Disclosure of diagnosis to family	Disclosure of diagnosis to neighbours or others
Adult male	Urban	+	+
	Rural	+	+/-
Adult female	Urban	+	+
	Rural	+	-
Adolescent boys	Urban	+	+
	Rural	+	+/-
Adolescent girls	Urban	+	+
	Rural	+	+
Staff TLMB		+/-	-
Total		**+**	**+/-**

+ = positive attitude, - = negative attitude, +/- = some of the people were positive and some reacted negatively
Disclosure of the stigmatised leprosy diagnosis is necessary in order to give targeted prophylaxis to household contacts and other selected close contacts of patients. All participants agreed that household members and nearby family should have this information in order to detect early signs of disease and to receive maximum protection in the form of a prophylactic medicine.

DISCUSSION

Prophylactic treatment with a single dose of rifampicin is known to provide protection against leprosy in close contacts of patients. In our study we found a positive attitude towards disclosure of the stigmatised leprosy diagnosis to household and nearby family members in order to provide them chemoprophylaxis. Participants from rural areas, especially the less educated adult participants, were not happy to share information on this diagnosis with neighbours and other social contacts as they feared social isolation when people knew about their disease. All participants had a positive attitude towards taking medicines as prophylaxis should one of their close contacts have leprosy, despite the fact that they were informed that this would not give them full protection against disease.

The study was performed among healthy individuals from three different areas in leprosy endemic districts of Bangladesh. Although the groups were not randomly chosen, we ensured that the two main religious groups in the area, as well different educational and socio-economic backgrounds, were represented. This resulted however, in a relatively high percentage of Hindu participants. Half of our participants were Hindu compared with only 10% Hindus in the general population of the area. However, we do not expect this difference to influence the outcomes of the study.

A possible limitation of the study is that only individuals without leprosy were consulted. It might have been difficult for them to imagine that they had leprosy, although the disease is widespread in the study area and thus many people might have been confronted with this disease. The advantage of interviewing healthy people is that community ideas and attitude towards leprosy are assessed. Since healthy people (contacts of patients) are also the target group for prophylaxis, their attitude towards leprosy and towards taking medicines as a preventive measure against this disease, whilst being symptom-free, is valuable as well. Furthermore, we also obtained information from TLMB staff who had extensive experience of working with leprosy patients in the area and thus could give examples on how patients actually react.

Despite enormous cultural diversity, people in a diverse range of endemic countries are confronted with social discrimination when diagnosed with leprosy. Although diminishing due to increasing knowledge about effective treatment options, fear and cultural beliefs about the disease still cause negative community behaviour towards patients, especially those with visible impairments [10,11]. Many patients in India and Nepal experience negative behaviour within their community and sometimes within their own family [12-14]. As a result many of them try to hide their disease. In Brazil decentralisation of health services for leprosy was not successful, since many patients do not want to take treatment for leprosy close to their homes, as they are afraid that they could be recognised. Some of them had not even informed their household members about their treatment [15].

The fact that many leprosy patients are reluctant to inform others about their disease can hamper disease control and cause late detection of the disease, when irreversible nerve damage and disabilities have already occurred. The same is described for other stigmatised diseases such as TB, HIV/Aids and mental illnesses. Controlling and treating these diseases without contributing towards stigma can be very difficult. It may be necessary for health workers to take restrictive measures towards patients with infectious diseases in situations where public health risks are involved. For example, it might be necessary to isolate infectious patients are from others. However, segregation or actions of health staff can cause negative community behaviour towards the patient, even continuing after the infection risks are eliminated or the disease is treated [16].

Although chemoprophylaxis for contacts of leprosy patients can be an effective addition to the current leprosy control programmes, we have to keep in mind the balance between controlling the disease and contributing towards stigma. In this study we found a positive attitude towards disclosure of the stigmatised leprosy diagnosis within the household and close family in all discussion groups, while TLMB staff reported problems with this as unusual. Household contacts of leprosy patients are the group at highest risk of getting infected [2]. Therefore chemoprophylaxis for household contacts of leprosy patients would be an effective and feasible option in disease control in Bangladesh and possibly also in nearby countries in the South Asian continent such as India, Nepal and Pakistan. Many participants in our study had objections to disclosing a leprosy diagnosis to contacts outside their own household. Informing other social contacts in the neighbourhood is likely to contribute towards stigmatisation of the individuals involved, but this may differ elsewhere in the world. When more people need to be protected, prophylaxis for a whole village or urban neighbourhood without disclosing information about a specific patient could be an option. This can be combined with more general health education about leprosy, which is the usual practice in leprosy control.

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CHAPTER 7

General discussion

ANSWERS TO THE RESEARCH QUESTIONS

In this thesis the association between determinants in the social environment and acquiring clinical leprosy is addressed. Socioeconomic factors and social contacts are chosen as the main determinants of study. In the general introduction of this thesis I presented four research questions, which were addressed in the articles presented in the previous chapters. In this chapter I provide a concise answer for each of the four questions and discuss methodological issues, conclusions and implications of the studies.

Research question 1:

Is there a relation between social contact patterns and acquiring clinical leprosy?

Answer:

In the case-control study carried out in a leprosy endemic area in northwest Bangladesh, new leprosy patients reported more intensive social contact patterns in the home and nearby neighbourhood than healthy controls.

The causative agent of leprosy *M. leprae,* is transmitted from person-to-person and humans are the main reservoir considered important for transmission [1,2]. Therefore social contact patterns are an important determinant in the transmission of the disease. Since social contact patterns are shaped by the social environment and influenced by cultural habits and economic circumstances, social contact patterns are bound to vary from region to region and even within population groups in the same region. The general social contact pattern in the leprosy endemic area of northwest Bangladesh was explored by means of focus group discussions (chapter 2). Social contact patterns are relevant for the transmission of leprosy only if they are both intensive and longstanding, because the disease is believed to have a relatively low level of infectiveness [2,3]. All discussion groups reported social contact patterns with a high relevance for the transmission of leprosy inside and around the home. In the home intergenerational contacts and contacts between people of different sex are common. Outside the home women and girls reported relevant contacts in the nearby neighbourhood only, while men also mentioned high relevant contacts beyond. This implies that in theory leprosy can be transmitted easily across age and sex groups in and around the home, while adult men might play a role in the transmission of leprosy from outside this relatively confined area.

With a case-control study we compared contact patterns of new leprosy cases with non-leprosy controls from the same endemic area (chapter 3). Each participant received a score for the intensity of their social contact patterns on three different levels; in the home, in the neighbourhood (village or urban ward) and outside this area. We found that leprosy patients

had a more intensive social contact pattern in the home and in the neighbourhood than the control group. Intensive contacts beyond the neighbourhood were not associated with clinical leprosy.

There are not many published studies actually addressing social contact patterns in relation to airborne infectious disease transmission. Although studies were carried out in Vietnam and South Africa, most were conducted in developed countries with different cultural practices than our study area. However, the contact profiles and implications for infectious disease transmission have similarities with the results of our study. In all studies, households were identified as the most important connective place for people of different age and sex [4-6]. Two studies concluded that households play an important bridging role in the transmission of airborne transmitted diseases between population subgroups [4,6]. In a study in South Africa the same role was assigned to public transport, where intergenerational mixing also takes place [6]. As in our study, several other studies indicated that social contacts outside the home are highly associated with age and sex [5,7,8] and people below the age of 20 years have the highest frequency of social contacts [6,7]. Because meeting places depend highly on the social environment, there are also major differences between the studies. Contacts during leisure activities, for example, were important in Europe but not Vietnam and South Africa, while public transport was only important in South Africa. Our study in Bangladesh is unique in showing a very marked difference in social contact patterns by gender.

Earlier studies showed that *M. leprae* spreads easily within households of infected persons [9]. We were able to confirm this and in addition we identified that social contacts within the neighbourhood were associated with leprosy as well. Social contacts within a household are confined to a limited number of people only and therefore it is likely that general mixing with different people in the neighbourhood plays an important role in the continuing transmission of *M. leprae* in leprosy endemic areas as well.

Research question 2:

How are socioeconomic determinants associated with the risk of acquiring clinical leprosy?

Answer:

Nutritional status was identified as main socioeconomic determinant associated with an increased risk of acquiring clinical leprosy.

Leprosy remains endemic in the poorest areas of the world indicating that socioeconomic determinants play an important role in leprosy [1]. Although we observed a decreasing trend in leprosy prevalence with an increasing socioeconomic status as measured with an asset index in our case-control study in northwest Bangladesh, a *'recent period of food shortage'* was the only

determinant associated significantly with clinical leprosy (chapter 4). Income, household size, educational level and crowding were not associated with leprosy in two different studies carried out in the same area in Bangladesh (chapter 4 and chapter 5). There is however much debate on how to measure the socioeconomic status, especially in low-income countries and different methods have yielded different results [10]. In the paragraph on methodological issues in this chapter we discuss the method used in our study in more detail.

Participants in the study were asked to report *'food shortage ever'* and *'food shortage in the last year'*. *'Food shortage in the last year'* coincides roughly with the start of symptoms of leprosy in the cases, as 70% of the patients reported the start of their symptoms between seven and twelve months before the interview (from September to December, 2008). This coincides with the annual period of seasonal food shortage in rural Bangladesh, from the end of September until November, just after the rainy season and before the main rice harvest in November and December. In this period there are few work opportunities, low household food stocks, and increased rice prices (chapter 4).

In poor rural communities in Bangladesh seasonal income changes are common. In our study the reported income changed from a monthly average of 3000 BDT (43 US$) to 9000 BDT (130 US$) per household. Seasonal income changes are closely related to daily expenditure on food and of influence on the nutritional status of the people in rural Bangladesh. Chronic energy deficiency (CED) based on body mass index (BMI) is high (between 60-70%) in all age and sex groups in rural Bangladesh. Seasonal differences in energy intake are also substantial in all age and sex groups [11]. The amount of rice consumed is quite stable, but expenditure on high nutritious and more expensive food decreases in months of low income [12]. A lower diversity of the diet was associated with malnutrition in mothers and children in Bangladesh [13], while a low BMI was associated with an increased mortality in adults [14].

Food shortage in the last year, as assessed in our study, represents a recent (short) period of poverty with limited expenditure on food, likely causing nutritional deficit. In contrast, an asset index as a proxy to measure wealth gives an indication of the long-term economic status of a household, since people tend not to sell their assets in seasonal short periods of low income, but only in longer-term poverty [10,15].

An association between food shortage and leprosy was also observed in Brazil [16]. However, in Brazil a period of food shortage at any time in life, as indicator of poverty in general, was found associated with leprosy, while in our study only a recent period of food shortage was associated with the disease. Although a higher percentage of leprosy cases also reported food shortage at any time of life in Bangladesh, this association was not statistically significant. Different case definitions of food shortage or differences in social norms regarding nutritional requirements between the countries could be an explanation for this difference. Food shortage however, may also be a less strong indicator of poverty in general in Bangladesh than in Brazil,

since the percentage of people who reported food shortage ever was much higher in Bangladesh (66.7% of the cases and 61.8% of the controls) than in Brazil (28% of the cases and 19% of the controls).

Nutritional status is known to influence the development of other infectious diseases such as respiratory infections, infectious diarrhoea, measles and malaria. These diseases are observed more commonly in malnourished children. Malnutrition affects the immune system negatively, causing infected individuals to be more vulnerable for developing a clinically apparent infection [17]. In tuberculosis, which has similarities to leprosy because it is also caused by a mycobacterium, nutritional deficit has been identified as an important factor in the development of clinical symptoms of disease [18]. A 'recent period of food shortage' as identified in our study as most important poverty-related factor associated with leprosy, is very likely to have reduced the immune status of individuals incubating *M. leprae*, causing the development of clinical leprosy. Alternatively, clinical symptoms of the disease could appear at the moment the immune system restores immediately after a period of low nutritional intake, since immune responses play an important role in the development of symptoms in leprosy (personal communication Dr. B. Naafs). This matter remains unresolved.

Research question 3:

Which patient related factors and social determinants are associated with an increased risk of leprosy amongst contacts?

Answer:

Being part of a cluster of two or more patients, female sex and young age were indentified as patient related factors associated with an increased risk of leprosy among their contacts.

In the COLEP cohort of leprosy patients and their contacts, active case finding was done 2, 4 and 6 years after the contacts received single dose rifampicin (SDR) or placebo as intervention (chapter 5). Significantly more new cases of leprosy were observed among contacts of index patients who were part of a cluster of two or more patients at intake. This implies that some of these new cases in the COLEP study might have had another source of infection than the index case. This idea was strengthened by the observation that the new case detection rate in children under 5 years at intake was much lower than that of the whole cohort. New cases in young children indicate recent transmission, while new cases among adults might have been infected up to 20 years ago. Therefore new cases among adults might have had another source of infection than the original leprosy patient selected for the study. This is not surprising because northwest Bangladesh is a leprosy endemic area.

Patients in whose contact group new cases were detected during the follow-up period were significantly more often female and younger than those without new cases in their contact group (chapter 5). This difference might be explained by differences in social contact patterns. Children and women have intensive social contacts relevant for the transmission of leprosy in their home and nearby neighbourhood, while male patients also have relevant contacts beyond this confined area (chapter 2). Intensive social contact patterns in the home and in the neighbourhood were associated with leprosy (chapter 3). In the COLEP study only contacts living nearby leprosy patients were included in the study; household contacts, neighbours, neighbours of neighbours and social contacts living in the vicinity of the index patient. While most social contacts of women and children are thus included, the social circuit of men reaches further away and some of their social contacts at risk might not have been included in the study population. New cases of leprosy among social contacts of male index patients who do not live in the vicinity may have been missed.

Research question 4:

How can social determinants be used effectively to improve leprosy control programmes?

Answer:

Knowledge of social contact patterns in a region can help to target leprosy control activities more accurately, while nutritional and socioeconomic support can be implemented in combination with leprosy control programmes in endemic areas to improve the outcome.

The studies described in this thesis show that determinants in the social environment play an important role in leprosy. Social contacts in the home and within the neighbourhood (village or urban ward) are both associated with clinical leprosy. In the home social contacts across age and sex groups are common, while outside the home mainly assortative mixing by age and gender occurs. Although social contact patterns itself are difficult to change, knowledge about social contact networks gives important information regarding risk groups and high-risk contact patterns in the population. This can be used to target control interventions more accurately, which are traditionally only directed at household members of the patient.

The important role of socioeconomic welfare, especially nutritional status was confirmed by the studies in this thesis. Improvements in socioeconomic status, leading to food security are of major importance to make leprosy control programmes successful.

We derived the following practical recommendations from the results of the studies in this thesis:

- Leprosy control interventions in endemic areas should not only target household contacts, but also consider other contacts living in the neighbourhood of a patient (chapter 2, chapter 3).
- Leprosy control programmes should consider differences in social contact patterns between male and female patients to identify contacts at risk (chapter 5).
- When a leprosy patient is part of a cluster of two or more patients (living near each other or in the same household), the risk of acquiring leprosy is increased for others living in the same neighbourhood. Therefore interventions should be targeted towards a much larger group of contacts and a whole village or urban ward may need to be included (chapter 5).
- Nutritional support for contacts of leprosy patients in poverty-stricken areas should be part of a leprosy control programme (chapter 4).
- Poverty alleviation and socioeconomic development in general is essential for achieving sustainable food security in endemic areas and therefore important to reduce the burden of leprosy (chapter 4).

Acceptability of proposed interventions by patients and their contacts should be taken into consideration when implementing control measures. Implementing these measures often requires disclosure of the stigmatizing diagnosis of leprosy. Promoting control and treatment of stigmatised diseases without contributing towards stigma of the individuals involved can be very difficult and challenging [19]. We assessed social acceptability of disclosure of the diagnosis and the attitude towards taking prophylactic medicines through focus group discussions with healthy individuals living in a leprosy endemic area in northwest Bangladesh (chapter 6). The study revealed that people would not object to disclosure of the diagnosis to household members and nearby family if they were diagnosed with leprosy, but most of the study participants were not willing to share this information with their neighbours and other social contacts due to stigma of the disease. All participants were willing to take prophylactic medicines if any of their close contacts were diagnosed with leprosy, even if full protection against leprosy was not guaranteed. We concluded that control activities for household contacts are socially acceptable, even if disclosure of diagnosis is necessary. Control measures for other categories of contacts likely to benefit would only be feasible without disclosure of patient information, for example in the form of mass campaigns for the whole population in the area (chapter 6).

METHODOLOGICAL ISSUES

Study design

We used different study designs to study aspects of the social environment in relation to leprosy. A qualitative design with focus group discussions was used to explore social contact patterns (chapter 2) and acceptability of disclosure of the diagnosis and implementation of interventions (chapter 6). We applied this qualitative research method because it allows a quick exploration of concepts without predefined assumptions. Results of this exploration were used to design the quantitative studies. We used a case-control study design to study determinants in the social environment in relation to clinical leprosy (chapter 3 and 4), while a prospective cohort study design was used to study patient characteristics and social determinants in relation to new cases among their contacts, as well as the effect of an intervention with SDR (chapter 5).

A limitation of these study designs is that they are not suitable to establish a causal relationship between social determinants and leprosy. In a case-control design an association between determinants and leprosy can be established, but causation can never be determined because cases are compared with healthy controls at one moment in time only. Although a prospective cohort design is in principle suitable to establish a cause-effect relationship, in our study this is only possible for the relationship between the intervention with SDR and new cases of leprosy developed during the follow-up period, since the time of intervention and appearance of new cases are both known. The time of infection and the time of changes in determinants of the social environment however, are both unknown. Most social determinants were measured at the time of intake only, while it is likely that most new patients detected during follow-up were already infected with *M. leprae* before the start of the study. Thus it is not possible to establish a causal relationship between social determinants with either clinical leprosy or infection with *M. leprae.*

Characteristics of the disease

In the studies in this thesis we could only study the association between determinants in the social environment and clinical leprosy. Individuals infected with *M. leprae* without clinical signs of disease are difficult to identify. They do not present themselves at a health facility and there is no reliable test to detect infection with *M. leprae*. The average incubation time of leprosy is estimated to be 2-5 years, but it can take 20 years or longer before clinical disease becomes apparent after a person is infected [1,2]. Changes in social contact patterns and socioeconomic status are possible during such long period. However, common alterations due to for example ageing or changing environment are expected to be similar for cases and controls and therefore accounted for by the study design in the case-control study, while such alterations are also not expected to be caused or influenced by subclinical infection with *M. leprae.* It is important to

realise that the diagnosis of leprosy is mainly based on clinical symptoms, since only in a limited number of cases *M. leprae* can be identified in a slit skin smear and a reliable diagnostic test is not available. Although the symptoms of leprosy are classical, the diagnosis of leprosy is not always straightforward.

Self reported data

Another limitation of the study is the use of self-reported data on social contacts, income, educational level and food shortage as measured by a questionnaire, which is by definition subjective. Although we tried to compose simple questions with categories that are familiar to the people in the study area, there may be differences in interpretation and valuing of social determinants due to the knowledge level of people with different educational background or age. People were asked to report on their regular pattern of social contacts at the time of interview, but recall bias will be of influence on reporting social contacts patterns that do not occur regularly (e.g. only a few times a year). By asking cases and controls exactly the same questions, we attempted to reduce the effect of the above forms of bias.

Social Contacts

To study the association between social contact patterns and leprosy, we first explored the social contact patterns in the region by means of focus group discussions. The social contact patterns identified were ordered based on perceived relevance for the transmission of infectious diseases and the information gathered was used to construct a questionnaire for the case-control study. We developed a questionnaire and scoring system specifically for this case-control study, because there was no method available that could be adapted to our situation. A diary method was used in Europe, Vietnam and South Africa to study contact patterns relevant for the spread of infectious diseases [4-7]. However, a diary method requires either registration over a long period or a very large study population. Because leprosy has a relatively low prevalence and keeping a diary for a long time is difficult in a developing country with high levels of illiteracy, using such method was not feasible. An advantage of a newly developed method is that it could be designed for the study area and that intensity as well as duration and frequency of social contacts could be included. A disadvantage is that the results are not completely applicable to other areas and that it is difficult to compare the results with other studies. We assessed the validity of the method by comparing the score results of the control population with the expected pattern of social contacts for the area [20,21] (chapter 2) and by a detailed analysis of the variables within each level (chapter 3, annex 2). As expected, social contacts on the first level, inside the home, were more intensive for people aged <20 years and belonging to large families, but were similar for male and female, and for people of different socioeconomic class. Males had higher scores for social contacts outside the home than females. Because we used

general categories and a simple scoring system, the overall pattern found in this study can be compared with other studies on airborne infectious diseases and social contact patterns.

Socioeconomic status

In the case-control study we used an asset index as proxy to measure the socioeconomic status. An index based on assets is an objective and easy to use instrument for measuring differences in wealth within a population, without the need for collecting data on income and expenditure. Data on assets are easy to collect and an index based on these data measures economic status over a longer period than consumption expenditure, since households are more likely to change consumption patterns than to sell assets or change housing in response to seasonal income changes [15,22].

There are also arguments against the use of an asset index to measure socioeconomic status as proxy for income and expenditure, because the method depends highly on the assets chosen for the index. A different set of assets or a limited number of assets yields different results [23-25]. Therefore we choose a set of assets based on the Bangladesh Demographic and Health Survey, the local version of the Demographic and Health Surveys (DHS) for Bangladesh [26]. This asset index based on items as used in the USAID sponsored DHS, which are carried out in 84 developing countries, has proven to be valuable for public health purposes [27]. In addition to the assets, we collected data on income, educational level, household composition, crowding, and food shortage to study a wider range of socioeconomic determinants with a possible association with leprosy. Since leprosy is a disease that causes disability and has a stigma, socioeconomic status of a leprosy patient can change due to the disease. To avoid confusion between cause and effect, we collected data from a group of newly diagnosed patients and asked the participants whether the disease had caused any changes in their life. Patients who reported changes due to the disease were excluded from the analysis.

CONCLUSIONS

In this thesis I show that determinants in the social environment play an important role in leprosy. Intensive social contact patterns in the home and neighbourhood (village or urban ward) are associated with clinical leprosy. This implies that both contacts of patients in the household and in the neighbourhood are at risk. This information can be used to target control interventions more accurately, which are traditionally only directed at household members of the patient. Due to cultural habits there are differences in contact patterns between males and females in Bangladesh. Women have their social contacts mainly in and around their home, while men also have social contacts reaching further away within and outside the neighbourhood.

Leprosy interventions should consider this difference and target a different group of contacts at risk for male than for female patients.

The social acceptability of interventions should be assessed before implementation, because disclosure of the stigmatizing leprosy diagnosis is often necessary. We showed that chemoprophylaxis with SDR is an effective and socially accepted intervention for household contacts of leprosy patients, even when this entails disclosure of the stigmatizing diagnosis of leprosy. Chemoprophylaxis for other categories of contacts that are likely to benefit would only be feasible without disclosure of patient information, for example in the form of mass campaigns.

Finally, I establish in this thesis the important role of socioeconomic welfare and nutritional status. Improvements in socioeconomic status and nutrition are very important for the success of leprosy control programmes and therefore I recommend policy makers to include nutritional support in leprosy control programmes and give priority to general poverty alleviation in leprosy endemic areas.

SUGGESTIONS FOR FURTHER RESEARCH

- Research into the role of nutritional status in acquiring clinical leprosy should receive further attention. Detailed information regarding specific nutritional deficits involved in clinical leprosy can be used to provide specific nutritional support.
- Priority should be given to the development of a cheap and simple test to diagnose leprosy and to indicate the risk for developing leprosy in people exposed to *M. leprae*.
- Although chemoprophylaxis with SDR and immunoprophylaxis with BCG have shown to prevent leprosy among contacts, operational research is required to establish its application in leprosy control programmes. Special attention should be given to selecting risk groups that benefit most from these interventions. Information from this thesis about social contact patterns can be used for further research in this area.

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Summary

The aim of this thesis is to study the association between determinants in the social environment and acquiring clinical leprosy in a leprosy endemic area. The thesis consists of an introduction, five scientific papers and a general discussion.

Throughout history leprosy has been surrounded by stigma and fear. The causative agent for the disease, *Mycobacterium leprae,* was discovered in 1873 and effective drugs became available about 70 years ago. In the '90 the World Health Organisation (WHO) aimed at the elimination of leprosy as public health problem by the year 2000, defined as reduction of leprosy prevalence below 1 per 10,000 population. Although impressive improvements have been made with control programmes based on early case detection and provision of multidrug therapy (MDT), the disease is still endemic in some of the poorest countries of the world. Contrary, leprosy disappeared from many other parts of the world before effective drugs became available, implying that the social environment plays an important role in leprosy.

This thesis focuses on social contact patterns and socioeconomic determinants as risk factors for leprosy. *M. leprae* is transmitted from person-to-person, most likely through droplet infection or direct skin-to-skin contact. Interaction between people through social contacts is an important factor in the transmission of *M. leprae*, although intensive contacts seem to be necessary to establish transmission. Social contact patterns and the social contact network in which people operate are influenced by socioeconomic and cultural factors, and are very specific for a certain region. Although a causal relationship between poverty and leprosy is difficult to establish, socioeconomic determinants are suggested to have a major influence on the continuing transmission of this infectious disease in the poorest regions of the world.

The research questions for this thesis are:

1. Is there a relation between social contact patterns and acquiring clinical leprosy?
2. How are socioeconomic determinants associated with the risk of acquiring clinical leprosy?
3. Which patient related factors and social determinants are associated with increased risk of leprosy amongst contacts?
4. How can social determinants be used effectively to improve leprosy control programmes?

After the introduction (Chapter 1), we describe in Chapter 2 the results of a qualitative study by means of focus group discussions in which the regular social contact pattern in northwest Bangladesh was explored. Healthy people from two different villages and an urban area participated in the discussions. The regular social contact patterns in the home, neighbourhood (village or urban ward) and outside this area, were described. The patterns were ordered regarding

the perceived relevance for transmission of airborne transmitted diseases with special focus on diseases like leprosy and tuberculosis. Men and women of different ages reported highly relevant social contact patterns inside and around the home. Outside the home women and girls reported relevant contacts limited to their neighbourhood, while men also mentioned high relevant contacts beyond this confined area. We used the data from this study to construct a questionnaire to compare contact patterns of newly diagnosed leprosy patients with healthy controls from the same area in a case-control study.

In Chapter 3 and 4 we present the results of this case-control study. In the study 90 recently diagnosed patients were compared with 199 healthy controls from the same leprosy endemic area in northwest Bangladesh. Chapter 3 focuses on social contact patterns and Chapter 4 on socioeconomic determinants. We show that clinical leprosy is associated with a more intensive social contact pattern in the home and in the neighbourhood. Social contacts beyond this confined area are not associated with leprosy. Although it was already known that *M. leprae* spreads easily within households of infected persons, we established that social contacts within the neighbourhood are also important for transmission in endemic areas. Furthermore, we reveal that a 'recent period of food shortage' and not poverty *per se* is the only socioeconomic factor significantly associated with the clinical manifestation of leprosy. We observed a decreasing trend in leprosy prevalence with an increasing socioeconomic status as measured with an asset index, but this trend was not statistically significant. The other socioeconomic factors taken into consideration (educational level, household size, crowding and income) were not associated with leprosy.

In Chapter 5 we describe the results of a cohort study assessing the impact of chemoprophylaxis with a single dose of rifampicin (SDR) in contacts of leprosy patients after 6 years of follow-up, and identify characteristics of leprosy index patients predicting the effectiveness of this intervention. The cohort consisted of 1037 patients and their 28,092 contacts participating in the trial with SDR in northwest Bangladesh, the COLEP study. In the first two years after the intervention there was a 57% reduction in leprosy incidence. After these first 2 years there was no additional effect measured. 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. Without intervention, leprosy was more common in contact groups of female patients and patients belonging to a cluster of two or more patients at intake. There were fewer new patients observed among contacts when the age of the index patient was higher. The intervention with SDR was most effective in contact groups of female index patients, while an enhanced effect was also observed in contact groups of patients belonging to a cluster of two or more leprosy patients at intake.

Although SDR is a promising intervention to prevent leprosy in close contacts of patients, application in control programmes often requires disclosure of the diagnosis of this stigmatizing

disease. In Chapter 6 we describe the results of a qualitative study by means of focus group discussions assessing social acceptability of disclosure of the diagnosis and attitude towards taking prophylactic medicines in a leprosy endemic area in northwest Bangladesh. The majority of the 136 healthy participants from two different villages and an urban ward would not object to disclosure of the diagnosis to household members and nearby family if they were diagnosed with leprosy. However, many participants were not willing to share this information with their neighbours and other social contacts. All healthy participants were willing to take chemoprophylaxis if any of their close contacts were diagnosed with leprosy, even after it was explained that full protection against leprosy was not guaranteed.

In this thesis we show that determinants in the social environment are important in leprosy. Knowledge regarding social contact structures can be used to target control interventions more accurately, while socioeconomic development and nutritional support can make leprosy control programmes more successful.

Based on the results of the studies presented in this thesis I formulated the following practical recommendations:

- Leprosy control interventions in endemic areas should not only target household contacts, but also consider other contacts living in the neighbourhood of a patient.
- Leprosy control programmes should consider differences in social contact patterns between male and female patients to identify contacts at risk.
- When a leprosy patient is part of a cluster of two or more patients (living near each other or in the same household), the risk of acquiring leprosy is increased for others living in the same neighbourhood. Therefore interventions should be targeted towards a much larger group of contacts and a whole village or urban ward may need to be included.
- Nutritional support for contacts of leprosy patients in poverty-stricken areas should be part of a leprosy control programme.
- Poverty alleviation and socioeconomic development in general is essential for achieving sustainable food security in endemic areas and therefore important to reduce the burden of leprosy.

Samenvatting

Het doel van dit proefschrift is het bestuderen van de relatie tussen determinanten in de sociale omgeving en het verkrijgen van de ziekte lepra in een gebied waar de ziekte endemisch is. Het proefschrift bestaat uit een introductie, vijf wetenschappelijke artikelen en een algemene discussie.

De ziekte lepra is door de eeuwen heen omgeven door angst en stigma. De verwekker van de ziekte, *Mycobacterium leprae,* werd in 1873 ontdekt en effectieve medicatie kwam ongeveer 70 jaar geleden beschikbaar. De Wereldgezondheids-organisatie (WHO) stelde zich in de jaren '90 ten doel lepra te elimineren voor het jaar 2000, waarbij eliminatie werd gedefinieerd als een prevalentie lager dan 1 per 10,000 inwoners. Hoewel er een goede vooruitgang werd geboekt met intensieve bestrijdingsprogramma's bestaande uit een combinatie van vroege opsporing en behandeling met een effectieve combinatietherapie (MDT), is de ziekte nog steeds endemisch in de armste gebieden van de wereld. Dit in tegenstelling tot andere delen van de wereld waar lepra al was verdwenen voordat effectieve medicatie beschikbaar kwam, wat impliceert dat de sociale omgeving een belangrijke rol speelt bij deze ziekte.

In dit proefschrift ligt de nadruk op sociale contacten en sociaal-economische omstandigheden als risico factor voor het verkrijgen van de ziekte lepra. *M. leprae* wordt van mens op mens overgedragen, hoogstwaarschijnlijk via aërogene druppelinfectie en direct huidcontact. Contact tussen verschillende mensen in de vorm van sociale contacten lijkt een belangrijk factor voor overdracht van de verwekker *M. Leprae*, hoewel een intensief of langdurig contact noodzakelijk lijkt om daadwerkelijk overdracht van te bewerkstelligen. Het patroon van sociale contacten en netwerken waarin iemand zich beweegt wordt in belangrijke mate beïnvloed door sociaal-economische en culturele factoren en is specifiek voor een bepaalde regio. Ondanks het feit dat een causale relatie tussen armoede en lepra moeilijk is aan te tonen, lijken sociaal-economische factoren een belangrijke rol te spelen in de voortgaande transmissie van de ziekte in de armste gebieden van de wereld.

De onderzoeksvragen voor dit proefschrift zijn:

1. Is er een relatie tussen sociale contactpatronen en het verkrijgen van klinische vormen van lepra?
2. Hoe zijn sociaal-economische determinanten geassocieerd met een verhoogd risico op het krijgen van klinische vormen van lepra?
3. Welke patiënt gerelateerde factoren en sociale determinanten zijn geassocieerd met een verhoogd risico op lepra voor contacten van een patiënt?

4. Hoe kunnen sociale determinanten effectief gebruikt worden om programma's voor leprabestrijding te verbeteren?

Na de introductie (hoofdstuk 1), beschrijven we in hoofdstuk 2 de resultaten van een kwalitatieve studie door middel van focus groep discussies waarbij sociale contactpatronen in noordwest Bangladesh in kaart werden gebracht. Gezonde personen uit twee dorpen en een stadswijk deden mee aan de groepsdiscussies. Contactpatronen in het huis, in de nabije leefomgeving (dorp of stadswijk) en buiten de leefomgeving werden besproken. De door de deelnemers gerapporteerde contactpatronen werden vervolgens geordend naar het verwachte risico op transmissie van door aërogene druppelinfectie overgedragen ziekten, met speciale aandacht voor ziekten zoals lepra en tuberculose. Mannen en vrouwen van verschillende leeftijden rapporteerden allen hoog relevante sociale contacten in en rond het huis. Buiten het huis rapporteerden vrouwen en meisjes alleen relevante contacten in de nabije leefomgeving, terwijl mannen ook relevante contacten buiten dit gebied noemden. De informatie over contactpatronen in deze regio werd gebruikt om een vragenlijst te ontwikkelen voor het vergelijken van sociale contacten van recent gediagnosticeerde leprapatiënten met die van gezonde controle personen uit dezelfde regio in een case-control studie.

In hoofdstuk 3 en 4 worden de resultaten van deze case-control studie beschreven. In deze studie werden 90 recent gediagnosticeerde leprapatiënten vergeleken met 199 gezonde personen uit dezelfde regio in het noordwesten van Bangladesh. In hoofdstuk 3 ligt de nadruk op sociale contactpatronen, terwijl hoofdstuk 4 sociaal-economische determinanten aan de orde stelt. Het krijgen van de ziekteverschijnselen van lepra blijkt geassocieerd met een intensiever contactpatroon in het huis en in de nabije leefomgeving. Sociale contacten buiten de leefomgeving blijken niet geassocieerd met lepra. Het was reeds bekend dat overdracht van *M. leprae* veelvuldig plaatsvindt onder huishoudcontacten van een patiënt. In deze studie tonen wij aan dat ook contacten in de nabije leefomgeving een belangrijke rol spelen bij de verspreiding van lepra in een endemisch gebied. Daarnaast tonen we aan dat niet armoede als zodanig, maar een recente periode van voedseltekort geassocieerd is met het krijgen van klinische vormen van lepra. Er werd wel een afnemende trend in lepra prevalentie gezien bij een toenemende economische status gemeten met een asset index, maar deze trend was niet statistisch significant. Andere sociaal economische determinanten die werden onderzocht (onderwijsniveau, grootte van het huishouden, overbevolking en inkomen) bleken niet geassocieerd met lepra.

In hoofdstuk 5 worden de resultaten gepresenteerd van een cohort studie waarbij het effect van chemoprofylaxe met een enkele dosis rifampicine (SDR) voor contacten van lepra patiënten werd onderzocht, 6 jaar na de interventie. Ook werd gekeken naar eigenschappen van de oorspronkelijke leprapatiënten die de effectiviteit van deze interventie positief beïnvloeden.

Het cohort bestond uit 1037 leprapatiënten en hun 28,092 contacten die meededen in de trial met SDR in het noordwesten van Bangladesh, de COLEP studie. In de eerste twee jaar na de interventie met SDR werd een 57% reductie waargenomen van de incidentie van lepra. Na deze eerste twee jaar werd er geen aanvullend effect meer gezien. Het effect van de interventie was alleen aanwezig bij contacten die daadwerkelijk SDR hadden gekregen, gezinsleden binnen eenzelfde contact groep die zelf geen SDR kregen bleken niet beschermd. Zonder interventie kwamen nieuwe lepra gevallen vaker voor in contact groepen van vrouwelijke patiënten en van patiënten die behoorden tot een cluster van twee of meer patiënten. Tevens werden er minder nieuwe patiënten gezien naarmate de oorspronkelijke leprapatiënt ouder was. De interventie met SDR bleek bij contactgroepen van vrouwelijke patiënten het meeste effectief. Daarnaast werd ook een positief effect van de interventie gemeten bij contacten van patiënten die behoorden tot een cluster van twee of meer patiënten.

Hoewel SDR een interventie is waarvan we veel kunnen verwachten in de preventie van lepra, is het voor de toepassing van deze interventie vaak nodig dat de diagnose van deze ziekte met een stigma bekend gemaakt wordt. Hoofdstuk 6 beschrijft de resultaten van een kwalitatieve studie door middel van focus groep discussies waarbij de acceptatie van het bekend maken van de diagnose lepra aan contacten werd besproken en waarin de bereidwilligheid van gezonde contacten ten aanzien van het nemen van chemoprofylaxe werd onderzocht. Een ruime meerderheid van de 136 gezonde deelnemers van twee verschillende dorpen en een stadswijk had geen problemen met het openbaar maken van de diagnose lepra aan huishoudcontacten en naaste familieleden, maar zouden de diagnose liever niet bekendmaken aan buren en andere sociale contacten in het dorp of de wijk. De deelnemers verklaarden unaniem dat ze chemoprofylaxe zouden nemen als ze te horen zouden krijgen dat één van hun naaste contacten lepra had, ook nadat hen was uitgelegd dat met deze medicatie volledige bescherming tegen lepra niet gegarandeerd kon worden.

In dit proefschrift hebben we aangetoond dat determinanten in de sociale omgeving een belangrijke rol spelen bij de ziekte lepra. Kennis over sociale contact patronen kan gebruikt worden om de doelgroepen voor interventies binnen programma's voor leprabestrijding beter te kunnen vaststellen, terwijl programma's voor sociaal-economische ontwikkeling en voedselzekerheid een positieve bijdrage kunnen leveren aan het succes van programma's voor leprabestrijding.

Naar aanleiding van de resultaten van het onderzoek zoals beschreven in dit proefschrift heb ik de volgende praktische aanbevelingen geformuleerd:

- Een interventie voor leprabestrijding moet in een endemisch gebied niet alleen aan huishoud contacten worden aangeboden, maar ook aan andere sociale contacten in het dorp of de stadswijk.

- Verschillen in sociale contactpatronen tussen mannelijke en vrouwelijke patiënten moeten worden meegewogen bij het identificeren van sociale contacten met een verhoogd risico op lepra.
- Als een leprapatiënt behoort tot een cluster van twee of meer patiënten (binnen het huishouden of naaste buren) is het risico om lepra te krijgen voor contacten in de naaste leefomgeving van deze patiënten verhoogd. Interventies zouden zich daarom moeten richten op een grotere groep mensen, bijvoorbeeld het gehele dorp of stadswijk.
- Voedselprogramma's zouden een onderdeel moeten vormen van lepra bestrijdingsprogramma's in lage inkomenregio's.
- Armoede bestrijding en sociaal-economische ontwikkeling in het algemeen is essentieel voor een duurzame voedselzekerheid in endemische gebieden en daarom belangrijk voor het verlagen van de ziektelast door lepra.

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What started with a short assignment in a research project in the northwest of Bangladesh ended in a doctoral thesis, I can hardly believe it! Of course it would not have been possible to write this thesis without the help and support of many people around me, to only some of whom it is possible to give particular mention here.

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I would also like to acknowledge my "co-promotor" Dr. Linda Oskam. Though we met only a few times in person, you were always the first one to respond to my e-mails, even when you were travelling somewhere around the globe. I would like to thank you for all the valuable comments on my papers and the inspiring ideas during the discussions we had.

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Curriculum Vitae

Sabiena Feenstra-Gols was born in Hoogezand-Sappemeer, the Netherlands on 10 January 1971. After her secondary education (VWO) in Veendam she studied Medicine at the University of Groningen. She graduated as medical doctor in 1996. After her graduation she started a specialization in Tropical Medicine. For this specialisation she worked as house officer in surgery and obstetrics/ gynaecology and completed a three months intensive training course in Tropical Diseases and International Health.

After getting her degree in Tropical Medicine in 1998 she worked in Pakistan for the International Water Management Institute (IWMI), were she did epidemiological research on the association of (waste)water use (domestic and for irrigation) and diarrheal diseases, helminths, malnutrition and malaria in a rural district. In 2000 she joined the Dutch NGO HealthNet in Cambodia and worked as medical advisor in an innovative ADB funded "contracting" basic health services project in Pereang district, Pre Veng province. In this health reform project an innovative financing scheme with user fees was developed and implemented. Sabiena was responsible to improve the quality of health care delivered in the health centres and hospitals managed and supervised by the project.

From 2002 to 2008 she worked for the regional Public Health Institute Hulpverlening Gelderland Midden (GGD) in Arnhem as medical doctor, consultant infectious disease control. In this job she was responsible for infectious disease control in the district, including surveillance and outbreak management. She was also responsible for STI/HIV control and the STI clinic for high risk-groups. She received training in Public Health and Infectious disease control at the NSPOH and obtained her "profiel registratie" as consultant infectious disease control in 2007. In 2008 she continued studying Public Health with the London school of Hygiene and Tropical Medicine resulting in an MSc Public Health degree in 2011.

In 2008 she went to Bangladesh with her family and started her research for Erasmus MC, Rotterdam and The Leprosy Mission, Bangladesh on leprosy and the social environment resulting in this thesis.

PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD student: Sabiena Feenstra-Gols	PhD period: 2009-2012
Erasmus MC Department: Public Health	Promotor: Prof.dr. J.H. Richardus

1. PhD training

	Year	Workload (Hours/ECTS)
Research skills and in-depth courses		
London School of Hygiene and Tropical Medicine (LSHTM): MSc in Public Health (distance learning)	2008-2011	90 ECTS (180 UK credits)
Modules:		
PH101 Basic Epidemiology	2008	
PH102 Basic statistics for Public Health and Policy	2008	
PH104 Principals of Social Research	2008	
PH108 Health Services	2008	
PH109 Health Policy, Process and Power	2008	
PH103 Introduction to Health Economics	2009	
PH204 Economic Evaluation	2009	
PH207 Health Care Evaluation	2009	
EP202 Statistical Methods in Epidemiology	2009	
ID301 Epidemiology and Control of Infectious Diseases in Developing Countries	2009	
ID501 HIV/AIDS	2010	
PH201 Analytical Models for Decision Making	2010	
PH208 Financial Management	2010	
ID502 Tuberculosis	2011	
PH212 Organisational Management	2011	

	Year	Workload (Hours/ECTS)
Seminars and workshops		
– TB and HIV – Breaking the vicious cycle symposium, AIGHD, Amsterdam	2012	4 hours
– Malaria, maternal and infant health; perspectives from Asia and Africa symposium, AIGHD, Amsterdam	2012	3 hours
– CEPHIR symposium Vatbaar voor visies?, Rotterdam	2011	2 hours
– 18e Transmissiedag Infectieziekten, RIVM, Amersfoort	2008	5 hours
– Bacteria and virusses: New approaches to epidemics and the use of vaccines - Patient care and public health on cross roads, Utrecht	2008	3 hours
– Plenaire vergadering Infectieziektebestrijding, Utrecht	2007	5 hours
– Congres Infectieuze Bedreigingen: Mythen, Missers en Maatwerk, Ede	2007	5 hours
– 17e Transmissiedag Infectieziekten, RIVM, Amersfoort	2007	5 hours
– Expertmeeting Surveillance soa en hiv, RIVM, Bilthoven	2007	2 hours

2. Teaching activities

	Year	Workload (Hours/ECTS)
Lecturing and supervising		
– Lecturing and supervising research assistants of the Leprosy Mission International, Nilphamari, Bangladesh	2009-2012	100 hours
– Supervising medical student during “keuze-co assistent-schap” at Hulpverlening Gelderland Midden, Arnhem	2007	20 hours
Other		
– Member of a technical working group on STI policy development in the Eastern part of the Netherlands.	2007-2008	30 hours