On the
spread of leprosy
in a heterogeneous population

Egil Fischer 2010

Colofon

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On the Spread of Leprosy in a Heterogeneous Population

De verspreiding van lepra in een heterogene populatie

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"Eenheid in het nodige, vrijheid in het onzekere, in alles de liefde"

Contents

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Introduction

General background on leprosy

Pathogen and disease

Leprosy or Hansen's disease is an infectious disease caused by the bacterium *Mycobacterium leprae* Hansen[1]. Most people are able to clear the bacterium before disease occurs, or are resistant against infection[2, 3, 4]. When the disease does develop, leprosy affects the skin, the peripheral nerves, mucosa of the upper respiratory tract and the eyes. The form of leprosy depends on the immune response of the patient. When the cellular immune response is strong enough to keep the infection localized, the tuberculoid form will develop. If the cellular response is insufficient or not present the bacterium can spread systemically and causes lepromatous leprosy. Lepromatous leprosy has many more bacilli (expressed as the bacterial index BI) in lesions, than the tuberculoid form. For treatment purposes, cases are therefore simply classified into paucibacillary (PB) or multibacillary leprosy (MB)[5, 6]. The scientific classification by Ridley-Jopling uses classes ranging from tuberculoid leprosy (TT) to lepromatous leprosy (LL)[7]. Between the poles of this spectrum a range of intermediate classes exists. The infection can cause nerve function impairments, leading to secondary complications, such as infection of untreated (small) wounds and ulcers on palms and soles. Nerve function impairment can develop gradually, or during periods of inflammation, called reactions. Type 1 or reversal reaction is a delayed immune response causing acute inflammation of nerve and skin lesion, and Type 2 or Erythema Nodosum Leprosum (ENL) is a reaction to circulating immune complexes in the blood[8]. The period between the infection and the first clinical signs of leprosy is

called the incubation period. The median incubation time is 3.5 years for paucibacillary leprosy and 10 years for multibacillary leprosy[2, 3]. The fact that very young children are found with symptomatic leprosy, and that some veterans develop leprosy over 20 years after returning from endemic areas[4] shows the wide variation in the incubation period.

Transmission of the infection

Although *M. leprae* remains viable for some time outside the human body[9], it is commonly accepted that the main route of infection is through direct transmission from an infectious person to a susceptible person[10]. Patients can shed many bacilli through their nose, and nasal carriage of healthy persons indicates that direct respiratory transmission through aerosols is the most likely route of transmission[11, 12], although skin-to-skin transmission is also considered to be possible[4]. Both routes require close and direct contact. Due to the differences in the number of bacilli and immune response between paucibacillary and multibacillary leprosy, patients with multibacillary leprosy are thought to be the only infectious individuals, or at least the most infectious individuals[2].

Treatment and control

The detection of leprosy is based on clinical signs: skin lesions, loss of sensitivity of skin lesions, and thickened nerves[8], thus established after physical examination. Case detection is based on passive detection of patients (i.e. self-reporting), active surveys and contact tracing, which of these interventions are implemented depends on the country[13]. The basis for leprosy control is treatment with multidrug therapy (MDT). This therapy was introduced after increasing drug resistance against dapsone monotherapy. MDT will render a patient non-infectious after the first dose[14]. The bacillus Calmette-Guérin (BCG) vaccine against tuberculosis is found to be protective against leprosy[15]. This vaccine is given at a very young age in most developing countries. The BCG strain is a laboratory strain of *M. bovis*, a bacterium related to both *M. tuberculosis* and *M. leprae*. A recent development in leprosy control is chemoprophylactic treatment with a single dose of rifampicin[16, 17, 18]. The results of clinical trials are promising with an overall reduction of 56% of new cases among contacts of leprosy patients in north west Bangladesh[17].

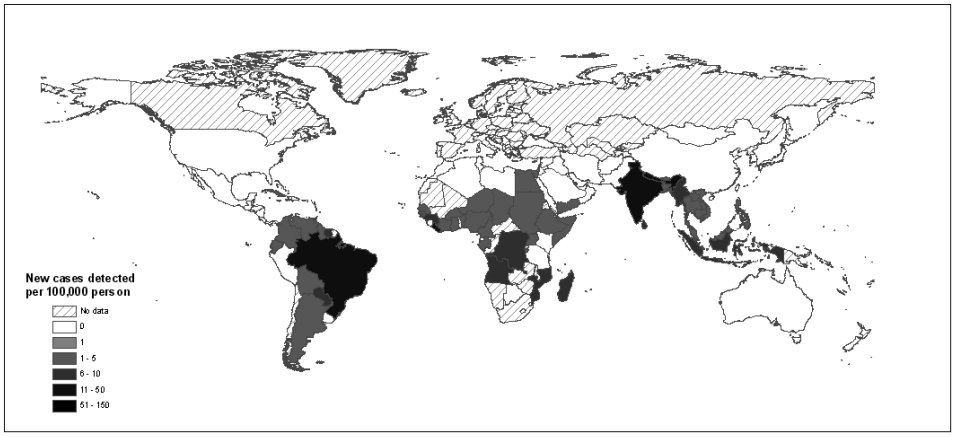

Figure 1.1: World wide new case detection rate in 2008 (Source: WHO [19])

New detection methods that are able to determine sub-clinical infections are currently being developed[20]. To identify sub-clinical infections with *M. leprae*, different approaches are needed for lepromatous leprosy and tuberculoid leprosy. The humoral response in lepromatous patients can be detected in serological assays[21, 22]. Antigen based tests could be a new diagnostic tool for the tuberculoid form that only gives a cellular immune response [23, 24].

Current epidemiological situation

In 2008, approximately 250,000 new leprosy cases were detected worldwide. Leprosy is almost exclusively found in tropical countries (see Figure 1.1). The majority of cases were found in India (54%) and Brazil (16%). Bangladesh reported 5249 new cases in 2008, which is a new case detection rate of 0.4 per 10,000 persons. However, the distribution over the country is unequal with high incidence areas in the southeast and north west of Bangladesh.

The number of new cases detected in 2008 was 370,000 cases less than in 2002. This enormous decrease however, is now levelling off. India has not seen a substantial decrease in the past 3 years. Brazil with 39 thousand new cases in 2008 has had a more or less equal number of new cases detected annually during the past 6 years.

Bangladesh has seen a steady decrease in newly detected cases, but the case detection remained the same in 2007 and 2008 [19].

Population heterogeneity

The population heterogeneity of the risk of leprosy underlies much of the work in this thesis. People differ in exposure to infection with *M. leprae* and in response to the infection after exposure. Figure 1.2 gives a schematic overview of heterogeneity as addressed in this thesis, compared to a homogeneous population. The forms of heterogeneity in the population studied in this thesis are contact heterogeneity, heterogeneity in susceptibility, and spatial heterogeneity. In the next sections, each of these heterogeneities is introduced.

Contact heterogeneity

Infection with a directly transmitted bacterial infection, such as *M. leprae*, needs contact between an infectious host and a susceptible host. By heterogeneity in the contact structure of a population, some individuals come into contact with infectious individuals and others not. In other situations, a difference in the intensity of or frequency of contact exists between individuals, which determines the chance of exposure to infection. Thus contact heterogeneity plays a major role in the infection dynamics of directly transmitted diseases[25]. In several studies, the differences in risk determined by the contact structure has been studied. In Bangladesh, close contacts of leprosy patients, such as household members, are at a higher risk of developing leprosy [26]. This has also been shown in other countries and continents[27, 28, 29, 30]. The role of close contacts in the epidemic differs between areas. In low incidence areas, the relative risk of contacts is higher than in high incidence areas[31]. In some high incidence situations, almost half of the population is a close contact of a leprosy patient[32].

Heterogeneity in susceptibility

Even if all exposure would be the same, some people react differently to infections than other. Also not all people that are exposed to *M. leprae* develop leprosy. It is not clear whether these individuals efficiently clear the bacilli or are resistant against infection[2, 3, 4]. It is thought that only a fraction (5-20%) of the population is

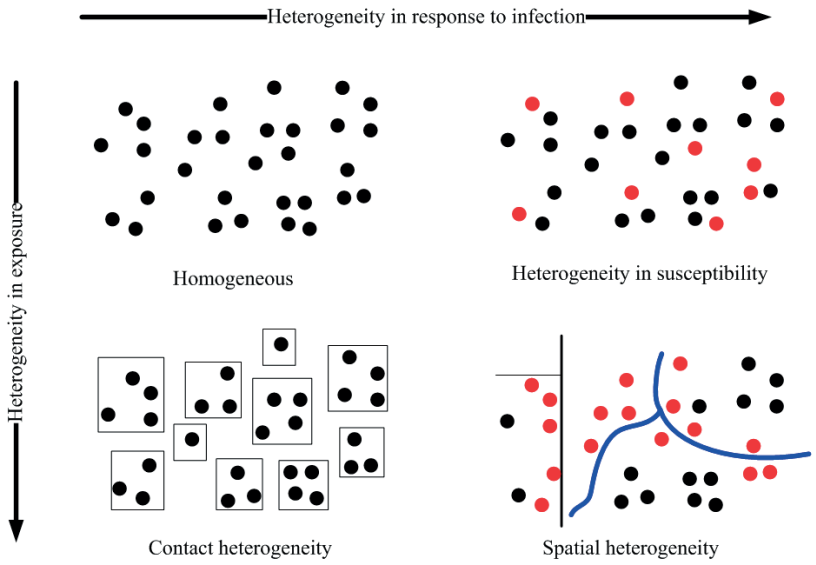

Figure 1.2: Population heterogeneity. From top to bottom, contact heterogeneity is introduced, and from left to right heterogeneity response to infection is added. The upper left panel shows a homogeneous population. The upper right panel shows heterogeneity in susceptibility, where the red dots indicate susceptible individuals. The left lower panel shows contact heterogeneity, in which the individuals (dots) within the groups (squares) have more intense contact than individuals of different groups. The right lower panel shows spatial heterogeneity, in which geographic features (river or road) determine the risk exposure and susceptibility (close to road or river).

susceptible to the development of leprosy after exposure[2, 3, 4]. Differences in susceptibility can be genetic or caused by environmental factors that alter the health status of a person. Genetic studies found an association of both susceptibility to leprosy[33, 34, 35] and the type of leprosy - tuberculoid or lepromatous - with genetic factors[36]. In an epidemiological study, Bakker et al.[27] found that the susceptibility was explained for approximately 50% by inheritance. Also, Moet et al.[37] found an association between leprosy prevalence and being a relative of a patient. It is difficult however, to separate genetic relationship from close contact status, such as household member[37]. Susceptibility could also be related to a common environment and the risk of family members might be caused by the fact that all household members share the same environment and socio-economic circumstances. Poverty has been shown to be a risk factor for leprosy at a population level[38].

Spatial heterogeneity

Spatial heterogeneity means that the occurrence of an infectious disease is not distributed evenly over space. Leprosy is found to be distributed unevenly in villages [27, 30], and also at higher aggregated area levels, such as districts[39, 40, 41]. The uneven spatial distribution of leprosy can be the result of contact heterogeneity, especially clustering at a low level, e.g. village level. If neighbours have intensive contact with each other, they will have a higher risk of infection[37]. This is expected to result in spatial clustering of cases in villages. However, other underlying spatial factors might determine the clustered occurrence of leprosy. It is, for example, associated with impoverished areas[39, 40].Also geographic features can determine the risk of leprosy. In Malawi, the leprosy incidence decreased with the distance of households to a river or lake shore, and an increased risk with the distance to a main road[41]. Leprosy is often described as rural disease[2, 41]. Clustering in urban areas however, has been reported in Brazil[39, 40]. Although the clustering of leprosy has been studied at different spatial levels, no studies are known that simultaneously address the village and regional level.

Mathematical modelling

Mathematical modelling has a long tradition in infectious disease epidemiology. The most famous model is the Kermack-McKendrick ODE model, or SIR-model[42]. In this model - and the family of models that are derived from it -, the population is divided into compartments with a certain disease state: Susceptible, Infectious and Recovered. A flow from one state to another depends on transition rate parameters from one state to another, e.g. rate of recovery. The calculation of the rate from S to I depends upon the fraction of the population being susceptible and the fraction being infectious. The SIR-model can be extended to whole series of related models with an exposed state (SEIR), or recovery to susceptibility (SIS) etc.[42]. Another modelling approach is microsimulation, in which individual life histories of fictitious persons are simulated[43]. An individual has both demographic and disease related characteristics, which change by stochastic processes. These models take the form of complex computer programs.

Modelling infectious diseases in a population structured by households

Of particular interest in modelling of human infectious disease epidemiology, is a population structured into households. Populations consist typically of many households of small size. The household members of an infectious person have typically a higher infection pressure than those living outside of the household. The household structure of a population has a pronounced effect on the epidemiology of infectious diseases. Household transmission has an amplifying effect on infection dynamics[44], and the initial epidemic growth rate also depends on the distribution of the household size[45]. Aggregation of susceptibles in households, when a population consists of both suceptible and resistant individuals, results in a higher endemic equilibrium [46]. Furthermore, the household structure has implications for intervention strategies, as the critical vaccination fraction for herd immunity is higher, when compliance to vaccination is determined at the level of households rather than at the individual level[47]. Above effects show important aspects of household structure for infectious disease epidemiology; the (exemplary) infections for which these results were derived, however, have a time-scale that is much smaller than that of the population changes. For many infections, such as influenza, the so-called short disease assumption, i.e. the dynamics of the infection are much faster than that of the host population, is valid with generation times for the infection of days. For leprosy, the time-scale at which the disease develops[2] and the infection spreads, is of the same magnitude as that of changes in the population, such as the changes in households. Introducing the demographic processes that drive the formation and dissolution of households over time is a challenge for infectious disease modelling[48]. In this thesis, such a model is developed for leprosy with a microsimulation approach.

Modelling of leprosy

Previous to the model developed in this thesis, two other mathematical models were described in the literature for leprosy[49, 50]. Both are compartmental models. Lechat et al.[49] assessed the impact of MDT with a fairly simple model. Meima et al.[50] developed a modelling framework, SIMLEP, in which they could investigate uncertainties in leprosy epidemiology. This modelling framework was used to investigate the disappearance of leprosy from Norway, for which was found that a model with heterogeneity in age of exposure, heterogeneity in susceptibility, and a long tail to the

distribution of the incubation period gave the best fit to the data[51]. Using the SIMLEP modelling framework to predict future trends shows that a failure to maintain early case detection would be devastating, and that elimination of leprosy can only be a long-term goal[3]. This model was not developed to grasp the intricacies of households or to mechanistically model the heterogeneity in susceptibility. In this thesis, a model is developed that is able to model these aspects of leprosy epidemiology, using the quantifications for the natural history of infection of Meima et al. [3].

Objectives and research questions

The overall objective of this thesis is to improve understanding of the infection dynamics of *M. leprae* in a heterogeneous population and to assess the efficacy of interventions targeted at household contacts of leprosy patients. This thesis contains results from simulation studies and from field studies in north west Bangladesh.

The main research questions that this thesis tries to answer are:

1. What are the causes of clustering of leprosy in households?
2. Which leprosy control strategy targeted at household members of leprosy patients performs best?
3. Does the increased risk for household contacts and neighbours in Bangladesh produce spatial clustering of leprosy?
4. At what levels of spatial aggregation does leprosy clustering occur in Bangladesh?
5. What geographic features are related to risk of leprosy in Bangladesh?

Overview of this thesis

In the first four chapters a microsimulation model is described, and it is used to study the causes of clustering of leprosy in households, and to assess the effect of interventions targeted at household contacts of patients. **Chapter 2** contains a detailed description of the microsimulation model, and its quantification. The model needs long computation times, which is a common problem in the use of microsimulation models for infectious diseases. In **Chapter 3**, a method is presented to reduce computation time for microsimulation of certain infectious diseases. In **Chapter 4** the model is used to see what mechanisms that produce heterogeneity in leprosy susceptibility can explain clustering within households. The microsimulation model is used to compare the efficacy of different interventions strategies in reducing the incidence of leprosy in **Chapter 5**. The microsimulation model used in the first chapters of this thesis simulates a population, which is only structured by households. The relation of households with neighbouring households is spatially in nature, as neighbours are defined by the position of their household. This will lead to spatial patterns of the

occurrence of leprosy. In **Chapter 6**, the actual distance in meters was compared between different contact categories, such as neighbour and social contact, in north west Bangladesh to determine the meaning of different contact categories for the spatial distribution. In **Chapter 7**, the spatial distribution of previously undetected leprosy cases and seropositivity to *M. leprae* specific antibodies at the village level in north west Bangladesh was studied. Finally in **Chapter 8**, the focus is extended to district level, and the spatial distribution of cases was studied in a retrospective analysis of cases detected in a regular control program in north west Bangladesh. **Chapter 9** contains a general discussion of all results, and the thesis is concluded by an English and Dutch summary and a glossary of terms.

2

SIMCOLEP, a microsimulation model of leprosy in a household structured population

E.A.J. Fischer, S.J. De Vlas, A. Meima, J.D.F. Habbema, J.H. Richardus
submitted

Background

Leprosy is a disease caused by infection with the bacterium *Mycobacterium leprae*. Leprosy evolves in a spectrum between two poles (tuberculoid and lepromatous leprosy). The infection is eventually cleared for those with tuberculoid leprosy, while the lepromatous form is chronic. Not all people are susceptible to leprosy, and a marked heterogeneity exists in this susceptibility. This may be because of a resistance against infection or a sufficiently fast clearance of the infection to prevent disease[2]. For those developing leprosy, the incubation period of the disease is long, with 4 to 11 years depending on the type of leprosy [3]. Especially contacts of known leprosy patients are at risk of developing leprosy. These individuals have a higher exposure, but could also be more likely to be susceptible than people in the general population due to shared environment –household– or familial relationship to the patient. Modeling can aid to extrapolate trial outcomes of one study to whole populations or from a short time frame to longer time periods. This provides a way to compare different control strategies. Modeling is also a way of getting insight into underlying natural mechanisms, e.g. the aforementioned heterogeneity in susceptibility. Models for leprosy

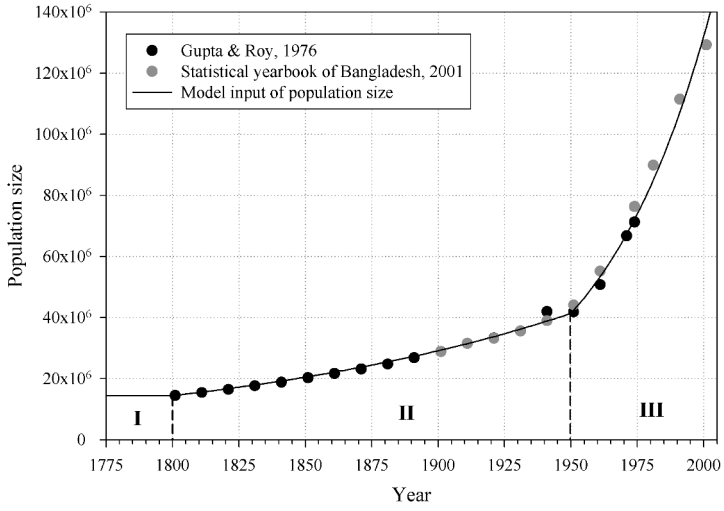

Figure 2.1: Population size of Bangladesh from 1775 to 2000. First official census was conducted in 1901[54]; other data points are estimates [55]. The solid line is exponential growth curve used as input for the model with three phases: (I) A constant population size (II) slow growth with rate 0.007 y^{-1}, and (III) fast growth with 0.0235^{-1}.

have up to now not taken into account the household structure of a population, and explicit genetic mechanisms[52, 50]. We aim to assess dynamics on a household level, thus the household structure of population needs to be incorporated. As leprosy has a long incubation period[2] the timescale at which the disease evolves and the timescale at which households changes are comparable. This means that a household often does not have the same composition at the end of the infection as it was at the moment of infection. Individuals including those infected, can have moved out or new (possibly infected) individuals can have moved into the household. We take up the challenge to explicitly model the formation and change of household [48]. The model will be parameterized for northwest Bangladesh[53] and fitted to the detailed disease data of a trial in the same area[37].

Microsimulation

SIMCOLEP simulates leprosy transmission in a population structured by households that form and dissolve during the simulation. The model is a microsimulation –or a stochastic individual-based model– [56]. The model simulates the life history of fictitious individuals, including the household formation, and the natural history of infection with *M. leprae*. The state of an individual changes during events that are scheduled in continuous time. The timing of events is determined by probability distributions, which is determined by the current state and history of an individual. The model is divided into two modules: a population module, and a disease module. The population module describes processes unrelated to disease or infection, such as birth, death and marriage. The disease module simulates processes of infection and disease, including interventions.

A computer program was written in JAVA 1.5.0 to make the calculations of the model using a similar structure as STDSIM [57]. To explicitly simulate an infectious disease requires the simulation of many interacting individuals, and can become computationally demanding. Reliable simulation of a relatively rare infectious disease, such as leprosy, requires a large population. To keep computation time within reasonable limits, we used the MUSIDH method [58] with a setting of 50 disease histories to 1 life history. In short this method implies that every demographic life history (birth, death etc.) is used as if 50 individual have exactly the same demographic life history, while disease events differ between these 50 individuals. This prevents the simulation of many demographic life histories.

Population module

The population grows with a time-dependent growth rate. In total we recognized three population growth phases (Figure 2.1) and choose to model population growth with exponential growth during these three phases. For the population before 1800, we assumed a constant population (i.e. a growth rate of 0 y^{-1}). The second phase of slow growth from 1800 until 1950 occurred with a rate of 0.007 y^{-1}. From 1950 onwards the population grows with a rate of 0.0235 y^{-1}. The population growth-curve after 1800 was obtained from extrapolations based on census data [59, 55]. The population size is kept at the required size by replacing deaths by births, and population growth

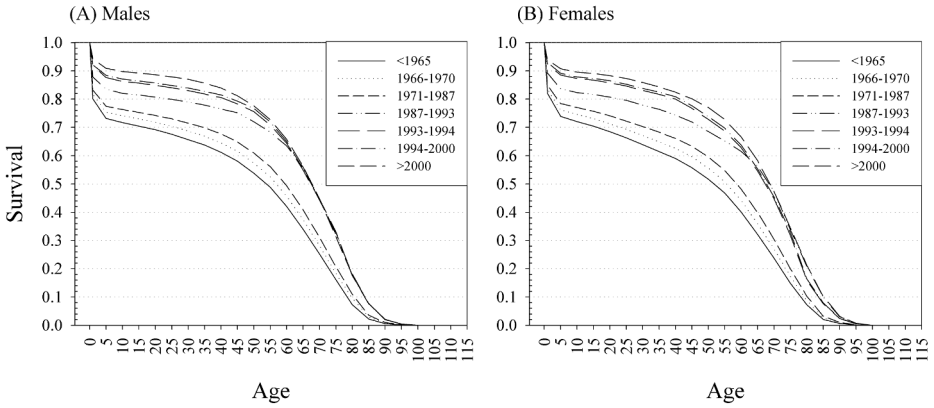

Figure 2.2: Input survival curves for males (A) and females (B) in Bangladesh for the years 1961 until 2000 [54]

is accomplished by additional births. We assumed a closed population, hence no migration.

At birth, a new individual is created and the age of death is determined by a sex-dependent survival curve, which changes with calendar time (Figure 2.2). We used the available survival data from 1961 until 2000 [59, 54]. Survival data previous to 1961 were not available, and therefore we used the survival curve of 1961 for all years previous to that.

The newly created individual is placed into a household in which a married female is available as mother. The actual mother is randomly selected from all married females weighed by her age. The age-weighed selection of a mother is based upon age specific birth rates [59]. The birth rates for 1995 are shown in Figure 2.3. Unmarried males and females can be coupled during wedding events, which are scheduled such that the proportion of married people in each age group matches census data (Figure 2.4). After the death of a married person, the surviving spouse is again a candidate for marriage. At marriage, 25% of couples create a new household; for the other couples the female will become member of the household of the male. In the latter case, the household will split up with a rate of 0.083 y^{-1} (i.e. after 12 years), and the

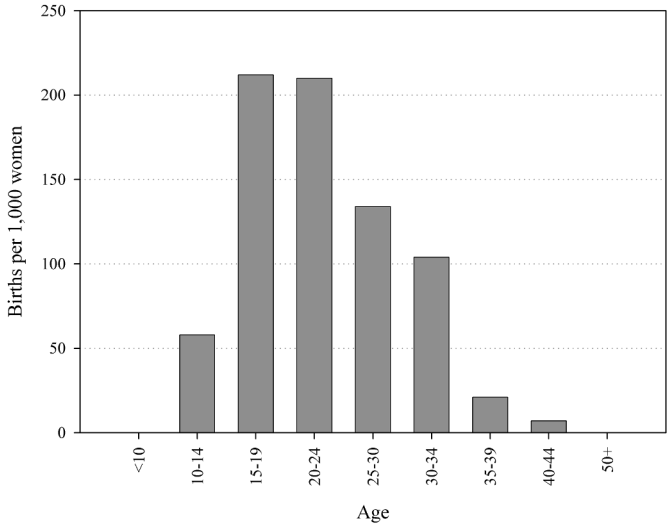

Figure 2.3: Example of the input of age specific birth rates for women (Bangladesh, 1995), given as the number of children born to 1,000 women in a specific age group [59].

married couple and their possible children will create a new household.

Movement other than by marriage takes place between households by 30% of non-married males. The age of movement is chosen randomly from a uniform distribution between 12 and 22 years of age. Twenty percent of these moving males create a new household. For the others a new household is randomly chosen weighed by the size of the household. The weight is 0.25 for households of size 1 and increase linearly to 1.0 at 4 and than linearly decreases to a weight of 0.0 for households of size 50. Hence, movement is most likely to households of size 4, that become households of size 5 after movement. In the simulations, household sizes maximized at 25 inhabitants. Data to directly quantify the parameters for the model of movement of people are unavailable, and therefore the above-mentioned values were obtained by calibrating the model to mimic the distribution of household sizes in Nilphamari district in Bangladesh and the percentage of people that moved during a 2-year period. The observed average

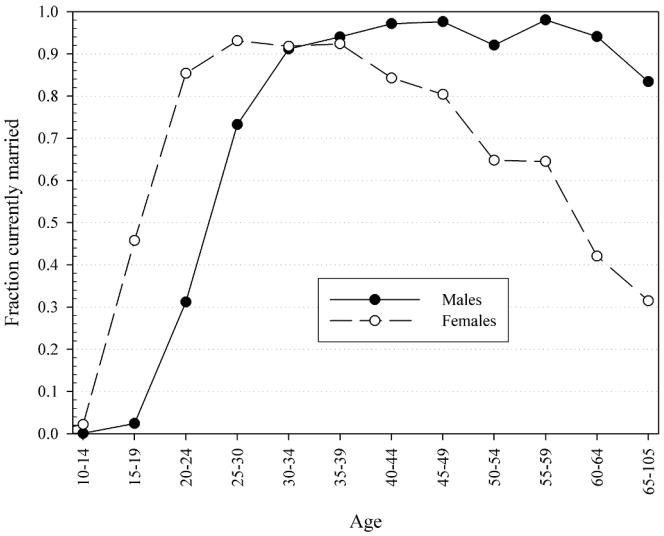

Figure 2.4: Example of the input of fraction males and females per age group currently married (Bangladesh,1991) [59].

household size was 4.6 (ranging from 3.9 to 5.9 between villages), and 3.1% of the population moved per year (ranging from 2.0% to 3.6% between villages) [53]. The calibration of parameters gave an average household size of 4.3 and the movement rate was 2.9% per year. The household size distribution did not significantly differ from the data [53] (χ^2 test, $p = 0.25$, Figure 2.5).

Disease module

The disease module exists of four separate, but interacting components: transmission, natural history of infection, allocation of susceptibility and type of leprosy, and interventions.

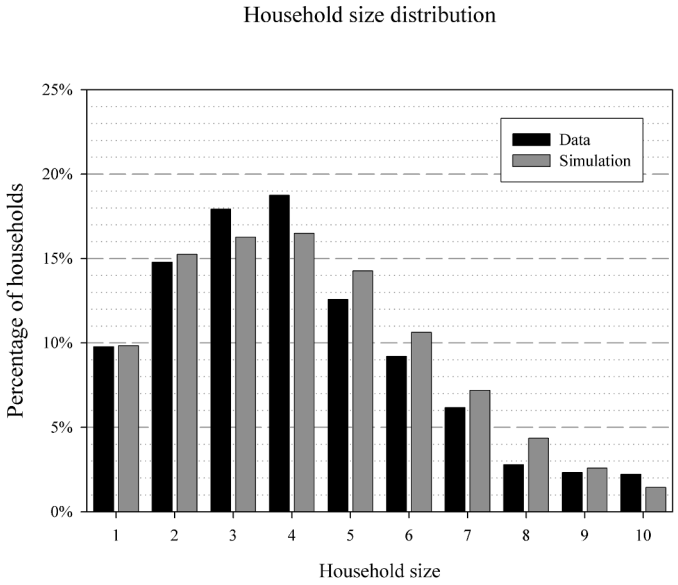

Figure 2.5: Result of calibration of simulation population module to the observed distribution of household size in Northwest Bangladesh in 2006[53] (N = 859). There is no significant difference between data and simulated distribution ($p = 0.25$, χ^2-test).

Transmission

Transmission occurs during events in which an infectious individual has contact with a susceptible individual. We modeled two transmission processes (1) in the general population and (2) an additional within-household transmission. The contacts in the general population are made indiscriminately to people within and outside the household of the infectious individual, while the within-household transmission takes place during contacts of household members.

With a contact between two individuals is meant that this contact event is "close-enough for transmission" of the infection. The actual probability of transmission during these close-enough contacts is scaled by the infectivity function. The infectivity function, $A(t)$, is the probability of transmission as a function of the time since infection, t. Here, the infectivity function is a continuous linear function from 0 to

1 during the asymptomatic state, and constant at 1 during the symptomatic state. Transmission events from an infectious individual to other individuals in the general population are timed according to a non-stationary Poisson process [60] with the rate function determined by the product of the population contact rate, c_{pop}, and the infectivity function, $A(t)$. Equation 2.1 gives the expected number of events during the period 0 to t. The next event is found by determining the expected time until 1 transmission event for a random variate U making use of the inverse of Equation 2.1, $\Lambda_{pop}^{-1}(t)$ [60]. Such a transmission process is called frequency dependent transmission (or mass action), which means that the number of contact events per individual per time unit (i.e. year) is independent of the population size.

$$\Lambda_{pop}(t) = c_{pop} \cdot \int_0^t A(\tau) d\tau \tag{2.1}$$

Additional to these infections, a within-household transmission process is modeled. A susceptible living in a household with one or more infectious individuals can be infected within the household. The within-household transmission process is modeled by density dependent transmission (or pseudo mass action), which means that the number of contact events per individual per time unit increases with the household size. The rate at which susceptible individuals are infected is determined by all infectious individuals in a household and the within-household contact rate, c_{hh}. For each couple of an infectious individual and a susceptible individual in a household, a transmission event is determined by c_{hh} and $A(t)$ similar to Equation 2.1. The susceptible individual will be infected during the first transmission. With I infectious individuals in a household the time until the transmission event is determined for I random variates of a uniform distribution $(U_1, \cdots, U_I)$ producing the minimal time until the transmission event.

$$T_{transmission} = \min\{\Lambda_{hh}^{-1}(-\ln U_1), \cdots, \Lambda_{hh}^{-1}(-\ln U_I)\} \tag{2.2}$$

Natural history of infection

The value of the infectivity function, the probability of detection and the rate of self-reporting depend on the state of the infection. The infection is modeled by discrete infection states. After infection individuals are either in the asymptomatic state, the symptomatic state, or the recovered state. We used the structure and estimates for

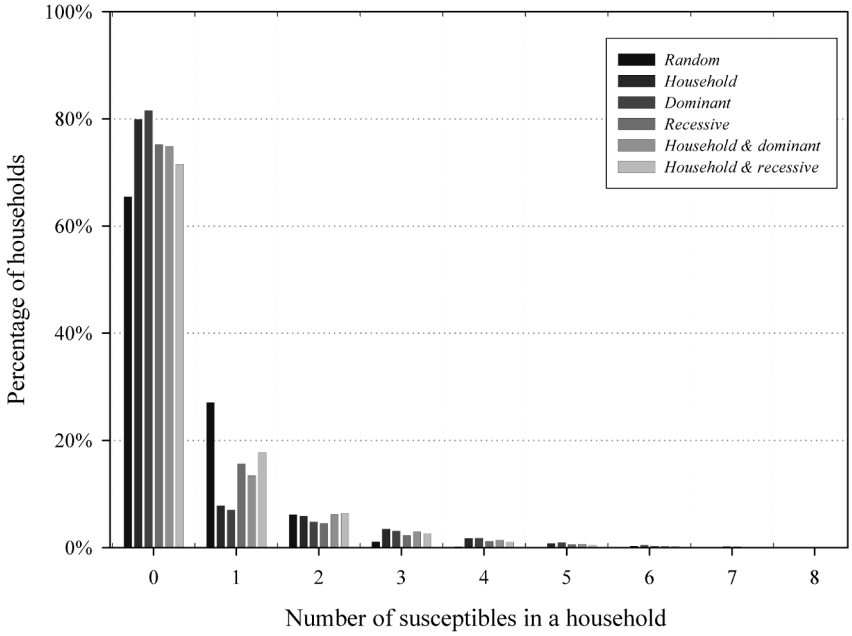

Figure 2.6: Distribution of susceptibles over households of all sizes (10% susceptibles).

the natural history of the infection as Meima et al. [3]. Infection and disease variables, such as detection probability and the infectivity function, have a value corresponding to the infection state, or for the infectivity function the proportion of time spent in the state. The model distinguishes never-susceptible and susceptible individuals. Simulations are done for 5%, 10% or 20% susceptibles in the population. Of the susceptible individuals will a fraction of 80% will go through a self-healing infection, and the remaining 20% of susceptibles becomes chronically infected [2, 3, 4].

The self-healing type is never infectious [3]. The duration of the asymptomatic state is gamma distributed with mean 4.2 years and a standard deviation of 1.9 years[2, 3]. In the symptomatic state, the self-healing type is detectable during examination and will be treated immediately after infection. The self-healing type is uninfected, and recovered without symptoms at the moment of self-healing. The time until self-healing from onset of symptoms is exponentially distributed with rate 0.2 (i.e. mean duration of 5 years). The self-healing type is assumed never to be infec-

tious. The chronic infection has an asymptomatic period with mean 11.1 years and standard deviation of 5.0 years, and will be symptomatic until treatment or death of the individual. During the asymptomatic period the infectivity of an individual, i.e. the probability of infecting during a sufficiently close enough contact, increases linear to one at first symptoms. Treatment is given directly at detection and makes an infectious individual immediately non-infectious. Relapse of disease after treatment for both chronic and self-healing infections occurs with a rate depending on calendar time. Between 1970 and 1990 dapsone monotherapy is given, and relapses occur with a rate of 0.015 y^{-1}, and after full implementation of multi-drug therapy (MDT) in 1990 the relapse rate is 0.001 y^{-1} [5]. Of all treated cases including those of the self-healing type, 90% will relapse as a chronic infection, and 10% as a self-healing infection[61].

Allocation of susceptibility and type of leprosy

The susceptibility of an individual is determined by one of six mechanisms of allocation of susceptibility and of the type of leprosy (self-healing or chronic infection):

- *Random*, Equal probability for each individual, i.e. random allocation of susceptibility and type of leprosy
- *Household*; Random sample of individuals in randomly selected households
- *Dominant* genes inherited from one or both parents; both susceptibility and the type of leprosy
- *Recessive* genes inherited from both parents; both susceptibility and the type of leprosy
- 50 % by *Household* and 50% by *dominant* genes
- 50 % by *Household* and 50% by *recessive* genes

For *Random*, individuals are determined to be never susceptible, self-healing or chronic randomly at birth. For *Household*, when a household is created, it is determined whether it contains susceptible inhabitants with in total 25% of the households containing susceptibles [62]. However, not all inhabitants of such a household will be susceptible, and at birth, it is determined whether or not an individual is susceptible,

when living in a susceptible household. For the three percentages of susceptibility in the population, 5%, 10% and 20%, respectively 20%, 40% and 80% of the inhabitants of the household is susceptible. The type of leprosy (self healing or chronic) is determined randomly for susceptible individuals. The genetic mechanisms are governed by two genes [36] (one for susceptibility and one for the type of leprosy). These genes are both either *dominant* or *recessive*. Children inherit one allele of a gene from both parents. The final combination of alleles - the genotype - then determines the phenotype consisting of susceptibility and type of leprosy. The fifth and sixth mechanisms are combinations of *Household* & *dominant* and *Household* & *recessive*. In these mechanisms, half of the susceptibles is susceptible due to their genetic make up, and the other half due to living in a susceptible household [27]. In Figure 2.6 is shown how the distribution of susceptibles over households is determined by the different susceptibility mechanisms. Due to the length of simulations (over 1000 simulated years) genetic drift causes divergence from the starting frequencies of phenotypes in the genetic scenarios. The proportion of alleles at the start of the simulations is taken such that the percentage susceptibles is 5%, 10% or 20% during the last 50 years of the simulations.

Leprosy control

The leprosy control program starts in 1970 with passive case detection and treatment. Detection delays are gamma distributed, and start with mean 12 years and standard deviation 3.5 years in 1970, and decreases to a mean of 2 years (standard deviation 1.4 years) in 1994 [63]. If a self-healing infection heals before the randomly determined passive case detection, the 'case' will not be detected. At the moment of passive case detection, the individual is diagnosed based on the infection state. Two diagnoses are possible mild disease and severe disease. Mild disease is the diagnosis for the symptomatic state of the self-healing type and severe disease for the symptomatic state of the chronic type. Household members of a detected case are subject to contact tracing (i.e. active case detection) from 1990 onwards. During contact tracing, the probability of a positive diagnosis is determined by the detection probability of the infection state of an individual. Contacts are followed up yearly for 3 consecutive annual visits at each of them 90% will be examined. Contacts can be diagnosed as "no disease" for individuals that are uninfected and in the asymptomatic states; furthermore 10% symptomatic cases are missed during examination and thus incor-

rectly given the diagnosis "no disease". The remaining 90% of symptomatic cases is diagnosed as mild disease for self-healing infections or severe disease for chronic infections. BCG, a vaccine used against tuberculosis, has a protective effect against leprosy. In this study, we choose a life-long protective effect of 60% against infection with *M. leprae* [64, 15]. Only BCG vaccination prior to infection with *M. leprae* has a protective effect. BCG vaccination of newly born children starts in 1974. The model starts with a BCG campaign in 1974 in which 40% of all children between age 0 and 10 are vaccinated. From 1975 until 1980, 40% of children are vaccinated. From 1980 until 1990 the BCG vaccination coverage increases up to 80% and on that level it remains until the end of simulations[65, 64].

Discussion

The microsimulation model is developed with the primary goal to evaluate intervention strategies targeted at household members. Therefore, an explicit modelling of household structure is required. Not only a static structured population, but the changes in households should also be taken into account, because the time scales of changes in households and progress of leprosy disease are similar. The distribution of susceptibility to leprosy over households should also be taken into account. Two major aspects of the model are novel: (1) household structure with explicit simulation of household formation and changes, and (2) mechanistic modelling of heterogeneity in susceptibility to leprosy. Explicitly modelling the formation and change of households is new in modelling of (leprosy) epidemiology[48]. The simulation of households is based on simple mechanistic rules, in which we assume that adolescents move randomly to other households, and newly married couples create a new household or the bride moves in with her husbands' family. With these relatively simple rules, we were able to reproduce the observed household distribution (Figure 2.5) and the observed movement rate. Because these rules can be directly quantified, the model can be validated by additional research. When such research provides evidence for additional mechanisms, these can easily be added to the model.

At this moment, the microsimulation model does not incorporate any relation between households. Both adolescent movement and partner choice for marriage occur randomly, while in reality these processes take place within a social network, i.e. adolescents moving to relatives and marriage in the same social group. Not

only for the demographic module, but also for disease module no relation between households is taken into account. This means that the probability of transmission between households is equal for all households, although for example neighbours have been shown to have an increased risk[37]. Additions to the model can be made to investigate the impact of such household contact structure on the epidemiology of leprosy. Defining and quantifying the interaction between households is, however, a remaining challenge.

The microsimulation approach provided a flexible way to mechanistically model the heterogeneity in susceptibility to leprosy. Mechanisms acting at the individual level produce population level outcomes in the distribution of susceptibles over households. The mechanisms were a household factor, genetic factors, but also the simplest assumption of susceptibility randomly distributed in the population. The distribution of susceptibles of households differs extensively between different mechanisms as shown in Figure 2.6. Hence, the effect of the different mechanisms on leprosy epidemiology is the most important aspect to study.

3

MUSIDH, Multiple Use of Simulated Demographic Histories, a novel method to reduce computation time in microsimulation models of infectious diseases

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Abstract

Microsimulation of infectious diseases requires simulation of many life histories of interacting individuals. In particular, relatively rare infections such as leprosy need to be studied in very large populations. Computation time increases disproportionally with the size of the simulated population. We present a novel method, MUSIDH, an acronym for Multiple Use of Simulated Demographic Histories, to reduce computation time. Demographic history refers to the processes of birth, death and all other demographic events that should be unrelated to the natural course of an infection, thus non-fatal infections. MUSIDH attaches a fixed number of infection histories to each demographic history, and these infection histories interact as if being the infection history of separate individuals. With two examples, mumps and leprosy, we show

that the method can give a factor 50 reduction in computation time at the cost of a small loss in precision. The largest reductions are obtained for rare infections with complex demographic histories.

Introduction

Microsimulation models are an important tool to study the epidemiology and control of infectious diseases (e.g. [3]). Describing both the demographic history and the infection history on the individual level gives a large flexibility in model formulation. The demographic history refers to processes such as birth, death, and other events such as movement from and to households [48]. The infection history concerns acquisition and loss of infection, together with the course of disease. Transmission of infection from one person to another leads to interactions between individual life histories. These interactions necessitate joint simulation of individual life histories. Ordering and management of their events at the right time will lead to computer time increasing disproportionally with the size of the population. The simulation of many interacting individuals thus becomes computational demanding. Especially reliable simulation of rare infections such as leprosy requires large populations.

In this paper, we present MUSIDH, an acronym for Multiple Use of Simulated Demographic Histories. This is a novel method to simulate infection dynamics in large populations with feasible computation times on a standard PC, without losing the ability to formulate the modelling of demographic and infection histories on an individual level. The method uses one demographic history for a fixed number of times, and each replication of the same demographic history is attached to several unique infection histories. Our method was inspired by the so-called super-individual concept [66]. We investigated the properties of MUSIDH for two examples of simulation models for infectious diseases, mumps and leprosy.

Method

In a conventional microsimulation, the combination of demographic history (DH) and infection history (IH) would form the life history of an individual. The DH and IH are simulated a sequence of state changes -e.g. from susceptible to infectious, unmarried to married-. MUSIDH attaches a fixed number of m unique IHs to each DH. We will

call m the MUSIDH-number, thus representing m separate individuals. For infection dynamics, the effective size of a population is thus obtained by multiplying the number of DH with this MUSIDH-number. The DH is simulated as in a conventional microsimulation, but now each state change applies to all attached IHs. Thus, e.g. birth and death are the same for each of the attached IHs of one DH.

The IHs do not interact in the same way as the DHs. To determine how the IHs interact, each IH is numbered by an index i between 1 and the MUSIDH-number m. Interaction between DHs applies only to IHs with the same index. In the examples given in this study, we model a population structured by households. Transmission within a household only applies to those IHs with the same index, and DHs within the same household. Interactions between IHs of different indices only occur with events in the general population – e.g. infectious contacts by random mixing – connecting IHs of different indices. Figure 3.1 is a graphical representation of MUSIDH for two DHs and m IHs attached to either one.

If the MUSIDH-number is 1, the MUSIDH-simulation is the full microsimulation, which serves as the 'gold standard'. In two examples, representing the infectious diseases mumps and leprosy, we compared outcomes of the full microsimulation with MUSIDH for MUSIDH-numbers 5, 10, 20, 50, 100 and 200.

Due to the stochastic nature microsimulation models, the outputs of single runs are variable, and the average output of a set of runs is usually considered as one result. Therefore, for all situations (i.e. the full microsimulation and the simulations with MUSIDH, all for both diseases) we ran the model 1,000 times. In particular the full microsimulation took too much time to have more single runs, which was why we developed the method in the first place. From these 1,000 single runs, we obtained distributions of results by randomly sampling 10,000 sets of 10, and 10,000 sets of 100 outputs. MUSIDH was compared to the full microsimulation regarding the deviation (in %) from the median and the fraction of results within the 95% interval of the full microsimulation results, i.e. the interval between the 2.5% and the 97.5% percentile.

Examples

We present two examples with simplified models of infectious diseases in a population with a dynamic household structure. In the models, households are established during marriages. Marriage is modelled explicitly, where individuals become candidate for

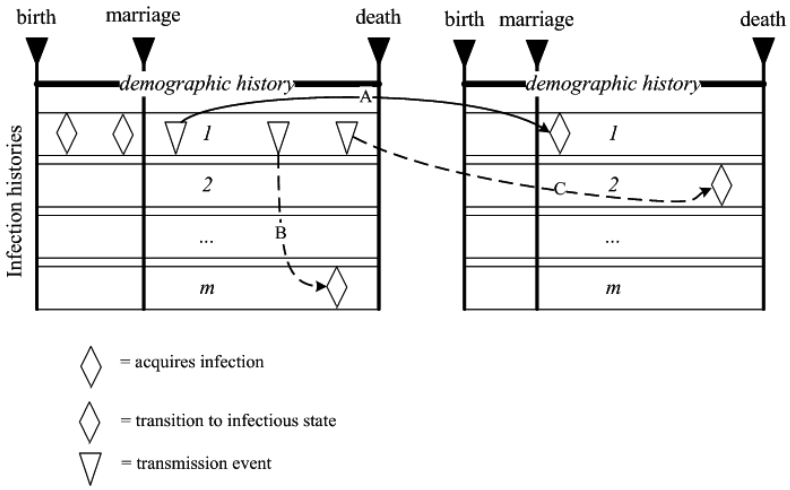

Figure 3.1: Schematic overview of two demographic histories (husband left and wife right) and MUSIDH-number m attached infection histories, depicted by rectangles. The open diamonds depict the moment at which infection is acquired. The filled diamonds are the moments at which transition towards the infectious state is made. Both demographic histories have three events, birth, death and marriage. These demographic histories are equal for all m attached infection histories, but the infection histories are different. In the first infection history of the left-hand individual, the simulated person has acquired infection and becomes infectious before marriage. This infection history leads to several transmission events (filled triangle) in which after marriage the spouse is infected within the household (arrow A). Transmission randomly in the population occurs (depicted by dotted arrows), in an infection history with the same demographic history, but different index (arrow B) and in an infection history with a different demographic history (arrow C).

marriage with a probability based upon their age, increasing linearly from 0.00 to 0.95 from age 15 to age 30. A constant population size is obtained by replacing each death with a birth. Age at death is determined by an exponential distribution with a fixed mortality rate.

The infection model is a stochastic form of the SEIR-model, including transmission within and between households. The SEIR-model contains four states: *Susceptible*, *Exposed*, *Infectious* and *Recovered* [67]. Individuals are born susceptible. After a possible infection they enter the exposed state, become infectious, and eventually recover. All durations are exponentially distributed. During the infectious period, infectious contacts to the general population are made according to a Poisson process. In ad-

Table 3.1: Parameter values for the mumps and leprosy examples

Parameter	**Value**	
	Mumps	**Leprosy**
Transmission rate within the general population	75 years^{-1}	5 years^{-1}
Transmission rate for each individual within a household with an infected person	365 years^{-1}	10 years^{-1}
Recovery rate	60.83 years^{-1}	-
Mortality rate	1/60 years^{-1}	1/60 years^{-1}
Fraction never susceptible	-	0.9
Transition rate from exposed to infectious	24.33 years^{-1}	0.1 years^{-1}
Effective population size	25,000	25,000
Length of simulation	100.2 years	1,000 years

dition, within-household transmission is modelled by a rate of transmission between an infectious IH and all susceptible IHs in a household. A susceptible IH becomes infected at the first of the transmission events originating from all infectious IHs in the household. The first infection was introduced at year 100 for both examples.

Mumps example: a highly contagious disease with a short infectious period

The first example is based upon the childhood disease mumps. The infection has a short latency period of 2 weeks, and also a short infectious period of 1 week (see table 3.1 in [67]). Mumps is highly contagious (see table 4.1 in [67]). The simulations were stopped after 100.2 years. As the modelling result we used the total number of cases during the epidemic. The simulations for the mumps example gave a typical epidemic response, where in the full microsimulation 91.5% (90.9% - 92.1%) of the population became infected during the epidemic. For all examples given, the median of the total number of cases during the epidemic simulation using MUSIDH deviated less than a half percent from the full microsimulation. On the other hand, the fraction of sampling distributions for MUSIDH between the 2.5% and 97.5% percentiles of the sampling distribution of the full microsimulation was rather low for higher MUSIDH-numbers (Table 3.2). This was due to the nearly structural deviation of the median, together with an almost negligible increase in variance with higher MUSIDH-numbers (see Figure 3.2). The method saved up to 110 seconds, which is an 18 times reduction in computation time.

Table 3.2: Results of the full microsimulation and the MUSIDH method for the mumps example. The effective population size is 25,000 for each run. The outcomes are resampled for 10,000 times in sets of 10 and 100 runs out of 1000 single runs, and the interval of the full microsimulation determined as the 2.5% and 97.5% percentile.

Size of the epidemic				
	Median (% diff.)	95% interval		Average
		Sets of 10 runs	Sets of 100 runs	run time (s)
Full [a] micro-simulation	22,885	22,835-22,935	22,870-22,901	116.5
MUSIDH[b] -number	Median (% diff.)	Fraction within 95% interval		Average
		Sets of 10 runs	Sets of 100 runs	run time (s)
5	22,893 (+0.03%)	0.92	0.81	13.9
10	22,916 (+0.14%)	0.74	0.10	9.8
20	22,921 (+0.16%)	0.69	0.08	7.9
50	22,891 (+0.03%)	0.67	0.66	6.8
100	22,845 (-0.17%)	0.43	0.04	6.5
200	22,780 (-0.46%)	0.19	0.00	6.3

[a] Full microsimulation runs are the "gold standard"
[b] Natural history of infection per individual.

Leprosy example: a low contagious disease with a long infectious period

The second example is based upon multibacillary leprosy, which is the type of leprosy that is considered to be infectious, and susceptibility to this type is thought to be innate. We have therefore added an additional state to the model: *Never susceptible*, meaning that they have life-long innate immunity. Ninety percent of the newborns enter the never susceptible state at birth. The latency period after infection of a susceptible person is on average 10 years, and thereafter a chronic infectious period is entered which continues till death [3]. Leprosy is low contagious. The simulation was stopped after 1,000 years. We compared the number of prevalent cases averaged over the last 100 years of the simulation, as the last 100 years can be considered as in quasi steady-state.

Depending on the MUSIDH number, the median number of prevalent cases in simulations differed between –8.4% and +2.1% of the gold standard. In contrast to mumps, now most sampled distributions were largely within the 95% interval of the

Table 3.3: Results of the full microsimulation and the MUSIDH method for the leprosy example. The effective population size is 25,000 for each run. The outcomes are resampled for 10,000 times in sets of 10 and 100 runs out of 1000 single runs, and the interval of the full microsimulation determined as the 2.5% and 97.5% percentile.

Number of prevalent cases at quasi steady-state				
	Median (% diff.)	95% interval		Average
		Sets of 10 runs	Sets of 100 runs	run time (s)
Full [a] micro-simulation	129.5	92.0-165.6	117.4-140.9	636.2
MUSIDH-[b] number	Median (% diff.)	Fraction within 95% interval		Average
		Sets of 10 runs	Sets of 100 runs	run time (s)
5	127.3 (-2.0%)	0.95	0.95	126.9
10	132.7 (+2.1%)	0.93	0.93	66.4
20	130.2 (+0.2%)	0.94	0.94	32.0
50	129.3 (-0.5%)	0.96	0.95	17.4
100	128.2 (-1.4%)	0.94	0.92	13.5
200	2119.0 (-8.4%)	0.90	0.76	11.5

[a] Full microsimulation runs are the "gold standard"
[b] Natural history of infection per individual.

full microsimulation (Table 3.3). The distribution of the full microsimulation runs has a wide variance, so that even large deviations by MUSIDH fell within the 95% interval (Figure 3.3). The full microsimulation runs took on average 10.6 minutes (636 seconds). The computation time reduced to 66 seconds with MUSIDH-number 10, and to 12 seconds for MUSIDH-number 200, which is a 55 times reduction.

Discussion

Our results show that MUSIDH reduces computation time for a complex microsimulation model, while sacrificing a little bit of accuracy. This reduction is obtained due to the simulation of smaller numbers of demographic histories. Therefore, the yield in computer time is highest for a model with a low number of infections in combination with a large population size, as in our leprosy example. This was shown by a maximum reduction in computation time of 18 versus 55 times for mumps versus leprosy.

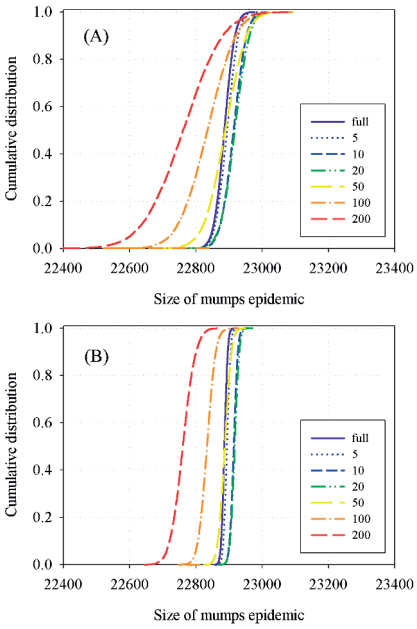

Figure 3.2: Cumulative distributions of the results of the mumps example for 10,000 sets of 10 outputs (A) and sets of 100 outputs (B) randomly sampled out of 1,000 single runs. The results are the size of the epidemic, i.e. the total number of cases during the whole epidemic. The distributions are shown for the full microsimulation and MUSIDH with 5, 10, 20, 50, 100, 200 infection histories for each demographic history.

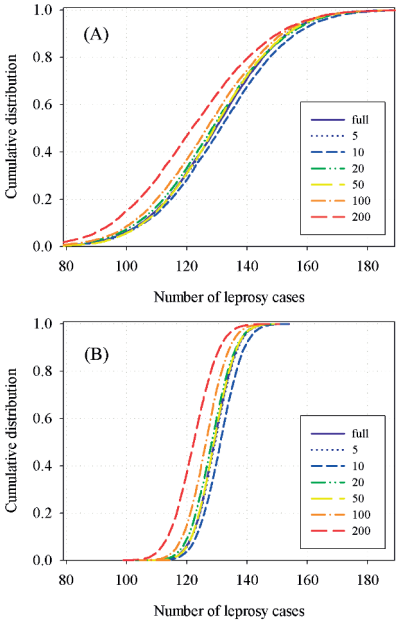

Figure 3.3: Cumulative distributions of the results of the leprosy example for 10,000 sets of 10 outputs (A) and sets of 100 outputs (B) randomly sampled out of 1,000 single runs. The results are the endemic steady state, determined by the average number of prevalent cases during the last 100 years of a run. The distributions are shown for the full microsimulation and MUSIDH with 5, 10, 20, 50, 100, 200 infection histories for each demographic history.

Our two examples show difference in the performance of the method. In the mumps example, MUSIDH gave a small deviation from that median, but this structural deviation shifted the distribution outside of the 95% interval of the narrow distribution around the median of the results of the full microsimulation. In the case of leprosy with a wider variation in the full microsimulation results, the deviation from the median is larger (up to 8.4%), but the distributions of the full microsimulation and MUSIDH have a large overlap. The low endemic level in the leprosy example contributes to the higher deviation from the median, as one infection represents 0.8% difference, while the measles example one extra infection raises the median with 0.004%. Before using the method extensively, it is advised to investigate the magnitude of the loss of precision for each specific simulation model.

The overlap of the distribution in the mumps-example is larger for MUSIDH-number 50 than for 10 or 20, when sampling sets of 100 (Table 3.2). The reason is that the distributions of simulation results are skewed, as the maximum number of cases is limited by the population size. An increase in variance will produce on average smaller values. For small MUSIDH-number, the average is shifted upwards in this example (Figure 3.2), while the variance hardly increases. Thus, for MUSIDH-numbers 10 and 20 with narrow distribution, the effect of the shift is large causing most of the results to be higher than those of the full microsimulation. For MUSIDH-number of 50, the higher variance of the distribution of the results gives lower values and a larger overlap with the distribution of the results from the full microsimulation. For MUSIDH-number 100 and 200, the variance increases even more, and the whole skewed distribution shifts more towards low values, causing little overlap with the full microsimulation results.

MUSIDH is not appropriate for all (infectious) diseases. As the method hands in accuracy it should only be used when it can substantially reduce computation time. For the most basic demographic history, i.e. only birth and death, the gain in computation time will usually be small. However, the time for detailed modelling of household events can be substantial. The prevalence of the infection is also of importance for the performance of MUSIDH. Without re-introduction, infections will always go extinct in a stochastic simulation. The time until extinction decreases with decreasing contagiousness, and decreasing population size [42]. Thus modelling of a rare, low contagious infection requires a large population. In a model, such as the leprosy example, many life histories are needed to obtain the required population

size, while many simulated persons will never come into contact with infection, the separate demographic histories will cost a lot of computation time.

Furthermore, it should be noted that the use of MUSIDH is limited to the models of diseases that do not substantially influence the demographic events for an individual (e.g. moments of death or leaving a household), and only a specific set of infectious diseases are appropriate. Typical examples are leprosy and – for western countries – children's diseases such as mumps, measles and chickenpox, as these diseases have almost no excess mortality and a morbidity with limited effect on population dynamics. Another example is lymphatic filariasis, of which a comprehensive microsimulation model exists [68].

There are different ways to reduce computation time of microsimulation models, and the use of more powerful computers is the most obvious alternative. Also, grid computing and initiatives such as Africa@home [69] allow researchers to compute on many computers at the same time. MUSIDH does not compete with these methods. Our study shows that MUSIDH provides a powerful additional option – although sacrificing a little accuracy – for a substantial further reduction of computation time.

4

Different mechanisms for heterogeneity in leprosy susceptibility can explain disease clustering within households

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submitted

Abstract

Background: The epidemiology of leprosy is characterized by heterogeneity in susceptibility and clustering of disease within households. We aim to assess the extent to which different mechanisms for heterogeneity in leprosy susceptibility can explain household clustering as observed in a large study among contacts of leprosy patients. Methods: We used a microsimulation model, parameterizing it with data from over 20,000 contacts of leprosy patients in Bangladesh. We simulated six mechanisms producing heterogeneity in susceptibility: (1) susceptibility was allocated at random to persons (i.e. no additional mechanism), (2) a household factor, (3, 4) a genetic factor (dominant or recessive), or (5, 6) half a household factor and half genetic. We further assumed that a fraction of 5%, 10%, and 20% of the population was susceptible, leading to a total of 18 scenarios to be fitted to the data. Results: We obtained an acceptable fit for each of the six mechanisms, thereby excluding none of the possible underlying mechanisms for heterogeneity of susceptibility to leprosy. However, the distribution of leprosy among contacts did differ between mechanisms, and predicted trends in the declining leprosy case detection were dependent on the assumed mecha-

nism, with genetic-based susceptibility showing the slowest decline. Conclusion: Even a large and detailed data set on contacts of leprosy patients could not unequivocally reveal the mechanism most likely responsible for heterogeneity in leprosy susceptibility. Future trends of leprosy case detection in the study area are expected to provide clues for distinguishing between mechanisms determining susceptibility to leprosy.

Background

Leprosy, caused by infection with *Mycobacterium leprae*, was detected in a quarter of a million people in 2008, and many more people are living with impairments caused by this disease.[19] Although the WHO goal of an on-treatment prevalence of less than 1 per 10,000 was reached world-wide[6], in many countries or regions case detection rates are well above this goal.[19]

Clustering of leprosy patients within households, families, and neighborhoods has been reported many times.[70, 27, 28, 37, 30] This clustering is partly due to a higher contact intensity, hence an elevated possibility of transmission between contacts. However, only a few people that are exposed to the infection, within or outside households, actually develop the disease.[2, 4] Introduction of leprosy on an island shows the heterogeneity in susceptibility most clearly, as the number of cases is limited to a proportion of the total population, smaller than expected given the initial rapid increase of cases.[71] The fraction of susceptible members of the population of the Indian subcontinent is thought to be approximately 10%.[2, 3, 4] We hypothesize that the clustering of leprosy in households is due to a combination of the increased exposure to infection and specific mechanisms that cluster susceptibility within households.

Association between genetic elements and leprosy susceptibility has been suggested previously.[72, 73] Leprosy develops in a spectrum of clinical forms, from self-healing to the chronic lepromatous type of leprosy. Recent studies with whole-genome screening in Viet Nam and Brazil indicate a two-step genetic mechanism in which leprosy susceptibility and the type of leprosy are determined by alleles of genes on different chromosomes.[36, 34] Epidemiological studies support the existence of a genetic factor for the risk of leprosy[27, 37], but these studies are not conclusive due to the fact that familial relationship and household membership are correlated.[27]

Another mechanism determining heterogeneity in leprosy susceptibility may explain the observed clustering of leprosy in household contacts. In Moet et al.[37],

the odds-ratio of having leprosy for close relatives is only marginally significant after adjusting for contact distance, e.g. household member, neighbor, or social contact. This result indicates that the risk of family members might be caused by a common (but yet unknown) risk factor in a household, such as poverty, which in Brazil has been shown to be a risk factor for leprosy.[38]

In this study, we analyze the data from the study by Moet et al[37] to quantify the level of within- and between-household transmission of *M. leprae*. Using a newly-developed microsimulation model, we attempt to distinguish between mechanisms causing heterogeneity in leprosy susceptibility. The study of Moet et al.[37] was performed in the context of a randomized controlled trial of the effect of chemoprophylaxis, and contains the data of 21,870 contacts of 1,037 leprosy patients detected by a rural health program in northwest Bangladesh. In this region, the new case detection rate has been declining in the last decades. This large and detailed dataset, in combination with our model, is used to investigate six mechanisms for heterogeneity of leprosy susceptibility. We assess the extent to which the distribution of cases among households can be explained by different mechanisms, with the ultimate goal of identifying the most likely ones.

Methods

Modeling leprosy and a household-structured population

We used microsimulation modeling, a technique in which life histories of fictitious individuals are simulated. Individual humans are the unit of modeling, and dynamics at the population level are obtained by aggregation of all individuals. Microsimulation has been employed for studies of infectious diseases with complex natural histories or complex patterns of individual contacts, e.g. helminthic parasites[74], sexually transmitted diseases[75, 57], malaria[76], influenza[77], and bovine tuberculosis[78]. To reduce the computation time of our microsimulation model, we made use of a recently developed method which increases the variation of the model outcomes, but gives a good approximation of the average outcome.[58]

Our model, called SIMCOLEP, simulates the spread of *M. leprae* in a population divided into households, and the development of leprosy by infected individuals. The model is based on and parameterized for the population[53] and leprosy epidemiology[37] in Nilphamari and Rangpur, Bangladesh. For a full description of

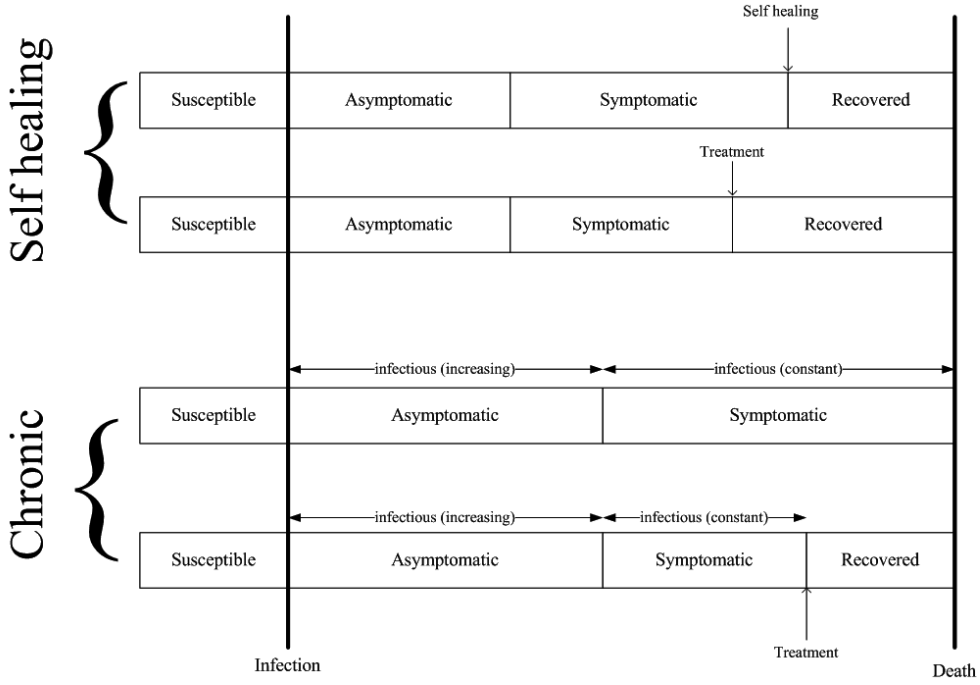

Figure 4.1: Natural history of infection from birth until death, for self-healing and chronic leprosy in the model. Both types of leprosy, self-healing and chronic, start in a susceptible state. Self-healing enters an asymptomatic state, progresses to the symptomatic or clinical state, is followed by self-healing or treatment, and finally transitions to the recovered state. The chronic form enters a different asymptomatic state after infection. Here, the infectivity, i.e. the probability of transmission during an adequate contact, increases with the duration in this state. When progressing to the symptomatic state, the infectivity reaches the maximum and remains constant. The individual will stay in this symptomatic state until death unless treatment is provided. Treatment results in a transition to the recovered state, in which the individual is no longer infectious.

SIMCOLEP and details of parameterization, see Chapter 2.

Demography is described by birth, death, and movement between households. A life table determines the life span of an individual. At birth, individuals are placed in the household of their mother, and individuals can move from one household to another existing or newly-created household during their lifetime. Individuals move at marriage, or during adolescence.[53]

Transmission occurs due to direct contact with infectious individuals. An infectious individual makes infectious contact with random individuals in the population at rate c_{pop} (contacts per year), multiplied by the probability of infection during a contact, i.e. the infectivity. Additionally, within a household containing one or more infectious individuals, each susceptible household member is infected at the minimum of times until an infectious contact from each infectious individual in the household. The timing of these infectious contacts is determined by the rate c_{hh} (contacts per year), and the infectivity. These two contact rates, c_{pop} and c_{hh}, are estimated by fitting the model to the data.

The natural history of the infection, schematically shown in Figure 4.1, is modeled following the model of Meima *et al.*[50]. Only susceptible individuals can become infected. We model two types of leprosy: either self-healing or chronic. After acquiring infection, the individual enters the asymptomatic state. Chronic infection will later progress to the symptomatic state, remaining until the individual dies or is treated. The chronic infection is infectious during both the asymptomatic and symptomatic states, with infectivity increasing linearly during the asymptomatic state. Together with the contact rates, c_{pop} and c_{hh}, the infectivity determines the rate at which new infectious contacts are made. Self-healing infections are never infectious, and proceed to the recovered state at the end of the symptomatic period. Both chronic and self-healing leprosy can be detected while symptomatic, subsequently treated, and cured.

We mimic the leprosy situation in the Nilphamari and Rangpur districts and thus also the control programs. Treatment becomes available in 1970, after which the average detection delay decreases from 12 years to 2 years in 1990.[3] Treatment in 1970 starts with dapsone monotherapy and is gradually replaced by multi-drug therapy (MDT) since 1985. MDT is fully implemented by 1990. The relapse rate decreases from 0.015 to 0.001 per year.[5, 63] From 1990 onwards, household members of newly detected patients are examined. Vaccination with Bacillus Calmette-Guérin

Table 4.1: Description of the six mechanisms determining the heterogeneity in susceptibility.

Mechanism	Description
Random	Equal probability for each individual, i.e. random allocation of susceptibility
Household	Random sample of individuals in randomly selected households (25% of all households)
Dominant	A dominant gene inherited from one or both parents
Recessive	A recessive gene inherited from both parents
Household & dominant	50:50 distribution of susceptibility by: 1. A dominant gene inherited from one or both parents or 2. A random sample of individuals in 25% randomly selected households
Household & recessive	50:50 distribution of susceptibility by: 1. A recessive gene inherited from both parents or 2. A random sample of individuals in 25% randomly selected households

(BCG) is protective against leprosy with a protective effect of 60%.[64, 15] BCG vaccination begins in 1974 with an initial coverage of 40%, rising to 80% in 1990[65].

Scenarios for heterogeneity of susceptibility in the population

We model a population in which a small fraction (5%, 10%, or 20%) is susceptible to leprosy. The majority of the population is not susceptible; these individuals do not develop symptoms and are never infectious. Allocation of susceptibility and the type of leprosy (self-healing or chronic) follows one of six mechanisms, which will be explained in more detail below, and is summarized in Table 4.1. In total, 18 scenarios - i.e. six mechanisms multiplied by three fractions of susceptibles - are fitted to data.

The simplest mechanism causing heterogeneity in leprosy susceptibility is random distribution of susceptibility over the population. We will indicate this mechanism with "*Random*". In the second mechanism, indicated by "*Household*", the inhabitants can be susceptible in 25% of the households[62] due to a common factor within

their shared household, such as poverty. Not all members of a susceptible household are susceptible, allowing for variation within households. The fraction of susceptibles within a household, multiplied by the 25% of households yields the total fraction of susceptibles in the population. For both the *Random* and the *Household* mechanisms, 80% of susceptibles display self-healing leprosy (determined by chance), and the remaining 20% develop the chronic type. The third and fourth mechanisms are genetic: Mendelian inheritance of one gene determining leprosy susceptibility, and a second gene determining leprosy type (self-healing or chronic). We consider two mechanisms where either both genes are dominant ("*Dominant*"), or both genes are recessive ("*Recessive*"). Finally we considered two mechanisms in which a household factor is combined with a dominant or a recessive genetic factor ("*Household & dominant*" and "*Household & recessive*"). Half of leprosy susceptibility is caused by a genetic mechanism, and the other half is due to living in a susceptible household.[27]

Fitting the model to data

The data used for fitting the model are the new case detection rate (number of new cases per 10,000), the prevalence of cases among contacts for different household sizes, and the prevalence of cases among different classes of relatives.[37] For each combination of the c_{pop} and c_{hh} contact rates within an 11 by 11 parameter grid, we calculate the log-likelihood of the outcomes of 100 simulation runs for the leprosy data in 2003.[37] To determine the parameter values with the highest likelihood, a regression model was fitted to the outcomes of the simulated grid points.[79] New simulations were performed with the most-likely parameter values to determine the detailed outcomes of the model at those parameter values. For each mechanism, simulations were continued until the year 2020 to predict future trends in new case detection. The appendix includes a detailed description of the fitting procedure, and outcomes of the simulations.

Results

Each of the six mechanisms could be fitted to the data for one or more of the fractions of susceptibles in the population (Figure 4.2). The assumed fraction of susceptibles in the population (5%, 10%, or 20%) determines, to a large extent, the value of the population contact rate, c_{pop}. This rate plays the predominant role in fitting the new case

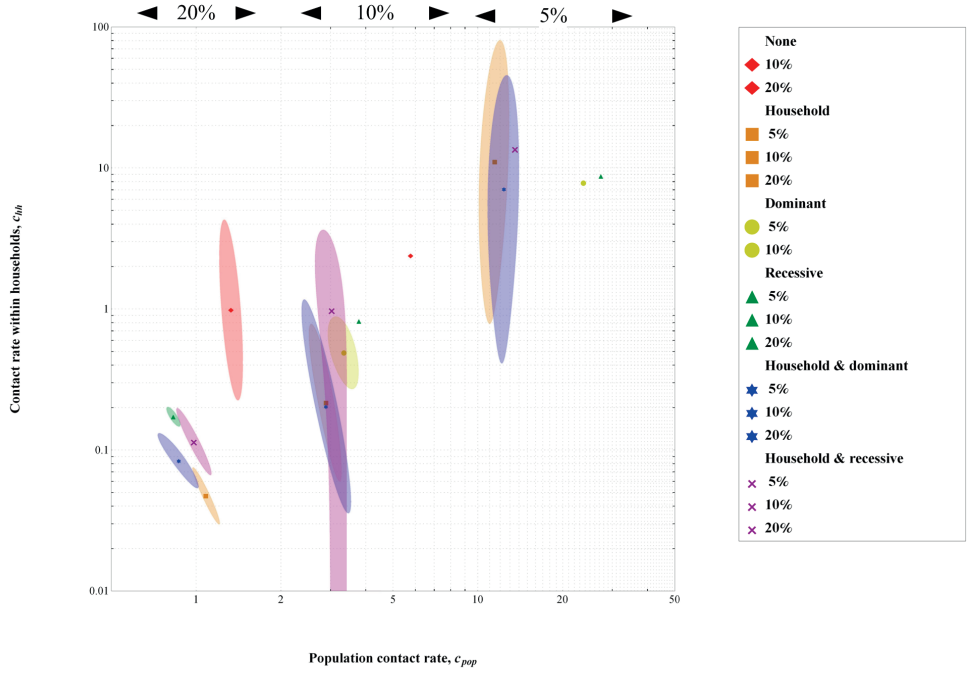

Figure 4.2: Best-fitting parameter combinations for the rate at which infectious contact is made in the population (contacts per year), c_{pop}, and the contact rate within a household (contact per year), c_{hh}, for six mechanisms of heterogeneity in leprosy susceptibility and three fractions of susceptibles. The markers indicate the best fit for each scenario. The shaded areas in the same color indicate the area in which the fit did not differ from the overall best fitting scenario ($P > 0.01$); not all mechanisms had an area with $P > 0.01$. The mechanisms *Random* (5% susceptibles) and *Dominant* (20% susceptibles) could not be fitted to the data, and are thus not shown.

detection data (data not shown). Two scenarios, the *Random* mechanism with 5% susceptibles in the population, and *Dominant* with 20% of the population susceptible, could not be fitted to the data. We observed that for *Random*, the within-household transmission rate, c_{hh}, and the contact rate in the population, c_{pop}, are high compared to the other mechanisms in which susceptibility is clustered within households (Figure 4.2). This result demonstrates an amplifying effect of clustering of susceptibility. More details of the fitting including figures of the simulations can be found in the appendix. Even though the mechanisms provide a comparable overall fit to the data, there are substantial differences in which aspects of the data are fitted best (Figure 4.3). For example, the prevalence among contacts by household size is similar for all household sizes in the *Random* mechanism, while the pattern for *Household* is skewed to low household size, and the genetic mechanisms show a peak at households of size six (Figure 4.3B). The distribution of cases among types of relationships also displays marked differences (Figure 4.3C). The *Household* mechanism results in a high prevalence among spouses, while the genetic mechanisms underestimate the prevalence among spouses. The genetic mechanisms differ in the prevalence among siblings, children, and parents; the prevalence among siblings is higher for *Recessive* than for *Dominant*. The results of the combined mechanisms are intermediate in comparison with those for the *Household* and genetic mechanisms.

For all six mechanisms, the current decrease in new case detection of leprosy is predicted to continue over the next decades (Figure 4.4). The decrease is slowest for both genetic mechanisms and fastest for *Household* and *Random*. The mechanisms that combine *Household* and the genetic mechanisms take an intermediate position.

Discussion and conclusions

Different mechanisms for heterogeneity of leprosy susceptibility can explain the observed clustering in household contacts of leprosy patients. The fit to aspects of the data - new case detection rate, household size, or relationship - depends on the assumed mechanism for heterogeneity in leprosy susceptibility. The predicted future decline in the new case detection rate also depends on these mechanisms. For this study, we had access to a large and detailed data set on clustering of leprosy within households,[37] and data from the same region providing essential information about household composition.[53] We used these data to quantify our microsimulation

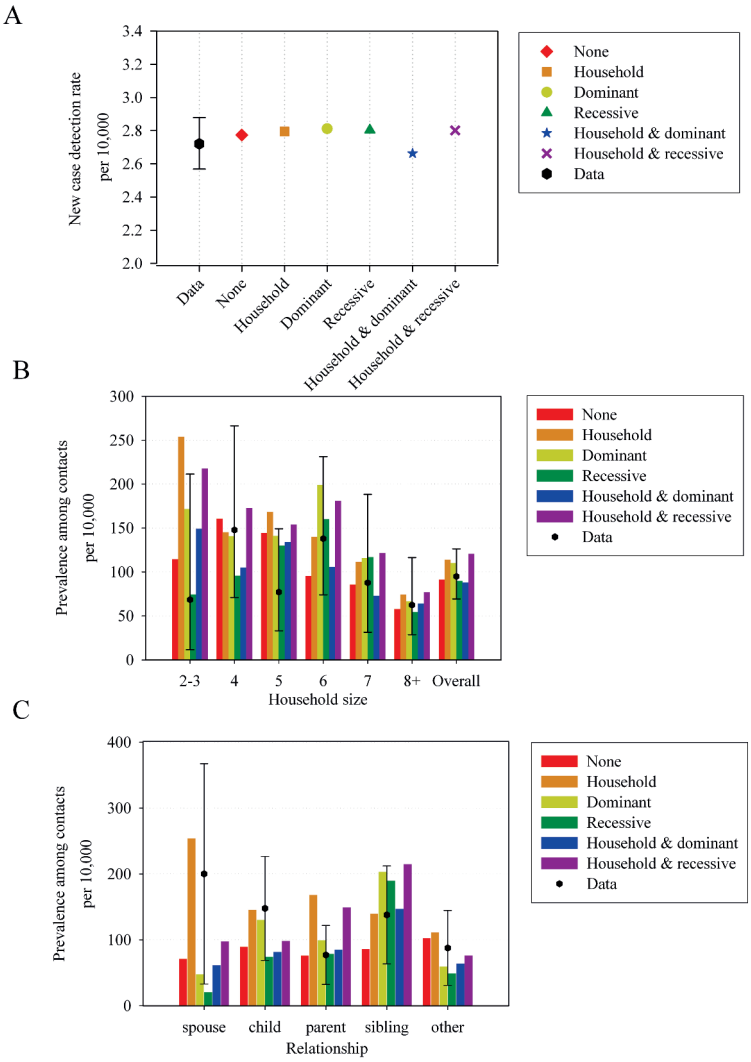

Figure 4.3: Comparison of model output with observations for six mechanisms of heterogeneity in leprosy susceptibility for best fitting percentage of susceptibles (see text). (A) New case detection rate per 10,000 inhabitants. The observed detection rate in 2003 is shown on the left, with 95% confidence interval. (B) Prevalence of leprosy among previously undiagnosed contacts of leprosy patients by household size. (C) Prevalence of leprosy among previously undiagnosed contacts of leprosy patients by relationship to the index patient.

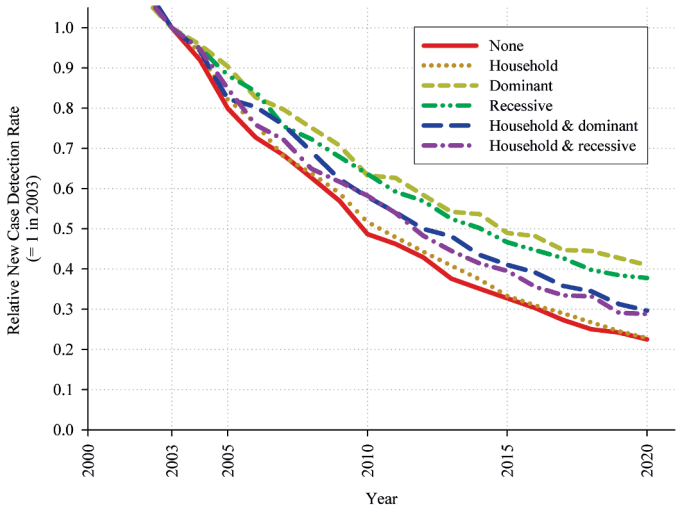

Figure 4.4: Trend in decline of the leprosy new case detection rate, relative to the new case detection rate in 2003 (value is 1 in 2003). The assumed fraction of susceptibles is 20% for *Random* and 10% for the other five mechanisms.

model. However, even with this large and detailed data set, we could not determine the most likely mechanism responsible for the heterogeneity of leprosy susceptibility, or even exclude one of the hypothesized mechanisms.

Our model shows that not assuming an explicit mechanism for susceptibility (*Random*) requires that both transmission parameters are much higher than for the other mechanisms. A short time until infection within household, i.e. a high c_{hh}, means that most susceptible household contacts will be infected relatively quickly after becoming a household contact. Without a mechanism that clusters susceptibility in a household, a high probability of infecting susceptible household contacts is needed to obtain the appropriate number of household contacts with leprosy. For the *Random* mechanism, c_{pop} is substantially higher than for the other mechanisms, which is in concordance with the existing theory that clustering of susceptible individuals in households increases the endemic level of infectious diseases with an equal transmission rate.[46]

Differences in the more detailed model output (Figure 4.3) give additional insight into the behavior of the assumed mechanisms for heterogeneity of leprosy suscep-

tibility. The six mechanisms differ in the distribution of cases over the household sizes. For the *Household* scenarios, relatively more cases occur in these small households (Figure 4.3B), as an individual may become susceptible when moving from a non-susceptible household to a susceptible household. Newly created households are small, and usually consist of a recently married couple. The move to a susceptible household after marriage is also reflected in the prevalence among spouses (Figure 4.3C).

In contrast, the disease prevalence peaks in moderately large households for the genetic mechanisms (Figure 4.3B). For these genetic mechanisms, the probability of having (related) susceptible housemates in small houses is small, while for larger households many inhabitants are related (siblings, children etc.), and the probability of susceptible housemates is high. Genetic mechanisms tend to underestimate the observed prevalence among spouses. This might be explained by marriage within the extended family, which occurs frequently in many cultures, but which has not been included in our model. The fit to the prevalence among spouses improves when assuming a mix of genetic and household factors responsible for leprosy susceptibility (i.e. *Household* & *Dominant* or *Household* & *Recessive*). Combining the scenarios produces results between the *Household* and genetic mechanism outcomes, with overall good fit, perhaps suggesting that multiple factors determine susceptibility to leprosy. We have fixed the contributions of each mechanism to 50% *Household* and 50% genetic[27], but with even better and more detailed data it may be possible to estimate these contributions more precisely in the future.

In the study area[37], the new case detection is declining, which is likely to continue in the coming years according to our predictions (Figure 4.4). However, the speed of decline will depend on the assumed heterogeneity mechanism. The speed of decline is observable in the coming decade, and will thus provide a clue to the underlying mechanism. Somewhat surprisingly, the model predicts the fastest decline for both the *Random* and *Household* mechanisms. These mechanisms differ considerably; the *Random* susceptibility is not clustered in households by an explicit mechanism, while the *Household* mechanism strongly clusters susceptibility. These equally fast declines are explained by our choice of 20% susceptibles in the population for *Random*, whereas we chose 10% for the other mechanisms. The difference in speed of decline between the *Household* mechanism and the genetic mechanisms can be explained by the consequences for contact tracing, which, together with self-reporting, is the only

way to detect leprosy in the model. For example, while the genetic mechanisms have a higher prevalence among siblings than the non-genetic mechanisms, these siblings will marry other people and form a household of their own, possibly escaping detection. Furthermore, the *Household* mechanism predicts a high prevalence among spouses, who are likely to be picked up by contact tracing.

In conclusion, in this study we have demonstrated that analysis and modeling of a large and detailed data set on contacts of leprosy patients could not unequivocally reveal the mechanism for the heterogeneity in leprosy susceptibility that is responsible for the clustering of the disease in households. However, future trends in new case detection can provide clues to determine the most likely candidate.

Acknowledgements

The discussion with Dr. David Pahan and Mr. Sumanto Chowdhury on the field situation and history of leprosy control in Nilphamari and Rangpur (Bangladesh) has helped us very much in designing and parameterizing our model. We thank Dr. Hans Moet for the use of his data on contacts of leprosy patients.

Appendix: Estimation of contact rate parameters, c_{pop} and c_{hh}

Likelihood functions

The two contact rates, c_{pop} and c_{hh}, were estimated by fitting the model to data from the DBLM registers in Nilphamari, and a study among contacts of leprosy patients by Moet *et al.*[37]. The model was fitted to three aspects of the data: (1) new case detection in 2003, (2) prevalence among contacts by 6 household size categories, and (3) the distribution of previously undetected cases among household contacts for 5 categories of relationship to the index patient. The microsimulation model produces estimates for each aspect of the data set under different values of c_{pop} and c_{hh}, which are compared to data by a log-likelihood function. The microsimulation model produces a new case detection rate as a function of c_{pop} and c_{hh}, denoted by $\lambda(c_{pop}, c_{hh})$. As matter of convenience, we will drop the notation for simulation outcomes as a function of the contact rates (e.g. λ means $\lambda(c_{pop}, c_{hh})$). In this section we reserve Greek letters for the simulation outcomes and Latin letters for data. The log-likelihood of the observed number of new case detection k is determined assuming a Poisson distribution with simulation outcome rate λ (Equation 4.1).

$$L_{NCDR}(\lambda \,|\, k) = \ln\frac{1}{k!} + k\ln(\lambda) - \lambda \tag{4.1}$$

The second aspect of the dataset determines the fit to the prevalence of previously undetected cases among household contacts. The parameters, α_i, are the simulated rates of the Poisson distribution for the size household size categories: 2+3, 4, 5, 6, 7, 8 or more inhabitants. Variables s_i indicate the observed number of cases for household size category i. The log-likelihood is the sum of Poisson log-likelihoods for all household sizes (Equation 4.2).

$$L_{Hhsize}(\alpha_1 \cdots \alpha_6 \,|\, s_1 \cdots s_6) = \sum_{i=1}^{6}\left(\frac{1}{s_i!} + s_i\ln(\alpha_i) - \alpha_i\right) \tag{4.2}$$

The third aspect determines the fit to the data on 5 categories of relationships to the index patient: spouse, child, parent, sibling or other relationships. The simulated probability for a person of relationship category i of being cases is indicated by π_i. The variables, r_i, give the number of cases in a relation category i. The total number of contacts of a certain relationship category is indicated with n_i. The log-likelihood

is the sum of Binomial log-likelihoods for all relationships (Equation 4.3).

$$L_{relation}(\pi_1..\pi_5 \,|\, r_1..r_5, n_1..n_5) = \sum_{i=1}^{5} \left(\frac{n_i!}{r_i!(n_i - r_i)!} + r_i \ln(\pi_i) + (n_i - r_i)\ln(1 - \pi_i) \right) \tag{4.3}$$

The overall log-likelihood was used to determine the fit of the combination of contact rates. The combination of contact rates with the highest log-likelihood is the best model quantification. The fit to all datasets are combined in the log-likelihood function 4.4. Constant C is the sum of the parts of Equations 4.1 to 4.3 that do not depend on simulation outcomes, only on the data, and are therefore equal for any assumed combination of c_{pop} and c_{hh}. This constant can be ignored for the maximization.

$$\begin{aligned} L(\lambda, \alpha_1 \cdots \alpha_6, \pi_1 \cdots \pi_5 \,|\, k, s_1 \cdots s_6, r_1 \cdots r_5, n_1 \cdots n_5) = C + \\ k \ \ln(\lambda) - \lambda + \\ \sum_{i=1}^{6} (s_i \ \ln(\alpha_i) - \alpha_i) + \\ \sum_{i=1}^{5} (r_i \ \ln(\pi_i) + (n_i - r_i) \ \ln \ (1 - \pi_i)) \end{aligned} \tag{4.4}$$

$$C = \ln \frac{1}{k!} + \sum_{i=1}^{6} \frac{1}{s_i} + \sum_{i=1}^{5} \frac{n_i!}{r_i!(n_i - r_i)!}$$

The log-likelihood ratio is the difference between the values of Equation 4.4 for two different parameters sets obtained from two different models. The log-likelihood ratio times -2 is approximately χ^2-distributed, which can be used to test whether two models are significantly different.

Metamodel

We use a regression model, as metamodel, fitted to the 11 x 11 parameter grid of simulations (Figure 4.5 an 4.6). The regression model is derived for the section of the grid in which the minimum is found. The regression model can be used to determine

the optimal parameter combination. The likelihood ratios were fitted to a polynomial regression model (Equation 4.5).

$$f(c_{pop}, c_{hh}) = b_0 + b_1 \cdot c_{pop} + b_2 \cdot c_{hh} + b_3 \cdot c_{pop} \cdot c_{hh} + b_4 \cdot c_{pop}^2 + b_5 \cdot c_{hh}^2 \qquad (4.5)$$

The regression model Equation 4.5 was estimated for all possible combinations of linear and log-transformed outcomes and parameters. For each scenario, the regression model with the transformations yielding the highest adjusted R^2-coefficient of determination- was used as metamodel. The metamodels were used to determine the best fitting parameter combination. The metamodel is used to find the optimal parameter values and the 95% confidence around such an optimum. Figure 4.5 and 4.6 show the results of the simulation grids, and plots of the metamodels. Thereafter, the log-likelihood was determined by the median of 9 times 100 runs of the simulation model for these parameter combinations (Table 4.2).

Table 4.2: Estimated best fitting parameter combination calculated from the meta-model. The model fits are determined by the median of 9 times 100 runs.

Mechanism	$\mathbf{c}_{pop}$	$\mathbf{c}_{hh}$	**Model fit**			**Total fit**
			L_{NCDR}[a]	L_{Hh}[b]	$L_{relationship}$[c]	L
5% susceptibles						
Random[d]	-	-	-	-	-	-
Household	11.50	11.07	1.1	2.3	13.1	16.5
Dominant	23.10	11.27	0.1	7.9	34.7	42.8
Recessive	27.36	8.76	4.1	10.2	38.3	52.6
Household & dominant	12.49	8.96	0.0	5.3	16.1	21.4
Household & recessive	13.57	13.70	1.4	8.2	17.8	27.5
10% susceptibles						
Random	5.70	2.44	0.5	19.3	28.5	48.4
Household	2.90	0.22	2.1	6.7	6.6	13.4
Dominant	3.35	0.49	1.3	5.8	13.0	20.0
Recessive	3.79	0.82	1.1	5.0	23.0	29.1
Household & dominant	2.90	0.20	0.5	6.3	7.4	11.4
Household & recessive	3.03	0.98	0.0	4.9	8.7	13.7
20% susceptibles						
Random	1.33	0.98	0.4	5.0	7.0	12.4
Household	1.08	0.05	3.5	6.5	8.9	18.9
Dominant[d]	-	-	-	-	-	-
Recessive	0.83	0.17	0.0	4.7	17.6	27.5
Household & dominant	0.87	0.08	0.1	3.6	10.8	14.5
Household & recessive	0.98	0.11	3.5	3.7	9.2	16.4

[a] New Case Detection Rate, Equation 4.1 minus constants.
[b] Household size, Equation 4.2 minus constants.
[c] Relationship with patient, Equation 4.3 minus constants.
[d] Only very poor fits.

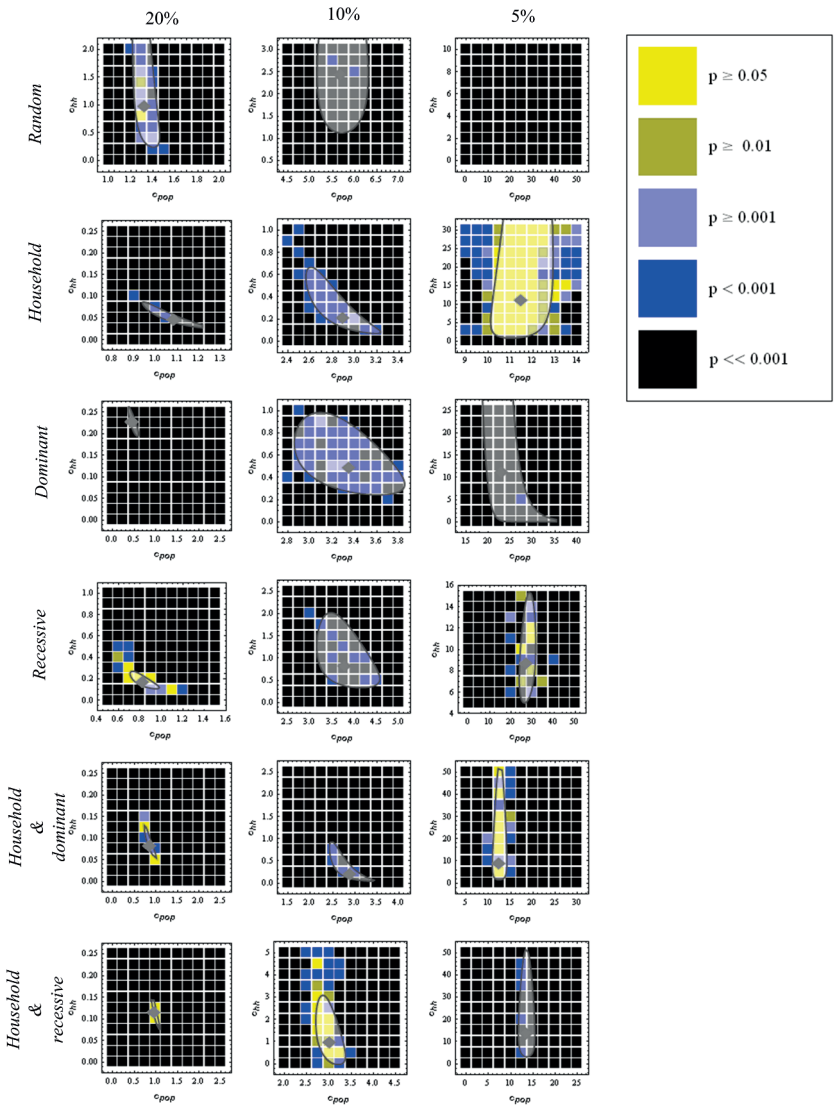

Figure 4.5: Fit to data. Simulated values and meta-models for all 18 scenarios. The color of the simulated grid points indicates the difference with the log-likelihood of the data. The grey diamond indicates the location of the best fitting parameters values resulting from the minimum of the metamodel. The surrounding thick bordered gray area gives the 95%-confidence area of the parameters. For each panel, the color of the simulated grid points indicates the difference with the minimum of the metamodel (i.e. the value for the parameter values indicated by the gray diamond).

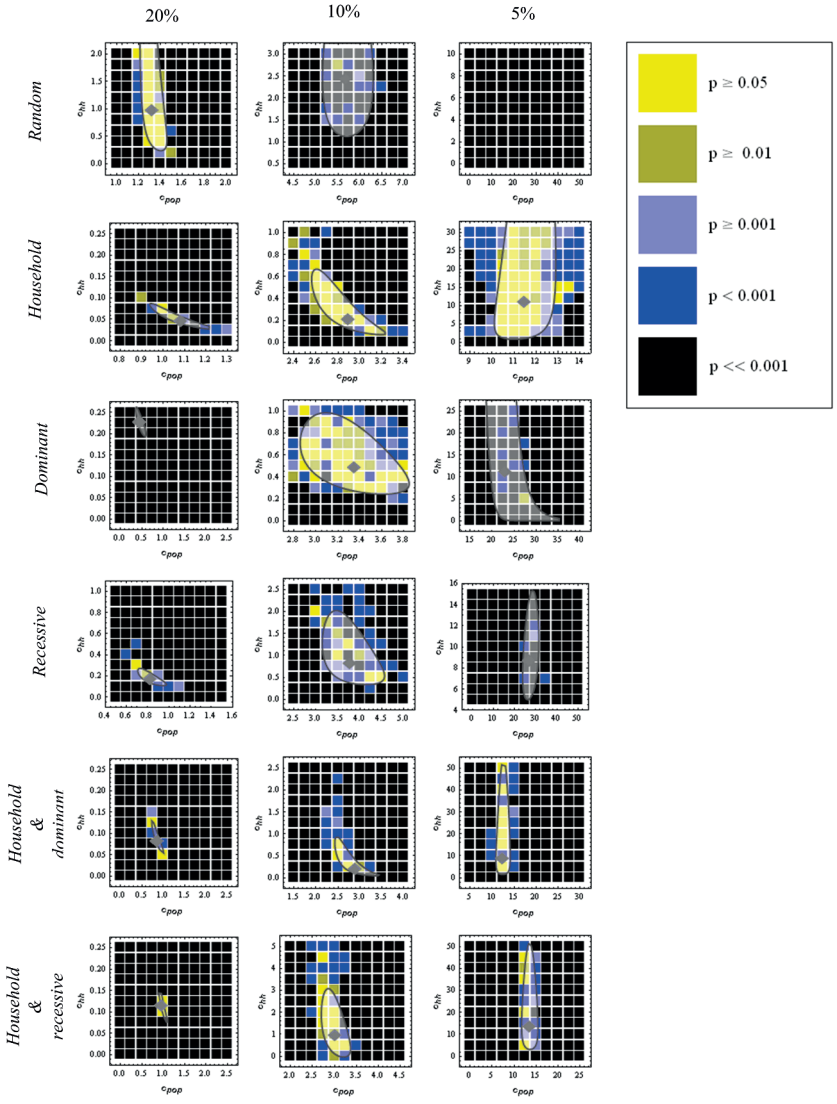

Figure 4.6: Fit relative to estimated best fit. Simulated values and meta-models for all scenarios. The color of the simulated grid points indicates the difference with the minimum of the best of all metamodels. The gray diamond indicates the location of the best fitting parameters values resulting from the minimum of the metamodel. The surrounding thick bordered gray area gives the 95%-confidence area of the parameters.

5

The long term effect of current and new interventions on the incidence of leprosy: a modeling study

E.A.J. Fischer, S.J. de Vlas, J.D.F. Habbema, J.H. Richardus
submitted

Abstract

Background Although the number of newly detected cases of leprosy has decreased globally, a quarter of a million new cases are detected annually, and eradication remains far away. Current options for leprosy prevention are tracing individuals in contact with patients and the BCG vaccination for infants. Future options may include chemoprophylaxis and early diagnosis of subclinical infections. This study compared the predicted trends in leprosy case detection for seven intervention scenarios in an area of Bangladesh, where the new case detection of leprosy has been declining since mid 1990's.

Methods and principal findings Seven leprosy intervention scenarios were investigated with a microsimulation model to predict future leprosy trends. The baseline scenario consists of passive case detection, multi-drug therapy, contact tracing, and BCG-vaccination of infants. The remaining six scenarios were modifications of the baseline, as follows: no contact tracing; with chemoprophylaxis; with early diagnosis of subclinical infections;replacing the BCG vaccine with a new tuberculosis vaccine

ineffective against *Mycobacterium leprae* ("no BCG"); no BCG with chemoprophylaxis ; no BCG with early diagnosis. Without contact tracing, the model predicted an initial drop in the new case detection rate due to a delay in detecting clinical cases among contacts. Eventually, this scenario led to new case detection rates higher than the baseline program. The model predicted that both chemoprophylaxis and early diagnosis would prevent new cases from due to a reduction of the infectious period of cases by detection or cure of these cases, while being subclinical. Also, replacing BCG would increase the new case detection rate of leprosy, but this effect could be offset with either chemoprophylaxis or early diagnosis.

Conclusions Our results showed that leprosy incidence in Bangladesh would be strongly reduced by good BCG coverage and contact tracing with additional early diagnosis followed by treatment of subclinical infections, or additional chemoprophylaxis among household contacts. This demonstrates the importance of developing an effective test for identifying subclinical infections and studies on the implementation of chemoprophylaxis.

Author Summary

Leprosy is a contagious disease that remains prevalent, despite the declining incidence worldwide over the last century. With approximately 250,000 new cases detected annually, leprosy is far from being eradicated. Leprosy can be treated with drugs after disease detection. Some cases can be prevented with a tuberculosis vaccine (BCG) that cross-reacts with the bacteria that causes leprosy. Furthermore, preventive drugs can reduce the number of new cases among people in contact with infectious patients, but this strategy has not yet become established in common practice. Also, a new test is under development for the detection of infections before the appearance of symptoms. In this study, we used a computer-model to assess the effectiveness of different potential leprosy control programs. Our results showed that the decline in incidence of leprosy would slow down or hold with the introduction of a new tuberculosis vaccine that is ineffective against leprosy. However, this effect could be offset with the implementation of effective tests for early diagnosis or the routine administration of preventative drugs to contacts of patients.

Introduction

The global new case detection rate of leprosy has dropped tremendously during last century, but with approximately 250,000 new cases detected annually, leprosy is far from being eradicated [19]. Currently, the primary strategy for controlling leprosy is detection and treatment with multidrug therapy (MDT). Although new interventions are under development, their potential impact on disease control is unknown. Recent clinical trials have indicated that a single chemoprophylactic dose of rifampicin given to individuals in contact with patients newly diagnosed with leprosy could protect these contacts against leprosy disease [17]. Furthermore, new tests are under development for identifying subclinical infections [24]. However, other recent developments are creating a cause for concern. For example, the integration of leprosy control activities into general health care programs has led to the cessation of actively finding cases and tracing contacts in many countries. Consequently, diagnosis is delayed; thus, patients have longer infectious periods, and more people in contact with patients will become infected. As another example, a new vaccine may replace the Bacillus Calmette-Guérin (BCG) tuberculosis vaccine, given to infants to prevent tuberculosis, but, which also protects against leprosy [3, 15] might in the future be replaced by more specific tuberculosis vaccines are under development [80] that do not induce cross-immunity to the bacteria responsible for leprosy, *Mycobacterium leprae*. Therefore, the effects of new interventions strategies should be tested in the context of other developments. Although the short-term effectiveness of new interventions can be assessed in trials, extrapolation to long-term effectiveness in the general population is difficult, due to the non-linear behavior of transmission dynamics. Dynamic simulation models are necessary to assess the impact of different intervention strategies on future trends in the new case detection rate of leprosy. We have developed a microsimulation model that simulates the transmission and control of leprosy (the SIMCOLEP model) taking into account the population structure of households [81]. The model is quantified by data from northwest Bangladesh [53, 37, 82]. This is an area with a well organized control program in which the new case detection has been decreasing since the mid-1990's. The new case detection rate is however one of the highest in Bangladesh. In this study, we used the model to predict future trends in the detection of new cases of leprosy over the next 50 years to explore the potential impact of seven different intervention strategies.

Methods

The model

The microsimulation model simulates the life history of fictitious individuals. These individuals are members of a household that is formed, changes, and dissolves during the simulation, based on the following rules: Individual household movement occurs during adolescence and after marriage. Some married couples start living in the household of the parents-in-law, and will form their own separate household after on average 12 years. The life span of individuals is drawn from a life-table at birth; the number of newborn individuals maintains the simulated population growth rate equal to the observed population growth rate; newly born individuals are placed into the household of their mothers; and mothers are drawn from the population of married women and weighted with an age-dependent fertility function. An individual that is susceptible to leprosy is defined as an individual that developed leprosy sometime during their lifetime, after acquiring the infection.The large majority (say 80-95%) of the population is assumed not to be susceptible to leprosy [2, 3, 4].The remaining 5-20% of the population is susceptible. For these individuals is assumed that 80% undergoes a self-healing infection and is never infectious to other individuals, and only 20% will become chronically infected and infectious [3]. The mechanisms underlying leprosy susceptibility is currently unknown [81]. Therefore, the model tested hypotheses for six different mechanisms: *Random* (no mechanism, but each individual has a fixed probability of being susceptible); *Household* susceptibility (all susceptibles live in a fraction of households, within these susceptible households a fraction of inhabitants is susceptible); *Dominant* (susceptibility was inherited by a dominant gene); *Recessive* (susceptibility was inherited by a recessive gene); *Household & dominant* (50% of susceptibility was determined by the *Household* and 50% by a *dominant* gene); *Household & recessive* inheritance (50% of susceptibility was determined by the *Household* and 50% by a *recessive*). As described in a previous paper [81], the model was unable to identify one single mechanism that could best explain the observed data. However, for *None* it turned out that 20% susceptibles provided the best fit, whereas this was 10% for the other mechanisms; for *Household* this 10% was established by assuming 25% of the households containing 40% susceptible individuals. The predicted trends in leprosy new case detection rates are reported here as the lowest, highest, and medians of the six hypothesized mechanisms

for each intervention scenario. The quantification of the model is based on the leprosy situation in 2003 and the control program of the last decades in the Nilphamari and Rangpur districts of Bangladesh [81]. This control program consisted of passive case detection, with in 2003 an average detection delay of 2 years, treatment with MDT, and active tracing of people in contact with patients. In this area, BCG vaccination was routinely given to newborn infants. Since the introduction of the BCG vaccination in 1974, the coverage had gradually expanded to 80% in 1990 and remained at that level in 2003 [65]. BCG had a protective effect of 60% [15]. For a detailed description of the model, see Chapter 2.

Intervention strategies

In the study we considered seven potential intervention scenarios for the future control of leprosy. The baseline scenario was the current leprosy control program in the Bangladesh study area, as described above. The other scenarios were modifications of the baseline control program, as follows: 1. No contact tracing; 2. With a single chemoprophylactic dose of rifampicin, which cured 50% of subclinical cases, for each individual in contact with a leprosy patient [17]; 3. With diagnosis of subclinical cases with a sensitivity of 70% [22] followed by effective treatment; 4. All newly born infants in the population receive a new tuberculosis vaccine that is ineffective against leprosy instead of BCG (no BCG); 5. The combination of no BCG and chemoprophylaxis; and 6. The combination of no BCG and early diagnosis with effective treatment. The intervention scenarios were calculated for immediate implementation.

Results

Table 5.1 shows the predictions of the new case detection rates at 25 years after the initiation of each intervention. Under the baseline control program, the different mechanisms that determined susceptibility showed up to three-fold differences in the predicted number of cases per 100,000 people. In Figure 5.1, the trends in the new case detection rates over 50 years are shown for all seven interventions under the assumption of the Household susceptibility mechanism. The other mechanisms give qualitatively comparable trends (see appendix); that is, when the intervention scenarios were ordered by the amount of reduction in new case detection rates, the order was identical for all mechanisms.

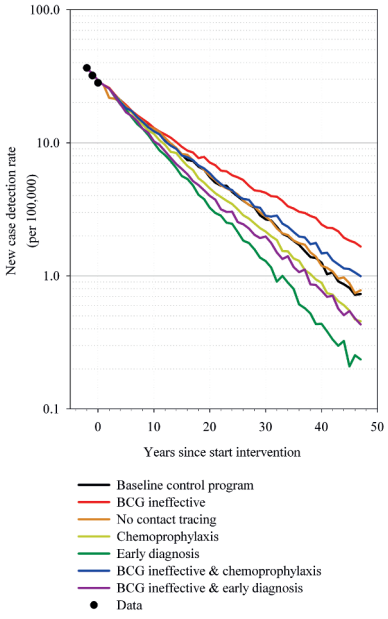

Figure 5.1: Predicted decline of the new case detection rate with seven intervention scenarios. The mechanism of susceptibility was "*Household*" in this example. The observed new case detection rates in the Nilphamari and Rangpur districts of Bangladesh for three years before starting the interventions are shown in black dots (Data).

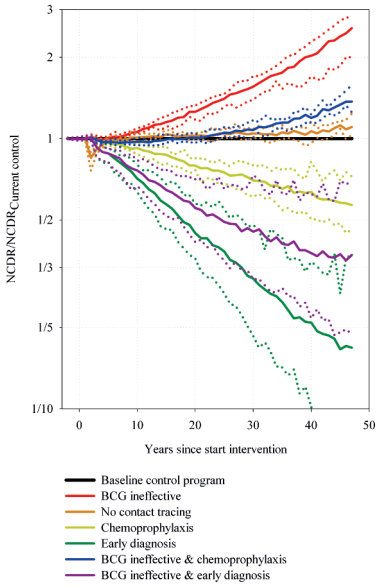

Figure 5.2: Predicted new case detection rates for six intervention scenarios compared to the baseline control program. The relative difference in new case detection rates is shown in comparison with the baseline leprosy control program (black line). For each intervention scenario simulations with different mechanisms of susceptibility to leprosy, as defined in chapter 4 are performed. For each intervention scenario, dotted lines show the smallest and largest deviations from the baseline control program; the same mechanisms for susceptibility were associated with the maximums and minimums of all scenarios. The solid line shows the median of all susceptibility mechanisms.

Table 5.1: Predicted new case detection rates (per 100,000) at 25 years after the introduction of the indicated intervention scenario for size mechanisms of leprosy susceptibility.

Intervention	**Mechanism determining susceptibility** *					
	Random	***Household***	***Dominant***	***Recessive***	***Household & dominant***	***Household & recessive***
Baseline control	3.4	4.0	10.4	8.2	5.6	4.6
No contact tracing	3.8	4.1	10.5	8.5	5.5	4.8
Chemoprophylaxis	2.8	3.2	6.9	5.9	4.1	3.4
Early diagnosis	1.1	2.1	2.7	2.6	2.1	2.0
No BCG	4.6	5.5	15.0	11.9	7.6	6.4
No BCG & Chemoprophylaxis	3.6	4.0	10.5	8.5	5.9	5.1
No BCG & Early diagnosis	1.2	2.5	3.7	3.7	2.9	2.8

* see main text for description of these mechanisms.

Either the cessation of contact tracing or the replacing BCG vaccine by a tuberculosis vaccine ineffective for leprosy (no BCG) would have detrimental effects on the rate of decline in leprosy (Figure 5.2). Twenty-five years after introduction of the ineffective vaccine (no BCG), the incidence of leprosy was predicted to increase by a factor of approximately 1.5 over the baseline(see Table 5.1).The cessation of contact tracing was predicted to have a smaller impact, with a marked drop in detection of new leprosy cases during the first few years. This sudden drop was due to the reduced number of examinations of people in contact with patients; thus, these cases would not be detected until later, through passive detection (self reporting).

Both chemoprophylaxis and early diagnosis were predicted to have substantial effects on the new case detection of leprosy (Figure 5.2). With no BCG, we showed that chemoprophylaxis would partially compensate for the predicted increase in new case detection rates. Furthermore, early diagnosis was predicted to more than compensate for the adverse effects of a leprosy-ineffective tuberculosis vaccine, and reduce the rate of new case detection compared to the baseline. The effects were more promising in the ongoing presence of the BCG vaccine. Under those conditions, at 25 years after the introduction of chemoprophylaxis, the new case detection rate was predicted to

be 25% lower than baseline control. Moreover, with the introduction of early diagnosis, the new case detection rate was predicted to halve the baseline incidence after 25 years (Table 5.1). Early diagnosis of infection allows the detection of subclinical cases, which need to be treated before the appearance of symptoms. The introduction of early diagnosis would increase the total number of detected cases (subclinical + clinical) in the first 18 years(see gray dashed drop line in Figure 5.3); but, over time, the number of new cases would finally fall below the number detected in the baseline control program (Figure 5.3). Figure 5.3 also shows the new cases detected under the chemoprophylaxis intervention strategy plus the subclinical cases that were cured by the chemoprophylactic intervention. After approximately 10 years (see gray dashed drop line in Figure 5.3) , the total number of newly detected cases + cured cases was lower than the number of newly detected cases under the baseline control program.

Discussion

This study used a microsimulation model to predict the future outcomes of the leprosy control program of Nilphamari and Rangpur districts in Bangladesh. This baseline program, from which very detailed information is available, consists of passive case detection, treatment with MDT, contact tracing, and infant BCG vaccination. The predicted rate of decline in new case detection would depend on the intervention scenario chosen over the next 50 years. If early diagnosis or chemoprophylaxis were added to the baseline program, a considerable reduction in the new case detection rate is predicted. Furthermore, these interventions were predicted to compensate for the adverse effect of replacing BCG by a leprosy-ineffective tuberculosis vaccine.

The quantification of the model was based on a large amount of detailed data from an area in Bangladesh [37]. The chemoprophylaxis intervention data were also based on this population [17]. Our microsimulation modeling approach was able to capture individual (stochastic) processes. Complex infection dynamics could thus be simulated on an individual basis. Aggregating the model outcomes enabled the analysis of trends at the population level.

The primary concern of this study was to estimate the relative, not the absolute, impact of the various interventions and take into account alternative hypotheses for mechanisms of susceptibility to leprosy. We compared the results based on different hypothesized mechanisms for susceptibility, because each of these mechanisms could be valid [81]. The quantitative results were sensitive to the mechanism chosen. Nevertheless, when the different interventions were ordered by the magnitude of effect, that order was identical for all the mechanisms of susceptibility. Thus, the qualitative results were robust, and suggested this order of effectiveness for the different interventions can be generalized. The current leprosy control program in the Nilphamari and Rangpur districts of Bangladesh is more extensive than usual.

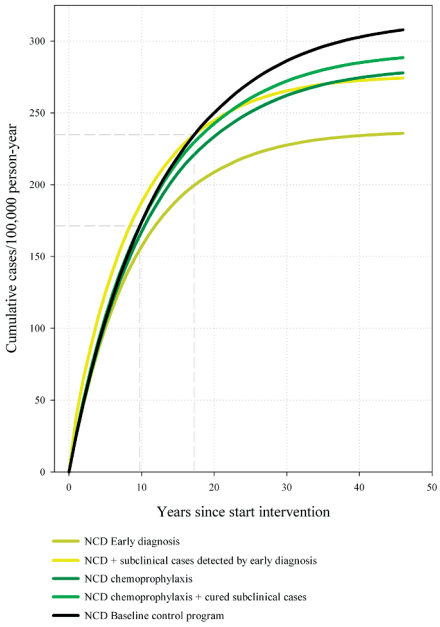

Figure 5.3: Cumulative cases of leprosy per person-year since starting the interventions.

The primary advantage of this program is the active tracing of individuals that had been in contact with patients newly diagnosed with leprosy. This contact tracing is not common among leprosy control programs. Our modelling showed that contact tracing and subsequent treatment of newly found patients could, in itself, contribute to a reduction in the transmission of *M. leprae* in the population. The new interventions chemoprophylaxis and early diagnosis (which necessarily include contact tracing) were predicted to have a clear added impact for leprosy control. We assumed that the effect of chemoprophylaxis with a single dose rifampicin (SDR) could prevent 50% of subclinical infections to develop leprosy. This assumption was based on the outcome of the COLEP trial (ISRCTN61223447) and represented the overall effect of SDR in the contacts. In the trial, this effect of SDR was a 56% reduction in new leprosy cases after two years for all contacts. The effect of SDR, however, varied among the different types of contacts, with a 49% prevention in neighbors, 54% prevention in

household contacts, and 76% prevention in social contacts [17]. Thus, the choice of contacts to be included in contact tracing and subsequent chemoprophylactic treatment is very important. Ideally, it should go beyond the immediate household of the index patient. The choice of the contact 'circle' will likely depend very much on the acceptance of contacts to be involved and the feasibility of running an extended program. Moreover, rather than providing chemoprophylaxis to all, one would prefer to first test for a subclinical infection and then treat individuals appropriately. Our modeling showed that identification and treatment of subclinical infections among household contacts had the largest effect in reducing transmission of *M. leprae* in the population. Part of the better performance of early diagnosis compared to chemoprophylaxis was that the early diagnosis strategy comprised three consecutive annual tests with 70% sensitivity, compared to a single round of rifampicin with a cure rate of 50%. Thus, more subclinical cases could be cured after the early diagnosis than with chemoprophylaxis. Meima et al. (2004) showed that a short detection delay is the key to the success of the current MDT-based leprosy control strategy. Detection of subclinical cases would be a major improvement because it would provide an even shorter detection delay. As shown in Figure 5.3, the detection of subclinical cases also reduced transmission, and the total number of new cases detected (clinical and subclinical) was predicted to eventually fall below the number of new cases detected under the baseline control program. Meima et al. (2004) also showed that the BCG vaccination may have a large impact on the expected incidence of leprosy in the population. The current knowledge about the effect of the BCG vaccination on leprosy [64, 15] strongly supports maintaining the current BCG vaccination practice. Alternatively, a leprosy-specific compound could be added to an improved tuberculosis vaccine in leprosy endemic areas.

Conclusions

Our results predicted that the leprosy incidence would be substantially reduced with good BCG vaccine coverage, and the combined strategies of contact tracing, early diagnosis, and either treatment of infection or chemoprophylaxis among household contacts. To effectively interrupt the transmission of *M. leprae*, it is crucial to continue developing chemoprophylaxis treatments and an effective test for diagnosing subclinical infections.

Acknowledgments

The quantification of the intervention strategies were based on discussions with Dr. Linda Oskam of KIT in Amsterdam (The Netherlands) and Dr. Annemiek Geluk of LUMC in Leiden (The Netherlands). We thank Dr. Bram Meima for his assistance in the construction of the model, and Dr. David Pahan and Mr. Sumanta Chowdhury for discussions on the appropriate parameters for the leprosy and population of Nilphamari and Rangpur districts in Bangladesh.

Appendix

The results for each of the six mechanisms of leprosy susceptibility is given in Figure 5.4. The baseline program (black line) included passive detection, multi-drug therapy, contact tracing, and an infant leprosy-preventative BCG vaccination given at the population level. The other six intervention strategies included the baseline program and, starting in 2003: introduction of a new tuberculosis vaccine ineffective against leprosy replacing BCG (red), no tracing of household contacts (orange), a single chemoprophylactic dose of rifampicin that cured 50% of subclinically infected contacts (yellow), early detection of 70% of subclinically infected contacts in each of 3 consecutive annual examinations (green), chemoprophylaxis plus introduction of a tuberculosis vaccine ineffective against leprosy(blue), and detection of subclinically infected contacts plus introduction of a tuberculosis vaccine ineffective against leprosy (purple). The data for new case detection rates in the Nilphamari and Rangpur districts of Bangladesh for three years before starting the interventions are shown in black dots.

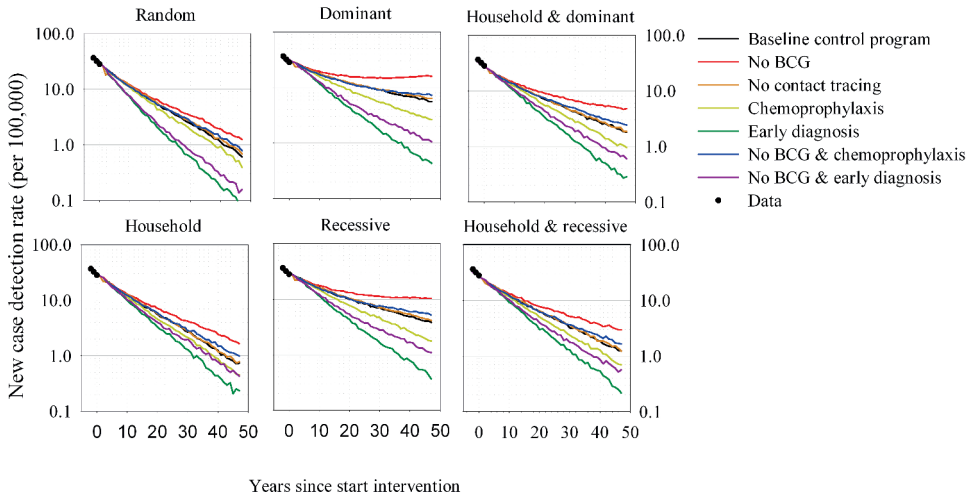

Figure 5.4: Predicted decline of the new case detection rate with seven intervention scenarios and six mechanisms of leprosy susceptiblity.

6

Social distance and spatial distance are not the same, observations on the use of GIS in leprosy epidemiology

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Summary

Contacts of leprosy patients have an higher risk of developing clinical leprosy. Being a contact is defined socially, but with the introduction of GIS in infectious disease epidemiology, it is necessary to relate spatial distance to social distance.

We measured the distances between patients and their socially defined contacts in north west Bangladesh. Contact categories differ in mean distance to the index patients. Sixty seven per cent of the high risk contacts lived within 10 meters, while all low risk contacts lived more than 10 meters from the index patient. Classification based on intervals of spatial distance creates categories that contain contacts of different socially defined categories, illustrated by a category of people living between 10 and 20 meters consisting of 47% of high risk contacts and 52% low risk contacts. Classification of contacts based on the spatial distance, as is done with GIS-techniques, produces other groups than with social definitions.

[1]Authors contributed equally to the manuscript

Short report

Contacts of leprosy patients have an increased risk of developing clinical leprosy themselves compared to non-contacts. Several risk factors add to this increased risk of which contact intensity is one important factor (reviewed in [26]). The contact intensity with patients is described using socially defined distances such as household member, neighbour and social contact.

Remote sensing (RS) and geographical information systems (GIS) are increasingly used in infectious disease epidemiology in general [83], and in recent years introduced into leprosy research as well [32]. GIS techniques are used to classify contact based upon the actual distance - in metres - to an index patient. However, the relation between such a classification based upon the actual distance and socially defined distances such as household member or neighbour are not known. With this short report we want to shed light on this issue.

We firstly studied whether a socially defined group has a certain typical distance, and secondly investigated the quantitative difference between direct (or Euclidean) distance and the walking distance. The latter was done because in the study area people live in small groups of houses (compounds). The houses contain one or several rooms. Some houses contain two separate households in different rooms. These households share a roof, but not the kitchen. A neighbour can live either on the same compound or on the next compound. A neighbour by definition lives under another roof. To take this organization of the houses into account, we investigated the direct distance - as would be done with GIS analysis - and the walking distance, which was defined as the distance an adult would take to walk from one house to the other.

The study was in northwest Bangladesh, which is a highly endemic area for leprosy and densely populated, and was part of a larger study (the COLEP study)[84] . We measured the distance between the houses of patients and the houses of contacts. Contacts were categorized socially based upon the topological position of the house in which they lived, sharing of the kitchen or by the intensity of contact [84]:

1. Those living under the same roof and using the same kitchen (KR)
2. Those living under a separate roof, but using the same kitchen (K)
3. Those living under the same roof, but not using the same kitchen (R)
4. Next-door neighbours (N1)

5. Neighbours of the neighbours (N2)

6. Social contacts, who stay in the same room at least 4 hours day^{-1} for 5 days a week (S)

The COLEP study included 1,037 newly detected index leprosy patients, with a group of on average twenty contacts each. From the index patients we randomly selected 40 patients and their contact groups. Of the selected groups, seven had partially or completely moved since intake into the COLEP study. These groups were excluded from the measurements. The remaining 33 groups contained 758 contacts living in 273 houses. We measured the distance between the front door of the index patients' house and the front door of the houses of contacts. Distances were not measured beyond 100 meters, and for the calculation of the mean distance this cut-off value was used. The results are shown in Table 6.1.

We found that 250 of the 273 houses of contacts (92%) were within the cut off value of 100 meters of the index patient. (Table 6.2) The 8% of contacts outside the 100 meter range were all social (S) contacts. The measurements in Table 6.1 showed an increase in the mean distance for contact categories in the order KR, K, N1, N2, and S (Kruskal-Wallis test for trend, $p < 0.001$). The socially defined contact categories KR and N1 can be grouped into a high risk group based upon the findings of Moet *et al.*[37] (we assume K to be high risk as well, although this was not found in Moet *et al.* because of the small numbers, see [37]). Of the contacts living within 10 m from the index patient, all were within the socially defined high risk group. Yet of the 70 houses in the high risk N1 category, 42 (60%) live beyond 10 m of the index patient. Of the 143 houses in the socially defined low risk group (N2 + S), none live within 10 meters of the index patient. A categorization based upon direct distance could be made, with the distance category "within-10-meters" coinciding largely with the established high risk contact group, and the distance "beyond-10-meters" with the low risk group.

But classification based upon distance is not the same as the socially defined categories. If one would have classified contact by distance categories with several 10 meters intervals, the category 10-20 meters would contain 47% N1, 47% N2 and 5% S contacts (see Table 6.2), mixing groups with different risks as found in [37], possibly resulting in a dilution of risk estimates. It is exactly these kind of classifications that are made in analyses with GIS techniques.

Table 6.1: Risk of leprosy and distance in meters between the front door of an index patient and the front door of contacts for each contact category.

Social distance group	**aOR [1] (95% CI)**	**P [1]**	**Social distance**	**N[2]**	**Distance in meters Mean (95%-CI)[3] Median**	
					Direct	**Walking**
KR	2.44 (1.44-4.12)	*0.001*	KR	28	-	-
K K	1.05 (0.52-2.13)	0.898	K	32	6.0 (5.4-6.7) 5.8	6.0 (5.4-6.7) 5.8
N1 +R [4]	1.69 (1.16-2.47)	*0.007*	N1[5]	70	12.9 (11.0-15.1) 10.9	20.3 (16.3-25.2) 17.6
N2 + S [4]	1	-	N2	88	28.4 (25.6-31.5) 26.5	43.9 (40.1-48.1) 39.8
			S	55	63.9 (52.9-77.1) 51.4	72.0 (63.3-81.8) 76.4

[1] From [37], adjusted for age, sex, WHO leprosy classification of index patient, genetic relation, presence of BGC scar, seropositivity for PGL-I antibodies against *M. leprae*.
[2] Number of measurements in each category.
[3] Mean and 95-% CI were calculated for the log-transformed data. The figures have been back transformed for an easier interpretation.
[4] Contact categories were grouped[37].
[5] There were no R-contacts in the sample of contact groups in this study.

However, the socially defined categorization has its limitations as well. It cannot be ruled out, for instance, that a N1 neighbour living further away has less contact than a N1 neighbour living nearby. So defining contact categories socially may as in Moet *et al.* [37] dilute risk estimates in another way.

The difference in classifying socially or by distance is further illustrated when we consider the measurements for walking distance, which can be related to effort of making contact. The walking and direct distances were equal as long as both houses were situated on the same compound. In this way we could determine that 36% of the N1 lived on the same compound, while all N2 and S lived on other compounds. The N1 group thus is heterogeneous in terms of location on the same compound.

Classifying contact based upon spatial distance is not the same as a classification based upon definitions of social distance. The best classification would render the most

homogeneous groups concerning risk of leprosy. Which one of these classifications is better for leprosy, cannot be determined by these data and is open for debate. Our result can differ when the population is distributed differently over dwelling – e.g. urban areas– or areas with a lower population density. In general our findings show that when contact is categorized either using GIS-techniques or socially, infectious disease epidemiologists should keep in mind that they may be mixing individuals with different contact intensities and thus risk of infection.

Acknowlegdements

We thank the American Leprosy Missions and The Leprosy Mission International for financial support of the COLEP study.

Table 6.2: Comparison of classification by social distance group and spatial distance, with intervals of 10 meters up to 50 meters and than a class of 50 to 100 meters and equal to and beyond 100 meters. Absolute number of houses and rounded percentage of socially defined distance for each actual distance category.

			Direct distance to index patient							
			< 10	10 - 20	20 - 30	30-40	40-50	50-100	= 100	Total
Social distance group	**High risk**	KR	28	-	-	-	-	-	-	28
			(32%)	-	-	-	-	-	-	(10%)
		K	31	1	-	-	-	-	-	32
			(36%)	(2%)	-	-	-	-	-	(12%)
		N1	28	30	11	1	-	-	-	70
			(32%)	(47%)	(24%)	(4%)	-	-	-	(26%)
		Subtotal	87	31	11	1	-	-	-	130
			(100%)	(49%)	(24%)	(4%)	-	-	-	(48%)
	Low risk	N2	-	30	24	16	12	6	-	88
			-	(47%)	(52%)	(64%)	(71%)	(55%)	-	(32%)
		S	-	3	11	8	5	5	23	55
			-	(5%)	(24%)	(32%)	(29%)	(45%)	(100%)	(20%)
		Subtotal	-	33	35	24	17	11	23	143
			-	(52%)	(76%)	(96%)	(100%)	(100%)	(100%)	(52%)
	Total		87	64	46	25	17	11	23	273
	(% of all)		(32%)	(23%)	(17%)	(9%)	(6%)	(4%)	(8%)	(100%)

7

The spatial distribution of leprosy in four villages in Bangladesh: An observational study

E.A.J. Fischer, D. Pahan, S.K. Chowdhury, L. Oskam, J.H. Richardus
BMC Infectious Diseases (2008),Vol. 8:125

Abstract

Background There is a higher case-detection rate for leprosy among spatially proximate contacts such as household members and neighbours. Spatial information regarding the clustering of leprosy can be used to improve intervention strategies. Identifying high-risk areas within villages around known cases can be helpful in finding new cases.

Methods Using geographic information systems, we created digital maps of four villages in a highly endemic area in northwest Bangladesh. The villages were surveyed three times over four years. The spatial pattern of the compounds –a small group of houses – was analysed, and we looked for spatial clusters of leprosy cases.

Results The four villages had a total population of 4,123. There were 14 previously treated patients and we identified 19 new leprosy patients during the observation period. However, we found no spatial clusters with a probability significantly different from the null hypothesis of random occurrence.

Conclusions Spatial analysis at the microlevel of villages in highly endemic areas does not appear to be useful for identifying clusters of patients. The search for clus-

tering should be extended to a higher aggregation level, such as the subdistrict or regional level. Additionally, in highly endemic areas, it appears to be more effective to target complete villages for contact tracing, rather than narrowly defined contact groups such as households.

Background

Identifying individuals with increased exposure to *Mycobacterium leprae,* the causative agent of leprosy, enhances the possibility of prevention or early diagnosis. Several studies have shown that household members and neighbours have an increased risk of leprosy [27, 37, 30], making them desirable targets for interventions such as preventive treatment [16, 37]. A study in Indonesia identified spatial clusters of cases on islands with extremely high incidence [27]. Spatial information can be used to improve the discovery of new cases and other interventions in high incidence areas [85].

In the Nilphamari district in Bangladesh, household members and close neighbours have an increased risk of contracting leprosy when compared with neighbours of neighbours and social contacts [37]. However, new cases among neighbours of neighbours and social contacts were still over three times more likely than in the general population [37, 82]. Because neighbours of neighbours and social contacts still live near patients [86], exposure to *M. leprae* is likely to cluster at a spatial level smaller than villages. Moet *et al.* [37] have shown that leprosy is aggregated at the household level and for adjacent neighbours, but the extent to which leprosy cases are spatially aggregated within complete villages is not known.

We believe that identifying neighbourhoods or areas with many previously undetected cases will improve efforts to find new cases. Here, we report on the spatial distribution of prevalent cases and cases that were found during two follow-up surveys with two-year intervals in four villages within in a highly endemic area. We attempted to identify spatial clusters of leprosy cases within these four villages using a spatial scan statistic [87, 88].

Methods

Study population and survey. As part of a larger previously conducted study [84], 20 administrative areas were randomly selected from two districts in northwest

Bangladesh.

The survey started at the northern borders of the areas and included all of the people present until approximately 1,000 people were examined. The groups were surveyed between November 2002 and February 2003. During the survey, people were asked about leprosy symptoms and a body check was performed. Those who were suspected of having leprosy were referred to a senior leprosy control officer and a doctor for confirmation. If the disease was confirmed, regular treatment was offered. The inhabitants who participated in the first survey were visited in the same months in 2004–2005 and 2006–2007, if they still lived in the same area. So that our results may be thoroughly understood, we have provided a summary of our survey methods. A more extensive description of the survey can be found elsewhere [37].

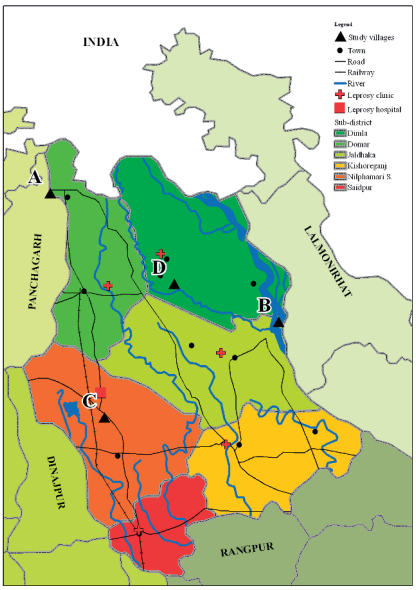

Figure 7.1: An overview map of the Nilphamari district showing several geographic features, such as towns, roads and rivers. The four selected villages are indicated by black triangles.

For the current study, we selected four groups out of the 20 groups, all within the Nilphamari district, because these were easily accessible. An overview map of the Nilphamari indicating the four selected villages is presented in Figure 7.1. We selected the sample populations with the highest number of cases during intake; three of the four selected population samples also had a high prevalence of anti–*M. leprae* IgM antibodies, which is thought to indicate increased exposure [37], most likely leading to an increased incidence of leprosy. Three groups were selected from a rural area and one from an urban area.

Map preparation and census data. Maps were prepared in January 2006 using hand-held global positioning system (GPS) units (Geko 201, Garmin, USA). The maps were drawn in ArcGIS 9.1 (ESRI, USA). Coordinates were collected for the

compounds and roads, and for some geographic features such as schools, mosques, and bodies of water. Compounds are small groups of 1 to 10 houses, often inhabited by one family. Digital maps were drawn using these geo-references and hand-drawn maps. The calculated centroids of compounds were used as census points. Participants were attributed to the nearest census points.
We recorded participants' death and migration since the 2003 study intake. If we were able to obtain the information, migrated or deceased people were attributed to the compound in which they lived during intake.

Statistical analysis. The spatial pattern of the compounds was determined by the average nearest neighbour index (ANNI). An ANNI smaller than 1 indicates a clustered pattern of compounds when compared with a random model [89]. The groups were scanned using spatial scan statistic to detect high prevalence clusters of cases. The scans were performed for purely spatial data, and imposed circular windows with flexible radii on all of the locations in the area. The number of cases within a window was assumed to follow a Poisson distribution under the null hypothesis. For each window, the likelihood was calculated for the observed cases and the expected cases under the null hypothesis. The window with the highest likelihood constituted the most likely cluster. The distribution of the maximum likelihood was determined by many random replications of the dataset under the null hypothesis. The p-value was then calculated by comparing the rank of the maximum likelihood of the real dataset with the ranks of the maximum likelihoods of the random datasets [87]. The analyses were performed with SatScan version 7.0 [88].

Ethical clearance. Ethical clearance was obtained from the ethical review committee of the Bangladesh Medical Research Council (reference numbers BMRC/ERC/2001-2004/799 and BMRC/ERC/2004-2007/1397).

Results

Area characteristics. Group A lived in an area near the Indian border. The total area of the village was 1.04 km^2. The village contained two schools for secondary education and a local police headquarters.

Group B was reached by crossing a large river. The east and west borders of the

Table 7.1: Study population, demographics, and number of newly detected leprosy cases in four sample populations.

		Population sample				
		A *rural*	*B* *rural*	*C* *urban*	*D* *rural*	*Total*
Population	Population size at intake	1008	1000	1107	1008	**4123**
	Mean age Male	20.1	22.2	17.5	21.6	**20.4**
	Female	22.2	21.9	22.5	24.5	**22.8**
	Both	21.4	22.1	20.5	23.3	**21.8**
	Proportion age < 15	0.57	0.55	0.56	0.49	**0.54**
	Sex ratio	0.7	1.0	0.7	0.7	**0.8**
Village	Compounds	219	167	253	253	**892**
	Inhabitants per compound	4.6	6.0	4.4	4.0	**4.6**
	Houses per compound	2.0	2.0	1.5	2.0	**1.9**
	Inhabitants per house	2.3	3.0	2.9	2.0	**2.5**
	Area (in km2)	1.04	1.39	0.31	1.82	**4.56**
Leprosy	RFT before intake*	3	3	8	0	**14**
	Case at intake	6	0	1	0	**7**
	Case at 1st follow up	3	0	2	1	**6**
	Case at 2nd follow up	1	0	5	0	**6**

* Released from leprosy treatment before the first survey.

village were delimited by the river embankments. The village contained no brick or concrete buildings, except for a mosque and a primary school. The total area of the village was 1.39 km^2. It bordered another village directly to the north.

The urban group C was located at the edge of the district capital and contained the largest population of the three groups. This urban ward had an area of only 0.31 km^2. Most of the compounds were north of an asphalt road leading to the town centre. Approximately one-third of the houses were built of brick or concrete. The office building of a large regional non-governmental organization was located on the south border.

Group D was located near a cluster of shops situated at the crossing of two major roads coming from the district capital and a nearby town. A lake surrounding by marshes bordered the village to the south. At 1.82 km^2, this village had the largest area of the four groups. The village contained two primary schools, two mosques, and several Hindu shrines.

Table 7.2: Spatial patterns of compounds and new cases in each population.

	Clustering of compounds		Clusters of cases							
			All cases		At intake		1^{st} follow up		2^{nd} follow up	
	ANNI [a]	Z-score	LLR[b]	p[c]	LLR[b]	p[c]	LLR[b]	p[c]	LLR[b]	p[c]
A	0.42	-17.6	3.2	0.60	5.9	0.13	3.0	0.51	-[d]	-[d]
B	0.30	-17.8	3.4	0.52	-[d]	-[d]	-[d]	-[d]	-[d]	-[d]
C	0.56	-14.7	4.2	0.81	4.5	0.18	1.8	0.65	4.4	0.14
D	0.30	-22.9	-[d]	-[d]	-[d]	-[d]	-[d]	-[d]	-[d]	-[d]

[a] Average Nearest Neighbour Index.
[b] Log likelihood ratio
[c] Determined by 999 Monte Carlo replications
[d] No calculation of log-likelihood ratio possible for none or 1 case – and thus no p-value –.

Study population. The total study population consisted of 4,123 people. The mean age at intake was 21.8 years. The proportion of children under 15 years was on average 0.54. People who were not at home during intake were not included in the study, which is the most likely explanation for the uneven sex ratios of groups A, C, and D (Table 7.1). In these groups, males were more likely than females to be at work in another area during the days on which intake took place. The people of group B worked in the fields near their home; thus, males and females were evenly included. The average compound size of 4.6 persons per compound was comparable with the census data on average household size for rural Bangladesh [59]. Compounds comprised 1.9 houses, on average.

At intake, 14 persons were known to have been released from treatment for leprosy prior to the study intake. Furthermore, there were seven newly diagnosed cases of leprosy. Of the seven cases, all had paucibacillary (PB) leprosy. There were no cases of multibacillary (MB) leprosy. After two years, six new cases were detected; one had MB leprosy, and the other five were diagnosed with PB leprosy. Finally, four years after study intake, another six new cases were detected, all of which were PB leprosy. The proportion of PB cases was not unexpected, given that the proportion of PB cases among the total cases detected in this district was approximately 0.8. During surveys, such as the one used in this study, the proportion of PB cases is higher than among voluntarily reported cases, because many less-severe cases can remain

otherwise undetected.

After two years, a total of 265 persons were lost to follow-up due to death (37) or migration (228). As far as we could determine either by registration at the clinics or by asking relatives, none of the deceased people had experienced clinical leprosy. One person who had migrated was diagnosed with leprosy at intake in group A, and could be attributed to the compound in which he was living at intake. Thirty persons moved within the areas; none of them had leprosy. At the time of the writing of this report, further details concerning persons lost to follow-up were not yet available.

Spatial patterns. Compounds were aggregated in space (Table 7.2). ANNI ranged between 0.30 and 0.56. Eyeballing of Figure 7.2 intuitively confirms the aggregated spatial pattern of the compounds, which were positioned in small groups and along the roads. The spatial scan statistic determined the location of the most likely cluster for each area. None of the four clusters were significantly different ($p < 0.05$) from the Poisson model.

Discussion

We could not identify clusters of leprosy at this spatial microlevel of 0.32–1.82 km^2, an area equivalent to a town ward or village. Thus, either at this level spatial clustering does not occur, or the force with which leprosy clusters is not strong enough to reveal spatial clustering using only a few population samples with a moderate number of cases. One would need to observe many of these areas (villages) to identify a limited number of possible clusters. Both of these explanations call into question the value of attempting to identify leprosy clusters at this level.

Spatial clustering of leprosy has been found on Indonesian islands with extremely high numbers of previously undetected cases [32, 27]. The power of the statistical tests for clustering was thus much greater than in our study. Furthermore, the studies by Bakker *et al.* [32] were conducted among populations living on remote islands. These island populations had a contact pattern that differed from our study population. The population in northwest Bangladesh is not confined to an archipelago of small islands, but lives in an easily accessible and densely populated area of the Indian subcontinent.

Although members of the same household as a person with leprosy have a much

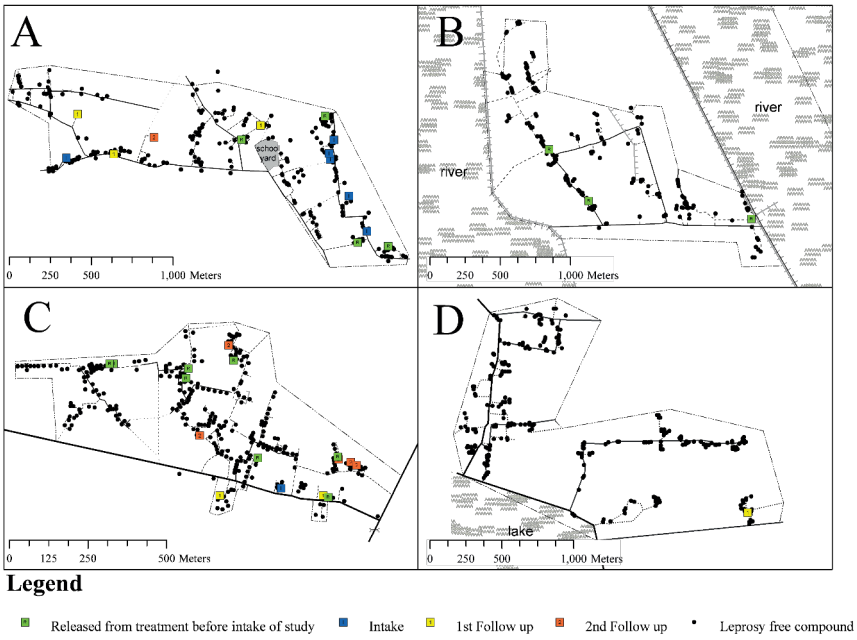

Figure 7.2: Newly detected cases by moment of detection (e.g. before intake, at intake, first follow up or second follow up) in four sample group areas. Compounds are depicted by a black dot. The dash-dotted (·····) line indicates the village or ward border. Other lines indicate roads, canals and river embankments. Compounds outside these borders are not included in the study, but some are shown on the maps to indicate the closeness of other villages.

higher relative risk of contracting leprosy [37], the number of non-household contacts (such as relatives and social contacts) is many times higher than that of household contacts [90]. However, as we have illustrated, we found no clusters of leprosy within the limited number of villages that we observed.

It is not easy to identify clusters of patients using spatial analysis at the microlevel of villages in highly endemic areas, compared with higher levels. In a separate paper, we found spatial clustering at the district level in the same area in Bangladesh [91]. In addition, Moet *et al.* [37] found large differences in previously undetected prevalence in the 20 population samples. Some of these population samples (e.g., group A in this study) had a previously undetected prevalence equal to that of close contacts [37].

Conclusions

The search for clustering should be extended to higher aggregation levels, such as subdistrict or regional levels. Thus, in highly endemic areas, it appears to be more effective to target complete villages for contact tracing, rather than narrowly defined contact groups such as households.

Acknowledgements

The leprosy control supervisors of the Rural Health Program (formerly DBLM) in Nilphamari are gratefully thanked for their efforts. The inhabitants of the study areas are thanked for their hospitality and cooperation. We acknowledge the important comments raised by two reviewers, which helped to improve an earlier version of this manuscript. We acknowledge the American Leprosy Missions for financial support of this study. EF is thankful for the financial support received from The Netherlands Leprosy Relief.

8

The spatial distribution of leprosy cases during 15 years of a leprosy control program in Bangladesh: an observational study

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Abstract

Background An uneven spatial distribution of leprosy can be caused by the influence of geography on the distribution of risk factors over the area, or by population characteristics that are heterogeneously distributed over the area. We studied the distribution of leprosy cases detected by a control program to identify spatial and spatio-temporal patterns of occurrence and to search for environmental risk factors for leprosy.

Methods The houses of 11,060 leprosy cases registered in the control area during a 15-year period (1989-2003) were traced back, added to a geographic database (GIS), and plotted on digital maps. We looked for clusters of cases in space and time. Furthermore, relationships with the proximity to geographic features, such as town centre, roads, rivers, and clinics, were studied.

Results Several spatio-temporal clusters were observed for voluntarily reported cases. The cases within and outside clusters did not differ in age at detection, percentage with multibacillary leprosy, or sex ratio. There was no indication of the spread from one point to other parts of the district, indicating a spatially stable endemic situation during the study period. The overall risk of leprosy in the district was not associated with roads, rivers, and leprosy clinics. The risk was highest within 1 kilometre of town centres and decreased with distance from town centres.

Conclusion The association of a risk of leprosy with the proximity to towns indicates that rural towns may play an important role in the epidemiology of leprosy in this district. Further research on the role of towns, particularly in rural areas, is warranted.

Background

New cases of leprosy are currently found primarily in tropical regions [92, 93], but the distribution within these regions is not uniform. Sixty eight percent of newly detected cases in 2005 were found in South-east Asia, 80% of which were detected in India. In the same year, another 13% of all cases worldwide were found in Brazil. The South-east Asian region and Brazil together accounted for 81% of all cases of leprosy detected in 2006 [93].

Within highly endemic regions, the occurrence of leprosy is also not uniformly distributed [39, 40, 41]. The distribution of leprosy in the Brazilian state of Ceará reflects socio-economic differences within the state [38, 39], whereas the explanation for the uneven distribution in another Brazilian state, São Paolo thought to be migratory movement towards the urban and developing areas in the centre of the state [40]. In the Malawian Karonga district, a positive relationship between the proximity of water and leprosy incidence was previously found [41]. The relationship between open water and leprosy was hypothesized based on observed associations with rainfall and coastal populations [2, 94], as well as evidence that the infectious agent, *Mycobacterium leprae,* survives longer outside the human body in humid compared to dry atmospheres [9]. In a locality with many rivers and other bodies of water, such as northwest Bangladesh, the relationship between leprosy and open water might be quite different.

Differences in the case detection rates can arise from differences in the accessibility of leprosy control facilities. In poor areas, travelling is expensive for the common people and the proximity to a leprosy control facility might increase the detection rate among the population. A study of the spatial distribution of leprosy can contribute to the knowledge about, or identification of, the underlying risk factors for the disease and the transmission patterns of *M. leprae*. A clustering of leprosy cases at the village level was not observed in the highly endemic Nilphamari district in northwest Bangladesh . In this paper we describe the spatial distribution of leprosy at the district level in the same area during the period of 1989 to 2003 and determined whether high case detection clusters were present in the district. We investigated the risk of leprosy in proximity to geographic factors that may have a relationship with the risk of leprosy, such as the environment (i.e. rivers and roads), a different population (i.e. towns), or enhanced availability of health services (i.e. leprosy clinics).

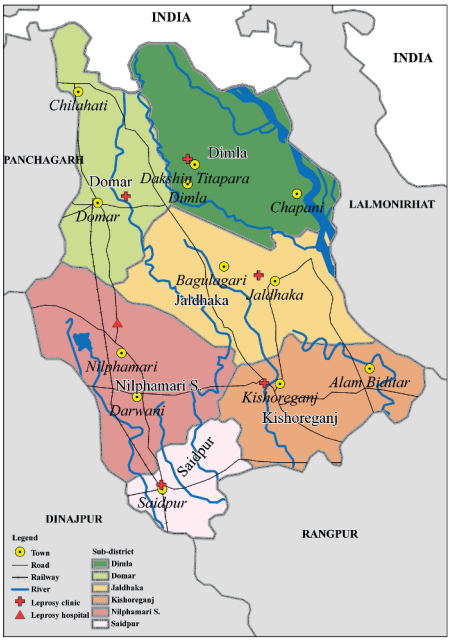

Figure 8.1: National, district, and sub-district borders, towns, clinics, rivers, roads, and railroad of Nilphamari district.

Methods

Study design

The study is a retrospective observational study on the spatial distribution of newly detected leprosy patients in northwest Bangladesh over a 15-year period.

Study area

The study was conducted in the Nilphamari district at 26°00′ N and 88°57′ E. The district has an area of 1640.9 km^2 and approximately 1.5 million inhabitants [59]. The district is divided into six sub-districts. Geographical and leprosy characteristics of the sub-districts are given in Table 8.1. The sub-districts Nilphamari Sadar and Saidpur contain two major urban areas, also called Nilphamari and Saidpur, with Saidpur city being the largest urban area. The district is mainly rural outside these urbanized areas. The Saidpur sub-district contains a large refugee population of over 38,000 stateless Bihari refugees. The refugee camp was created near Saidpur city after the Bangladesh war for independence in the early 1970's [95]. One of the major rivers of Bangladesh, the Tista River, flows through the north-east part of the district and several smaller rivers cross the district. A map of Nilphamari district is presented in Figure 8.1.

The Danish Bangladesh Leprosy Mission (DBLM) was established in this area in 1977. Since that time, more than 95% of registered leprosy patients have been treated by DBLM. The project area also covers the neighboring districts of Rangpur, Thakurgoan, and Panchagar. The DBLM has been responsible for leprosy control in these four districts since 1994. Multidrug therapy (MDT) was completely introduced in the project area by 1991 [96].

Study population

The study population existed of all leprosy patients diagnosed and registered between January 1, 1989 and December 31, 2003 at one of the DBLM clinics and living in Nilphamari district. Case registration was done according to the DBLM guidelines [97].World Health Organization (WHO) leprosy classification [6], and the mode of detection were registered. A DBLM leprosy control supervisor confirmed all cases before registration and subsequent treatment. Uncertain cases were referred to the leprosy control officer or DBLM medical officer for confirmation. An independent inspector assessed the program in 2001 and found an over-diagnosis of only 3.4% [98]. For the current study, we used the existing patient database and added spatial data.

Table 8.1: Leprosy, population, and geographic characteristics of the sub-districts.

Sub-district	Cases	Person-years	NCDR*	Area ($\mathbf{km^2}$)	Towns	Clinics
Nilphamari Sadar	2,501	5,003,010	0.50	249.8	2	1
Saidpur	1,654	3,375,432	0.49	339.2	1	1
Kishoregonj	1,002	4,140,829	0.24	332.8	2	1
Jaldhaka	2,215	3,791,886	0.58	338.8	2	1
Domar	1,647	2,910,790	0.57	256.3	2	1
Dimla	2,041	3,125,001	0.65	124.1	3	1
Total	11,060	22,346,947	0.49	1640.9	12	6

* New case detection rate per 1,000 person-years

Mode of detection

As the data was from a running control program, the cases were detected by different modes of detection [63]: voluntary reporting, surveys, and contract tracing. Voluntarily reported cases, apart from cases presented voluntarily at a clinic, included those referred by a professional health worker or other informed respected person (i.e. village doctors, teachers, or health workers). Surveys consisted of school or village surveys and were performed during the entire study period. During these school or village surveys, the students of a school or the population of a certain area with an assumed high prevalence of leprosy were examined. Contact tracing was always practised after a voluntarily reported case was confirmed and continued for 2 to 5 yearly visits, depending on the leprosy classification [97].

The occurrence of spatio-temporal clusters of high rates of detection was investigated separately for each mode of detection. The characteristics of patients within clusters were compared to patients living outside the clusters. The position of the houses of patients grouped by mode of detection was studied in relation to towns, rivers, roads, and leprosy clinics separately.

However, we focus on voluntarily reported cases because, in this control program, these cases are thought to give the best representation of the incidence of leprosy. Surveys normally tend to give a better picture of the real prevalence than voluntarily reported cases. In this control program, however, surveys were performed depending on the number of cases previously voluntarily reported in a village or school. Results of cases detected by surveys or contact tracing can be found in the supplementary information in the appendix.

Location of patients

During the current study, the houses in which patients lived at the time of diagnosis were traced back by specially trained staff. We note that this is not necessarily the location at which the patient became infected. Another possibility would have been to use location at which the patient lived when the first signs of disease were found. The location where the patient lived during diagnosis, however, could be determined more accurately, and we assume that the difference with the location at which the first signs occurred is not very different on the scale of a whole district. The coordinates were measured using a handheld GPS-unit (Geko 201 Garmin^{TM}) between January and November 2006. Cases were excluded if the patient was registered to live in a district other than Nilphamari or if the house was outside Nilphamari district according to our digital map. Finally, those whose home coordinates could not be obtained were excluded from analysis, in addition to patients for whom the mode of detection was unknown.

Geographic and spatial data sets

A population density map with a grid cell of $30''$ by $30''$ resolution was obtained from the Gridded Population of the World version 3, beta version. [99] The population densities for each grid cell were calculated by pycnophylactic smoothing based on sub-district population counts. The population density maps were made for the population in 1995 and 2000 based upon 1991 and 2001 census data assuming an exponential growth of the population [100].

Digital maps of the administrative boundaries of the districts and sub-districts of Bangladesh were obtained from the Food and Agricultural Organization of the United Nations [101]. Road, populated places, and hydrographical data were obtained from downloadable data of the geocommunity [102].

Statistical analyses

Case detection was plotted against time and tested for a temporal cluster [87]. A temporal cluster is a period in which case detection was higher than expected for cases randomly distributed over the study period. The likelihood that the case detection originated at random during a period was calculated assuming a Poisson distribution

of cases among the population. A likelihood ratio test was used to obtain a p-value for the most likely cluster.

The area was tested for a high incidence of spatio-temporal clusters of cases separately for each detection mode using the spatio-temporal permutation test. The spatio-temporal permutation test [103] is a non-parametric test making use of the information from the case distribution. This test compares the observed number of cases during a time period in a circular area with the expected number cases if the spatial and temporal location of all cases were independent. The comparison is made for a cylindrical window with a circular geographic base and with height corresponding to the length of the time period. Both the circular base (the area) and the height of the cylinder (the time period) are flexible. The likelihood that the case detection in a certain space-time window originated by chance was calculated under the assumption that no space-time interaction exists. The expected cases in a certain area were calculated based upon the number of cases observed at that location during the entire study period and the number of cases in the whole district during that time frame. Therefore, this method adjusts for the pure spatial and pure temporal incidence. The probability that a cluster did not originate by chance was determined by Monte Carlo hypothesis testing based upon the most likely cluster [103]. We restricted the test to clusters of a length of at least 1 year and at most 25% of the population without geographic overlap. Only space-time windows with more than the number of expected cases, i.e. high incidence clusters, were tested.

We compared the cases within and outside spatio-temporal clusters by calculating the distance to towns, rivers, roads, and clinics; the average age at detection; the percentage of multibacillary (MB)leprosy; and the sex ratio. For distance to towns, we took the distance measured from the centre of town.

For the analysis of the proximity of towns, rivers, clinics, and roads, we used Poisson regression with a correction for over-dispersion. We calculated distances to the geographic features and used the distance and square distance as continuous variables in separate models, and we fitted a model with categorical variables of distance in categories of 1 km. We fitted a univariate model with only the explanatory variable and multivariate model with all variables (i.e. distance to town, river, clinic, and road).

Software

Data entry was done in Microsoft Access 2000™and ArcGIS™9.1 was used for the visualization and processing of spatial data using a plug-in tool to count cases [104]. The temporal and spatio-temporal cluster analyses were performed with the SaTScan program, version 7.0.3 [88]. Poisson regressions were performed in R© 2.6.0 [105].

Ethical clearance

The informed consent of the house inhabitants was obtained verbally. Ethical clearance was obtained from the ethical review committee of the Bangladesh Medical Research Council (reference number BMRC/ERC/2004-2007/1397).

Results

During the study-period, 12,602 newly detected leprosy patients were registered at clinics in Nilphamari district. We were not able to find the locations for 881 patients, and another 661 were either registered as living outside the district or found to live outside the district during this study. This left 11,060 cases for which we were able to obtain the coordinates of their house. Patients that could not be traced back, i.e. missing cases, were originally detected, on average, seven months earlier in the study period than the included cases. The percentage of males and year of birth were not different for missing and included cases. Forty percent of the missing cases were MB compared to twenty-eight percent of the included cases, which was a significant difference (see appendix).

Of all 11,060 cases, 5170 were reported voluntarily, 1048 were found by contact tracing, and 4651 by school and village surveys. For 191 cases the detection method was unknown. The percentage of females was higher among cases detected actively than among voluntarily reported cases. The percentage of MB leprosy was higher among the voluntarily reported cases than among contact tracing, and it was lowest for cases detected during surveys.

The detection rate increased until a peak in 1994 (Figure 8.2). From 1995 onwards, the number of detected cases decreased over time. The annual decline in cases was 6.44% (95% CI 4.24-8.64). A pure temporal cluster was identified between April 1994 and November 1996 consisting of primarily paucibacillary (PB) cases. This was

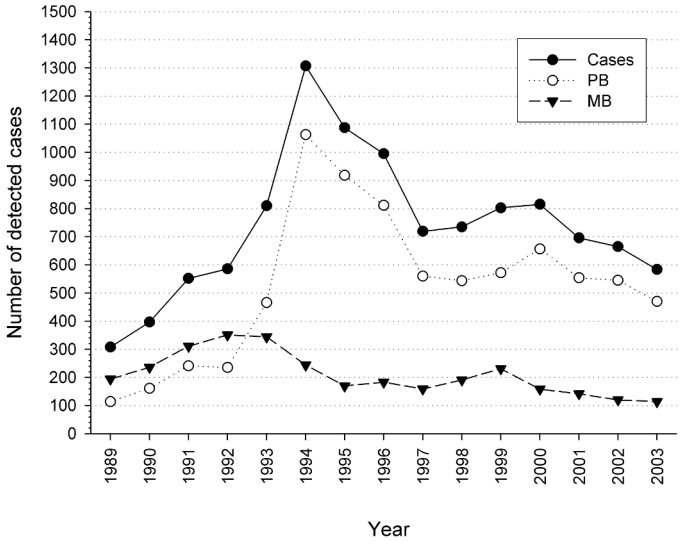

Figure 8.2: Temporal distribution of the included cases detected in Nilphamari district between 1989 and 2003. PB, paucibacillary; MB, multibacillary.

caused by an intensification of surveys during this period (Figure 8.2).

Many spatio-temporal clusters were found for all grouped cases and overlapped with those of the separate detection methods (Figure 8.3). The spatio-temporal permutation test found six clusters of voluntarily reported cases, five of contact tracing, and 20 clusters of cases found during surveys (see Table 8.2, Figure 8.3 and appendix). Most clusters had a time period of 1 or 2 years, but one cluster of survey-detected cases had a time span of 4 years. This cluster contained Saidpur city. For each detection mode, the cases within clusters did not differ in age at detection, percentage females, or the percentage of MB leprosy compared to cases outside the clusters (see Table 8.2 and appendix). Furthermore, the cases within a spatio-temporal cluster did not live nearer to or further from towns, roads, clinics, or rivers for any of the detection modes. Cases within the same area were not accounted to the spatio-temporal cluster if their diagnosis was outside the time frame of the cluster.

Table 8.2: Spatio-temporal clustering of voluntarily reported cases. Characteristics of the most likely spatio-temporal cluster and secondary clusters that do not geographically overlap and $p > 0.05$.

Nr.	Start - End	Cases	**% females**	Age at registration		% MB*
1	Jan'91-Dec'92	57	38.6% (32.4-44.7)	28.4	(0-61.0)	70.2% (64.7-75.6)
2	Jan'00-Dec'02	145	33.8% (30.2-37.4)	31.2	(3.7-58.7)	22.8% (19.9-25.6)
3	Jan'02-Dec'02	26	30.8% (22.6-39.0)	37.4	(10.0-64.8)	26.9% (19.4-34.5)
4	Jan'94-Dec'94	25	20.0% (13.7- 26.3)	31.9	(0-68.6)	40.0% (30.6-49.4)
5	Jan'93-Dec'94	24	58.3% (48.6-68.1)	26.8	(0-58.0)	20.8% (14.2-27.4)
6	Jan'93-Dec'94	84	36.9% (31.9-41.9)	34.1	(3.2- 65.0)	38.1% (33.1-43.1)
All clusters		361	35.7% (33.4-38.1)	31.7	(1.7-61.6)	35.2% (32.8-37.5)
Outside clusters		4809	36.0% (35.4-36.7)	31.7	(0-65.0)	38.9% (38.2-39.5)
All		5170	36.0% (35.4-36.6)	31.7	(0.9-62.1)	38.6% (38.0-39.3)

* Multibacillary cases

For voluntarily reported cases, the leprosy detection rate was higher near towns (Table 8.3). This seems to contradict the previous finding that cases within spatio-temporal clusters do not live nearer to towns. However, areas with a high incidence of cases throughout the entire study period do not constitute a spatio-temporal cluster. These areas can add to the risk calculated for proximity to towns. The rate decreases steeply in the first kilometres from the town. The rate of leprosy was two times lower at a distance of more than 1 to 2 kilometres from a town than the rate within 0 to 1 kilometre from town (adjusted rate ratio 0.512, 95% CI 0.387-0.677). The distance to roads was negatively related to the detection of new cases. However, the decrease in new case detection was not monotonous, with higher rates between 6 and 10 kilometres than between 2 and 6 kilometres. The rate of leprosy did not show a relationship with the distance to water (see appendix). Also, for clinics, the rate of newly detected leprosy did not change with distance (see appendix).

Discussion

Our first observation was a clustering of cases in a space-time window. These kind of spatio-temporal clusters depict 'outbreaks' of cases detected by voluntary reporting. Several explanations for these 'outbreaks' are possible; the most obvious is an underlying increase in the incidence of leprosy, i.e. a real outbreak of disease. An increased awareness among the population, however, can also cause an 'outbreak of detection'.

Table 8.3: Leprosy detection rate of voluntarily reported cases by distance to towns. The adjusted rate ratios are estimates from a model including distance to clinics, rivers, and roads.

Distance to town	**Univariate**	**95% CI**	**Adjusted**	**95% CI**
Linear	0.890	(0.866-0.914)	0.922	(0.895 - 0.950)
Quadratic	0.990	(0.988- 0.993)	0.993	(0.990 - 0.995)
Category				
0-1 km	1		1	
1-2 km	0.450	(0.342 - 0.592)	0.512	(0.387 - 0.677)
2-3 km	0.309	(0.238 - 0.403)	0.414	(0.313 - 0.549)
3-4 km	0.287	(0.221 - 0.373)	0.392	(0.294 - 0.521)
4-5 km	0.291	(0.225 - 0.376)	0.392	(0.292 - 0.525)
5-6 km	0.268	(0.206 - 0.348)	0.360	(0.264 - 0.491)
6-7 km	0.248	(0.186 - 0.329)	0.319	(0.228 - 0.446)
7-8 km	0.256	(0.190 - 0.344)	0.305	(0.215 - 0.433)
8-9 km	0.312	(0.227 - 0.429)	0.365	(0.252 - 0.527)
9-10 km	0.132	(0.072 - 0.240)	0.168	(0.090 - 0.314)
10-11 km	0.086	(0.033 - 0.222)	0.148	(0.056 - 0.392)
11-12 km	0.059	(0.012 - 0.301)	0.126	(0.025 - 0.649)
>12 km	0.082	(0.010 - 0.699)	0.270	(0.031 - 2.361)

Finally, an 'outbreak' is also observed when the population grows faster in some areas than others while the risk remains the same. Our analytical approach cannot correct for this phenomenon [103]. However, the population has grown in the whole district [59], and clusters would be expected later in the observation period, whereas the most likely cluster was found between 1991 and 1992. The detection increased dramatically in the years 1992 to 1994 due to improved organization in the leprosy control program. The most likely cluster was found prior to this period, showing that the spatio-temporal clusters both need a spatial *and* a temporal component, i.e. the analysis corrects for pure temporal clusters.

This leaves increased awareness and underlying increased incidence as potential explanations. If the spatio-temporal clusters are caused by an increased awareness among the population, differences would be expected in the percentage of cases with MB leprosy and the age at detection. Increased awareness results in less time between the first symptoms and reporting. A shorter delay in detection would lead to a decrease in the percentage with MB leprosy, as more PB leprosy would be found

before possible self-healing or progression from PB to MB leprosy. Also, the age at detection would be lower. Neither was observed for these clusters; thus, an underlying high incidence of leprosy can be assumed responsible for this pattern. However, we found no specific determinants (e.g. age at detection or proportion of MB leprosy) that could explain the high incidence in the clusters.

Our second observation was with regard to the spread of disease in time. Contrary to the anecdotal observation of the introduction and subsequent spread of leprosy by Bangladeshi refugees returning from India after the war for independence in 1972, we did not observe a spread of leprosy from Saidpur city to other areas in the district, nor could we identify patterns of spread or retraction in the district during the study period. New leprosy cases appeared more or less consistently over the whole district during the 15 years of observation, indicating a stable endemic situation in space and time.

Finally, our third observation concerns geographic determinants of leprosy risk. We found a clear relation with proximity to towns, especially in the first kilometres, and the risk of leprosy. Leprosy is thought of as a rural disease [2], but our results show that rural towns, i.e. moderately sized towns in a rural area, contain many cases. The sharp decline within the first kilometres might indicate that it is not the distance to town, but the difference between urban and rural populations, influencing leprosy epidemiology. There are several possible explanations. First, as suggested by others, it could be the result of selective migration towards these towns [39, 40]. Second, a higher awareness among the urban population is possible. Third, the circumstances in these towns are favourable for the transmission of *M. leprae*. We recommend further studies of leprosy in urban areas and towns in rural areas. If urban areas are an important source of transmission, improvements are possible by focusing more on urban leprosy control.

The rate of new leprosy cases was higher in the proximity of roads. In another setting, the risk of leprosy was found to be increased with more distance from roads. That study was based on active surveys and indicated an under-reporting with increased distance from a road [41]. In our study, all methods of detection had a higher risk of leprosy near roads; therefore, this is not the explanation for our findings. Our results can be explained by the fact that major roads connect the towns, and people living near roads also tend to live near towns. However, our maps only contained the major roads. Though roads are present in the north-eastern sub-district of Domar,

these are not major roads and not present in our analysis. The results for roads are not clear from our observations, and maps of all roads instead of only the major roads might give a different result.

The proximity to a clinic might increase the possibilities of voluntary reporting, but we found no relationship with the proximity to a clinic. The distance to clinics does not seem to be an obstacle for reporting leprosy.

The proximity of water has been hypothesized to be a risk factor for leprosy transmission [2], and Sterne *et al.* [41] found an association with the proximity to rivers. The increased risk would be due to the longer lifetime of *M. leprae* outside the body in a humid atmosphere, as opposed to a dry atmosphere [9, 2]. In Nilphamari, a relationship with the proximity to rivers was not found. In this district, it is unlikely that the proximity to water would increase the risk of leprosy, as almost 60% of the population lives within 2 kilometres of a river, and most live much nearer to other bodies of water, such as rice paddies. Furthermore, the relative humidity does not drop below 60% and the yearly average is 80% [59].

Our study gives a thorough spatial description of the cases found during a leprosy control program, and this approach can possibly bias our results in several ways. We retrospectively traced back patients; therefore, a proportion of the cases could not be found. The demographic characteristics, including age and sex, were not different from the included patients. The missing cases, however, contained proportionally more MB cases. The reason for this is not clear, but this difference is not likely to introduce a bias in our analysis, as there is no evidence to expect that MB cases were distributed differently than PB cases. The population density maps on which we base some of the estimates were constructed by the interpolation of sub-district data [100]. The population of Nilphamari district is less smoothly distributed than suggested by these interpolated population maps. For towns, the population density will be underestimated, resulting in higher estimates for the rate of leprosy. However, these estimates are the best available population density estimates. The results obtained using this data should be interpreted cautiously, but are useful to directing new lines of research.

Conclusions

We found that the risk of leprosy is associated with the proximity to towns, but not roads, clinics, and rivers. Although our estimates for towns may be too high due to the use of population density maps based on interpolated census data, the elevated detection of new cases for all modes of detection near and in towns indicates that rural towns play an important role in the epidemiology of leprosy in this district. Further research on the role of towns in rural areas is warranted.

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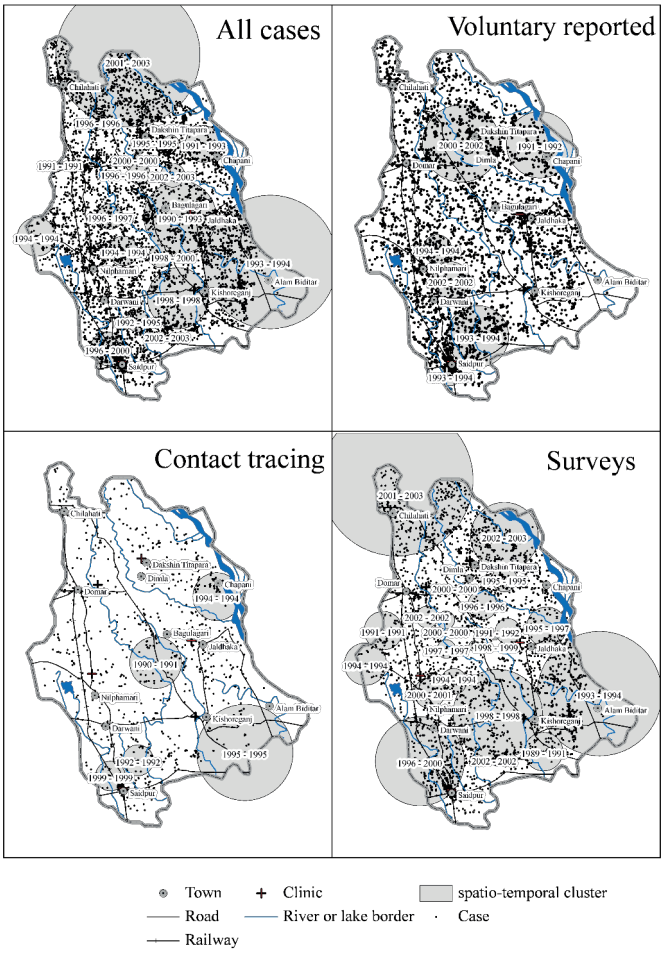

Figure 8.3: The cases registered between 1989 and 2003 in Nilphamari district (top left). Cases per detection mode and spatio-temporal clusters of leprosy cases detected in Nilphamari district for modes of detection, voluntarily reporting (top right), contact tracing (bottom left), and surveys (bottom right).

Appendix

Table 8.4: Characteristics of included cases and missing data. The characteristics of the patients for whom no district was registered, are given in the first row. The second row gives the information of the people registered as living in Nilphamari. The included cases were only those confirmed by their spatial location. The last row gives the totals of the missing data and the included cases.

	Characteristic	Missing data	Included cases	
No sub-district registered	%-males	56%	100%	
	Registration date	9-July-1996	29-Dec-1995	*
	%MB	41%	60%	
	Age at 1-1-'04	39.8	51.1	
	Total	197	5	
Sub-district within	%-males	59%	59%	
Nilphamari district	Registration date	6-Feb-1996	24-Oct-1996	*
	%MB	39%	28%	*
	Ageat1-1-'04	39.9	38.4	
	Total	684	11055	
Total	%-males	58%	40%	
	Registration date	12-Mar-1996	24-Oct-1996	*
	%MB	59%	28%	*
	Age at 1-1-'04	39.9	38.4	
	Total	881	11060	

* significant difference between missing data and included cases($p<0.05$)

Table 8.5: Clusters of cases found by contact tracing. This table shows the characteristics of the most likely spatio-temporal cluster and secondary clusters that do have no geographical overlap and $p > 0.05$.

Cluster	Start	End	Cases	%females		Age at registration		%MB	
1	Jan'94	Dec'94	27	55.6%	(46.2%-64.9%)	31.4	(0.2-62.6)	14.8%	(10.1%-19.6%)
2	Jan'95	Dec'95	18	66.7%	(56.4%-76.9%)	29.4	(29.4 - 29.4)	5.6%	(3.1% - 8.0%)
3	Jan'99	Dec'99	147	71.4%	(60.7%-82.1%)	17.6	(17.0-18.3)	21.4%	(12.6% - 30.2%)
4	Jan'92	Dec'92	11	54.5%	(39.9%-69.2%)	21.5	(20.9-22.0)	54.5%	(39.9%-69.2%)
5	Jan'90	Dec'91	35	31.4%	(24.3%-38.6%)	23.4	(22.9-23.8)	37.1%	(29.4%-44.9%)
All clusters			105	51.4%	(46.7%-56.2%)	25.5	(-3.2-54.2)	25.7%	(22.1%-29.4%)
Outside cluster			943	44.8%	(43.2%-46.3%)	26.3	(25.3-27.2)	29.6%	(28.3%-30.9%)
All			1048	45.4%	(43.9%-46.9%)	26.2	(-6.0-58.4)	29.2%	(27.9%-30.5%)

Table 8.6: Clusters of cases found by active surveys. This table shows the characteristics of the most likely spatio-temporal cluster and secondary clusters that do have no geographical overlap and $p > 0.05$.

Cluster	Start	End	Cases	%females		Age at registration		%MB	
1	Jan'93	Dec'94	255	43.5%	(40.5%-46.5%)	30.8	(0.0-64.6)	13.3%	(11.9%-14.8%)
2	Jan'96	Dec'00	274	58.8%	(55.9%-61.6%)	27.3	(0.0-57.0)	9.1%	(8.1%-10.1%)
3	Jan'98	Dec'99	34	50.0%	(41.6%-58.4%)	34.4	(3.3-65.5)	11.8%	(8.3%-15.3%)
4	Jan'02	Dec'03	72	41.7%	(36.1%-47.3%)	28.7	(0.0-62.1)	6.9%	(5.5%-8.4%)
5	Jan'98	Dec'98	58	50.0%	(43.6%-56.4%)	30.1	(0.0-61.7)	13.8%	(10.7%-16.9%)
6	Jan'89	Dec'91	14	50.0%	(36.9%-63.1%)	34.7	(1.0-68.4)	50.0%	(36.9%-63.1%)
7	Jan'94	Dec'94	34	38.2%	(30.3%-46.2%)	32.0	(0.0-76.4)	14.7%	(10.5%-18.9%)
8	Jan'01	Dec'03	109	45.0%	(40.3%-49.6%)	33.1	(3.2-63.1)	11.9%	(10.0%-13.9%)
9	Jan'96	Dec'96	21	47.6%	(37.0%-58.3%)	36.8	(11.5-62.1)	28.6%	(19.8%-37.3%)
10	Jan'02	Dec'02	1	100.0%		15.0		0.0%	
11	Jan'00	Dec'00	11	54.5%	(39.9%-69.2%)	24.0	(0.0-55.6)	9.1%	(4.2%-14.0%)
12	Jan'95	Dec'95	29	41.4%	(32.6%-50.2%)	32.2	(5.1-59.2)	3.4%	(2.2%-4.7%)
13	Jan'97	Dec'97	9	66.7%	(52.1%-81.2%)	19.6	(0.0-55.0)	0.0%	(0.0% - 0.0%)
14	Jan'02	Dec'02	12	33.3%	(20.8%- 45.9%)	38.3	(2.2-74.5)	0.0%	(0.0% - 0.0%)
15	Jan'00	Dec'01	27	70.4%	(62.5%-78.2%)	30.9	(0.0-63.1)	3.7%	(2.4% - 5.0%)
16	Jan'94	Dec'94	27	33.3%	(25.0%-41.7%)	36.4	(0.0-74.0)	18.5%	(12.8% - 24.2%)
17	Jan'91	Dec'91	8	37.5%	(21.3%-53.7%)	27.3	(0.0-61.8)	37.5%	(21.3%-53.7%)
18	Jan'00	Dec'00	12	75.0%	(64.4%-85.6%)	41.1	(2.3-79.9)	0.0%	(0.0%- 0.0%)
19	Jan'95	Dec'97	41	43.9%	(36.4%-51.4%)	40.4	(7.3-73.5)	7.3%	(5.2%-9.4%)
20	Jan'91	Dec'92	8	37.5%	(21.3%-53.7%)	20.4	(0.0 - 48.3)	37.5%	(21.3%-53.7%)
Allclusters			1056	49.0%	(47.5%-50.5%)	46.9	(14.7 - 79.0)	11.7%	(11.1% - 12.4%)
Outsideclusters			3595	46.3%	(45.4%-47.1%)	31.6	(0.0-63.5)	17.0%	(16.6%-17.5%)
All			4651	46.9%	(46.2%- 47.6%)	31.4	(0.0-63.3)	15.8%	(15.4%-16.2%)

Table 8.7: Change of voluntarily reported leprosy detection rate by distance to roads, rivers and clinics. Adjusted rate ratios are estimates from a model including distance to town, clinic, river or road.

Distance	Univariate	95%-CI	Adjusted	95%-CI
Road				
Linear	0.911	(0.894-0.929)	0.934	(0.915-0.953)
Quadratic	0.995	(0.993-0.996)	0.996	(0.999-1.002)
Category				
0-1 km	1			
1-2 km	0.624	(0.450-0.864)	0.721	(0.519-1.002)
2-3 km	0.348	(0.252-0.482)	0.489	(0.349-0.684)
3-4 km	0.326	(0.238-0.446)	0.465	(0.333-0.649)
4-5 km	0.278	(0.203-0.381)	0.424	(0.301-0.597)
5-6 km	0.274	(0.201-0.374)	0.465	(0.328-0.659)
6-7 km	0.308	(0.227-0.419)	0.555	(0.390-0.789)
7-8 km	0.310	(0.228-0.422)	0.558	(0.391-0.797)
8-9 km	0.353	(0.258-0.481)	0.621	(0.436-0.884)
9-10 km	0.275	(0.193-0.391)	0.493	(0.337-0.721)
10-11 km	0.150	(0.090-0.249)	0.275	(0.162-0.466)
11-12 km	0.166	(0.095-0.289)	0.286	(0.161-0.508)
12-13 km	0.092	(0.044-0.194)	0.152	(0.072-0.325)
13-14 km	0.130	(0.057-0.294)	0.195	(0.085-0.446)
14-15 km	0.124	(0.050-0.307)	0.197	(0.079-0.492)
15-16 km	0.115	(0.042-0.315)	0.189	(0.068-0.525)
16-17 km	0.063	(0.014-0.289)	0.098	(0.021-0.457)
17-18 km	0.095	(0.026-0.351)	0.154	(0.041-0.580)
18-19 km	0.092	(0.018-0.472)	0.156	(0.030-0.810)
19-20 km	0.334	(0.095-1.173)	0.542	(0.148-1.984)
>20km	0.448	(0.114-1.762)	0.691	(0.165-2.891)

Distance	Univariate	95%-CI	Adjusted	95%-CI
River				
Linear	1.028	(0.988-1.070)	1.033	(0.992-1.075)
Quadratic	0.998	(0.990-1.005)	0.998	(0.996-1.012)
Category				
0-1 km	1			
1-2 km	1.417	(1.220-1.645)	1.295	(1.112-1.509)
2-3 km	1.342	(1.124-1.603)	1.278	(1.066-1.533)
3-4 km	1.403	(1.143-1.721)	1.280	(1.037-1.580)
4-5 km	1.142	(0.869-1.501)	1.083	(0.821-1.429)
5-6 km	0.790	(0.508-1.227)	0.868	(0.556-1.356)
6-7 km	0.914	(0.394-2.121)	0.870	(0.371-2.039)
7-8 km	0.373	(0.044-3.147)	0.348	(0.041-2.958)
Clinic				
Linear	0.963	(0.939-0.987)	1.006	(0.981-1.033)
Quadratic	0.997	(0.995-0.999)	1.000	(0.999-1.004)
Category				
0-1 km	1			
1-2 km	0.634	(0.537-0.749)	0.787	(0.662-0.937)
2-3 km	0.763	(0.640-0.910)	0.978	(0.811-1.179)
3-4 km	0.681	(0.545-0.850)	0.857	(0.680-1.081)
4-5 km	0.821	(0.636-1.060)	0.992	(0.761-1.293)
5-6 km	0.858	(0.601-1.225)	0.996	(0.690-1.438)
6-7 km	1.034	(0.698-1.531)	1.362	(0.904-2.053)
7-8 km	0.937	(0.598-1.470)	1.202	(0.762-1.896)
8-9 km	0.576	(0.311-1.066)	0.826	(0.443-1.538)
9-10 km	0.671	(0.367-1.228)	1.066	(0.577-1.969)
10-11km	0.552	(0.261-1.166)	0.777	(0.365-1.653)
11-12 km	1.114	(0.602-2.062)	1.696	(0.904-3.180)
12-13 km	0.767	(0.359-1.638)	1.184	(0.545-2.569)
13-14 km	0.182	(0.027-1.227)	0.441	(0.064-3.014)
14-15 km	0.048	(0.001-3.371)	0.192	(0.003-13.854)
>15 km	0.142	(0.007-2.895)	0.553	(0.026-11.683)

Table 8.8: Change of survey leprosy detection rate by distance to roads, rivers and clinics. Adjusted rate ratios are estimates from a model including distance to town ,and clinic, river or road.

Distance	Univariate	95%-CI	Adjusted	95%-CI
Town				
Linear	0.942	(0.915-0.970)	0.945	(0.915-0.976)
Quadratic	0.996	(0.993-0.998)	0.996	(0.993-0.999)
Category				
0-1 km	1			
1-2 km	0.556	(0.390-0.792)	0.616	(0.430-0.882)
2-3 km	0.411	(0.294-0.577)	0.525	(0.368-0.749)
3-4 km	0.422	(0.303-0.588)	0.541	(0.379-0.774)
4-5 km	0.413	(0.297-0.573)	0.505	(0.350-0.728)
5-6 km	0.374	(0.268-0.523)	0.432	(0.294-0.634)
6-7 km	0.388	(0.274-0.551)	0.423	(0.282-0.632)
7-8 km	0.408	(0.285-0.585)	0.407	(0.268-0.616)
8-9 km	0.460	(0.313-0.677)	0.412	(0.265-0.639)
9-10 km	0.297	(0.167-0.529)	0.285	(0.155-0.524)
10-11 km	0.172	(0.068-0.434)	0.216	(0.084-0.558)
11-12 km	0.319	(0.120-0.845)	0.492	(0.180-1.342)
>12 km	0.354	(0.087-1.446)	0.803	(0.186-3.468)
Clinic				
Linear	1.032	(1.009-1.056)	1.065	(1.039-1.091)
Quadratic	1.002	(1.000-1.004)	1.004	(0.999-1.005)
Category				
0-1 km	1			
1-2 km	0.631	(0.517-0.770)	0.732	(0.595-0.900)
2-3 km	0.833	(0.679-1.022)	1.000	(0.806-1.240)
3-4 km	0.780	(0.606-1.004)	0.921	(0.709-1.197)

Distance	Univariate	95%-CI	Adjusted	95%-CI
4-5 km	0.916	(0.684-1.226)	1.034	(0.764-1.399)
5-6 km	1.187	(0.822-1.716)	1.293	(0.887-1.887)
6-7 km	1.660	(1.137-2.423)	2.211	(1.501-3.255)
7-8 km	1.653	(1.094-2.498)	1.923	(1.263-2.929)
8-9 km	1.757	(1.139-2.709)	2.094	(1.343-3.265)
9-10 km	1.312	(0.777-2.216)	1.756	(1.024-3.011)
10-11km	1.251	(0.685-2.282)	1.515	(0.821-2.796)
11-12 km	1.898	(1.073-3.357)	2.324	(1.294-4.176)
12-13 km	1.075	(0.497-2.324)	1.425	(0.648-3.136)
13-14 km	0.318	(0.056-1.798)	0.678	(0.118-3.910)
14-15 km	0.059	(0.001-5.760)	0.189	(0.002-18.657)
>15 km	0.089	(0.001-8.605)	0.284	(0.003-28.217)
Road				
Linear	0.954	(0.934-0.973)	0.955	(0.934-0.976)
Quadratic	0.997	(0.995-0.998)	0.997	(0.999-1.002)
Category				
0-1 km	1			
1-2 km	0.838	(0.545-1.288)	0.923	(0.598-1.423)
2-3 km	0.434	(0.281-0.670)	0.560	(0.359-0.875)
3-4 km	0.375	(0.245-0.575)	0.463	(0.296-0.725)
4-5 km	0.405	(0.268-0.613)	0.530	(0.340-0.825)
5-6 km	0.401	(0.266-0.603)	0.572	(0.365-0.895)
6-7 km	0.503	(0.337-0.749)	0.751	(0.481-1.174)
7-8 km	0.546	(0.367-0.812)	0.802	(0.513-1.255)
8-9 km	0.664	(0.446-0.988)	0.961	(0.618-1.495)
9-10 km	0.466	(0.301-0.723)	0.664	(0.415-1.061)
10-11 km	0.284	(0.161-0.502)	0.370	(0.204-0.670)
11-12 km	0.286	(0.152-0.538)	0.366	(0.190-0.704)
12-13 km	0.192	(0.090-0.412)	0.226	(0.103-0.497)
13-14 km	0.276	(0.121-0.627)	0.297	(0.128-0.687)
14-15 km	0.295	(0.125-0.698)	0.391	(0.163-0.936)

Distance	Univariate	95%-CI	Adjusted	95%-CI
15-16 km	0.192	(0.064-0.582)	0.284	(0.093-0.870)
16-17 km	0.105	(0.020-0.552)	0.147	(0.028-0.781)
17-18 km	0.159	(0.038-0.661)	0.227	(0.054-0.961)
18-19 km	0.111	(0.014-0.884)	0.152	(0.019-1.234)
19-20 km	0.327	(0.056-1.912)	0.340	(0.056-2.055)
>20km	0.075	(0.001-7.382)	0.066	(0.001-6.587)
River				
Linear	1.042	(0.997-1.089)	1.051	(1.005-1.100)
Quadratic	1.000	(0.991-1.008)	1.001	(0.996-1.013)
Category				
0-1 km	1	-		
1-2 km	1.340	(1.129-1.590)	1.293	(1.085-1.540)
2-3 km	1.325	(1.083-1.620)	1.264	(1.029-1.554)
3-4 km	1.656	(1.332-2.059)	1.465	(1.170-1.835)
4-5 km	0.969	(0.696-1.349)	0.902	(0.644-1.262)
5-6 km	0.944	(0.597-1.493)	1.078	(0.677-1.715)
6-7 km	0.661	(0.217-2.018)	0.568	(0.185-1.749)
7-8 km	0.516	(0.067-4.006)	0.437	(0.056-3.427)

Table 8.9: Change of contact tracing leprosy detection rate by distance to roads, rivers and clinics. Adjusted rate ratios are estimates from a model including distance to town ,and clinic, river or road.

Distance	Univariate	95%-CI	Adjusted	95%-CI
Town				
Linear	0.900	(0.860-0.942)	0.892	(0.849-0.937)
Quadratic	0.992	(0.988-0.996)	0.992	(0.998-1.007)
Category				
0-1 km	1			

Distance	Univariate	95%-CI	Adjusted	95%-CI
1-2 km	0.451	(0.285-0.715)	0.503	(0.314-0.806)
2-3 km	0.292	(0.187-0.457)	0.355	(0.220-0.572)
3-4 km	0.257	(0.164-0.402)	0.279	(0.170-0.458)
4-5 km	0.287	(0.186-0.443)	0.302	(0.184-0.497)
5-6 km	0.207	(0.130-0.330)	0.201	(0.117-0.346)
6-7 km	0.297	(0.187-0.470)	0.265	(0.153-0.459)
7-8 km	0.305	(0.189-0.491)	0.237	(0.133-0.420)
8-9 km	0.267	(0.153-0.467)	0.185	(0.098-0.352)
9-10 km	0.144	(0.055-0.381)	0.110	(0.040-0.303)
10-11 km	0.078	(0.015-0.415)	0.077	(0.014-0.415)
11-12 km	0.081	(0.008-0.838)	0.100	(0.009-1.046)
>12 km	0.296	(0.044-2.008)	0.580	(0.080-4.209)
Clinic				
Linear	0.602	(0.446-0.813)	0.738	(0.539-1.011)
Quadratic	0.787	(0.578-1.073)	0.995	(0.716-1.381)
Category	1			
0-1 km	0.716	(0.487-1.054)	0.918	(0.614-1.373)
1-2 km	1.009	(0.666-1.528)	1.249	(0.809-1.927)
2-3 km	1.022	(0.570-1.833)	1.193	(0.655-2.172)
3-4 km	1.785	(1.037-3.071)	2.363	(1.337-4.178)
4-5 km	1.506	(0.795-2.853)	1.712	(0.893-3.284)
5-6 km	1.584	(0.808-3.107)	2.044	(1.025-4.077)
6-7 km	0.994	(0.409-2.414)	1.471	(0.592-3.656)
7-8 km	1.624	(0.740-3.567)	2.348	(1.047-5.266)
8-9 km	2.207	(1.005-4.847)	2.999	(1.329-6.767)
> 10 km	1.163	(0.387-3.493)	1.608	(0.520-4.967)
Road				
Linear	0.962	(0.933-0.991)	0.975	(0.944-1.006)
Quadratic	0.997	(0.996-0.999)	0.998	(0.999-1.003)

Distance	Univariate	95%-CI	Adjusted	95%-CI
Category				
0-1 km	1			
1-2 km	0.645	(0.347-1.199)	0.768	(0.411-1.435)
2-3 km	0.310	(0.164-0.586)	0.484	(0.251-0.933)
3-4 km	0.365	(0.202-0.657)	0.612	(0.327-1.146)
4-5 km	0.285	(0.156-0.521)	0.528	(0.275-1.011)
5-6 km	0.341	(0.192-0.607)	0.729	(0.382-1.388)
6-7 km	0.448	(0.256-0.782)	0.984	(0.520-1.864)
7-8 km	0.403	(0.228-0.711)	0.872	(0.455-1.673)
8-9 km	0.555	(0.318-0.971)	1.219	(0.650-2.285)
9-10 km	0.486	(0.267-0.885)	1.034	(0.543-1.971)
10-11 km	0.303	(0.141-0.653)	0.547	(0.244-1.223)
11-12 km	0.197	(0.073-0.533)	0.327	(0.117-0.911)
12-13 km	0.203	(0.073-0.566)	0.316	(0.110-0.910)
13-14 km	0.189	(0.050-0.712)	0.255	(0.067-0.974)
14-15 km	0.130	(0.024-0.710)	0.204	(0.037-1.136)
15-16 km	0.302	(0.087-1.056)	0.593	(0.165-2.130)
$>$ 16 km	0.197	(0.036-1.078)	0.406	(0.072-2.291)
River				
Linear	0.981	(0.915-1.052)	0.991	(0.923-1.064)
Quadratic	0.989	(0.976-1.003)	0.991	(0.993-1.022)
Category				
0-1 km	1			
1-2 km	1.359	(1.062-1.740)	1.277	(0.992-1.644)
2-3 km	1.117	(0.821-1.520)	1.019	(0.743-1.399)
3-4 km	1.378	(0.984-1.930)	1.189	(0.839-1.686)
4-5 km	0.546	(0.294-1.015)	0.509	(0.272-0.952)
5-6 km	0.949	(0.489-1.840)	1.150	(0.587-2.253)
6-7 km	0.482	(0.073-3.192)	0.418	(0.062-2.795)

9

General discussion

Scope of the thesis

This thesis deals with spread of *Mycobacterium leprae* in a heterogeneous population, with the objective to understand the role of heterogeneity in leprosy epidemiology and control. In the first part of this thesis, a microsimulation model is developed to study the role of household structure, and heterogeneity in the susceptibility to leprosy. Interventions targeted at household members are evaluated using this model. In the second part of this thesis a closer look is taken at the spatial patterns of leprosy at village level and at district level.

Answering the research questions

What are the causes of clustering of leprosy in households?

Clustering within households of leprosy can be caused by an as yet not established mechanism that aggregates susceptibility in households, but irrespective of the underlying mechanism an assumption of additional within household transmission is needed to obtain the observed clustering of leprosy in households.

Each of six hypothesized mechanisms for the heterogeneity of leprosy can explain observed clustering in households (Chapter 4). The hypothesized mechanisms differed in the allocation of susceptibility; the mechanisms included totally random allocation of susceptibility, a household based factor, genetic predisposition and combinations of these last two mechanisms. Based on the fit of the model results to the data, none

of the mechanisms could be excluded. However, for each mechanism, additionally within-household transmission is needed for to obtain the observed clustering of leprosy within households. Population studies in the 1980's and 1990's suggested the existence of a gene - or group of genes - determining susceptibility to leprosy[72, 73]. In the past decade specific genetic polymorphisms were found that are associated with leprosy[36, 106, 35]. The genetic hypothesis is supported by epidemiological studies showing an increased risk for relatives to develop leprosy[37, 27]. In Chapter 4 was shown that it is possible to reproduce the distribution of leprosy among contacts in scenarios where heterogeneity in susceptibility is based only on genes. The genetic scenarios, however, underestimate the risk of spouses and overestimate the risk of siblings, suggesting the need for other mechanisms. Leprosy is more prevalent in impoverished populations[38, 40]. This might be explained by reduced immunity due to poor health status[38], or increased exposure to *M. leprae* due to housing conditions or crowding[107]. The outcomes of the model (Chapter 4) show that a hypothetical household factor that determines susceptibility, can reproduce the observed clustering of leprosy in households[37]. Under this hypothesis, however, the model predicts an unexpected high risk in small households. This can be explained by the fact that there is no correlation between crowding and susceptibility in the model. Secondly, under this mechanism susceptibility was a factor attributed to a household, hence individuals that move from one household to another can become susceptible after moving. Because movement between households happens predominantly at marriage these individuals are living as recently married couple in small households. This high risk for small households is contrary to a study from Indonesia, which only shows an increased risk for large households[107], but in the study area of this thesis no such relation with household size was found (Chapter 4). The hypothesized household factor could be poverty. The influence of poverty on the occurrence of leprosy has been studied at population level, but it would be interesting to study the relation between poverty and leprosy at a household or individual level. The combined scenarios with both a household factor and a gene gave the best overall fit to the data, and also performed well under different assumptions regarding the percentage of susceptibles in the population (Chapter 4). Although this cannot be considered as formal proof, these modelling findings support a multifactorial origin of susceptibility to leprosy. This outcome, together with the results of epidemiological field studies[37, 27, 38, 40] and genome wide screening[106, 35], strongly suggest that the heterogeneity of sus-

ceptibility to leprosy is caused by a combination of genetic and environmental factors. Quantification of the model to similar data sets for other countries (e.g. Indonesia[27]) will give additional insight in the mechanisms underlying heterogeneity in susceptibility to leprosy. It is also a way to further validate the microsimulation. The research in this thesis showed that predictions on the effect of control might be quantitatively different when assuming different underlying mechanisms for susceptibility. Therefore, a better understanding of these mechanisms is needed before the microsimulation model developed in this thesis can be used for quantitative predictions. In conclusion, the results of the microsimulation study could not falsify any of the hypothesized mechanisms. However, heterogeneity in susceptibility to leprosy is most likely a combination of household and genetic factors, because the model with a household factor and genetic factors performed best, and because of the strong support for both factors in other studies[37, 27, 36, 106, 35].

Which leprosy control strategy targeted at household members of leprosy patients performs best?

Intervention strategies that shorten the infectious period are most effective in reducing the future incidence of leprosy. Such interventions include detection of subclinical infections (early diagnosis) and chemoprophylaxis.

This result is robust under different assumptions on the mechanism underlying heterogeneity of susceptibility. With each susceptibility mechanism, the ordering of strategies with regard to reduction of incidence was equal. However, the quantitative predictions for these mechanisms differ greatly both for the current control and for new interventions. The infectious period, which is the period during which an individual can infect others, is shortened by early diagnosis. Shorter detection delays will lead to lower incidences [3]. With new interventions targeting subclinical cases, the infectious period can be reduced even further. Approximately 75% of new infections occur during the subclinical phase of infectious cases with an average detection delay of 2 years (Chapter 2). Only when new infections caused by subclinical patients are not enough to sustain the epidemic, effective control is possible [108]. Strategies targeting subclinical cases can be expected to advance the prospect of eliminating leprosy in terms of reducing the incidence to zero, which has not been the case with the current control strategy based on the provision of multidrug therapy to clinical

cases of leprosy. The detection delay is strongly correlated with the severity of leprosy [109]. An intervention targeting subclinical infections will reduce the occurrence of nerve damage and resulting disabilities considerably. Hence, early diagnosis and chemoprophylaxis are important interventions for the control of leprosy. Chemoprophylaxis with a single dose of rifampicin has shown to be effective in contacts of leprosy patients [17], but implementation studies need to be performed to establish the cost-effectiveness, feasibility and acceptability of this intervention in the field. As rifampicin is an important drug against *M. leprae* and *M. tuberculosis*, regular assessment of resistance of both mycobacteria should be done in an area where rifampicin is used as chemoprophylaxis [18]. Early diagnosis, i.e. detecting subclinical cases, is expected to perform better than chemoprophylaxis in reducing the number of new cases (Chapter 5). A reliable test for early diagnosis, although not (yet) available, needs to perform well under field circumstances and must be affordable for routine use in contact tracing. In the scenario analyses of chapter 5, such a hypothetical test was used in three consecutive contact visits. Hence, the results are valid when a cheap and easy-to-use test becomes available. This strategy does not have the disadvantage of treating uninfected people [18]. The treatment regimen for subclinical cases needs to be determined. Treating these cases with the regular multidrug therapy regimen (either MB or PB) that leprosy patients receive might not be necessary, but it is not known to what extend the course can be reduced. In conclusion, the development of a cheap and easy test for subclinical infection is the most important step forward in the control of leprosy. Chemoprophylaxis will also reduce transmission and further implementation studies should be encouraged.

Does the increased risk for household contacts and neighbours in Bangladesh produce spatial clustering of leprosy?

No clustering of leprosy was found within villages. Therefore it is unlikely that increased risk at the micro level of household members and neighbours produces clustering at village and thus higher aggregation level, i.e. district level.

There are three explanations for not finding clustering within villages: Firstly, the risk of neighbours is equal to the risk of village members. The four villages studied in Chapter 7 are a sample from twenty villages studied by Moet *et al.* [82]. They found a large variation in the number of previously undiagnosed leprosy patients

during the active survey in these twenty villages. Ten out of twenty villages had no cases and in the others it ranged from one to six previously undiagnosed leprosy patients. The prevalence reported previously in surveys also varied from 0.1 to 0.5 per 1,000 population [82]. In villages with a high prevalence many more people are in contact with leprosy patients than in villages with a low prevalence. Everybody in these villages can be considered as a contact of a leprosy patient. This explanation implies that spatial clusters do not occur at village level. Secondly, the force of clustering is too weak to be observed in a study with four villages and in total only 33 cases, including those known before the active survey [82]. I define the force of clustering as the strength with which new cases arise among individuals spatially close to a patient compared to new cases arising among individuals not living spatially close. The number of new cases among household members was high (15.6/1,000), for neighbours it was less (8.7/1,000) in villages with 0.1 to 0.5 previously registered cases [37]. However, social contacts had a prevalence of 4.9/1,000, and most social contacts live in the same village as the patient but not necessarily close (Chapter 6). These social contacts disrupt the spatial clustering by adding risk to spatially distant contacts. Hence the force of clustering is not strong. It is therefore necessary to survey many cases (or villages) to find a cluster. With much higher prevalence, clustering at the village level can indeed be found for similar risks of spatially close contacts[110]. Thirdly, it should be taken into account how clusters are spatially defined. The study in Chapter 7 uses circular windows to detect spatial clusters. In this way, it includes all individuals within a certain direct distance from the patients. Using direct distance to measure clustering in concentric circles will group individuals of contact categories with different levels of contact (Chapter 6), therefore not resulting in spatial clusters. In conclusion, clustering did not occur in the four villages, because 1) the clusters do not exist because all inhabitants of villages are at high risk; 2) clusters could not be found in this study because the strength of clustering is low and too few villages were observed; 3) clusters have another shape than circular. Although defining contact groups by location from a newly detected case might seem an easy and efficient method, trying to identify high-risk spatial clusters within villages is not a useful approach in leprosy control in this area in Bangladesh.

At what levels of spatial aggregation does leprosy clustering occur in Bangladesh?

Within villages no clusters were found, but extensive spatial and spatio-temporal clustering is observed at district level

In the previous section, the reasons why no clustering was found at village level , of which lack of power might be one. With over 11,000 cases at district level, the ability to detect clusters was much greater than in the villages. Clusters at district level are larger than a single village (Chapter 8), and contain usually a number of villages. These larger areas could be targeted for surveys or more intense awareness campaigns. It should, however, be taken into account that the clusters reported in Chapter 8 are spatio-temporal clusters, hence only found for a certain time frame. An analysis of the areas or cases might reveal that the clustering is a result of increased case finding because of intensified surveillance or community awareness, rather than an increased underlying prevalence. Hence, health services in areas with high case detection rate are not necessarily performing badly on leprosy control. In conclusion, clustering at district level can more easily be detected due to the high number of cases. Clusters at district level contain one of more villages. The possible cause of existence of clusters needs to be investigated before taking management decisions. The database collected for Chapter 8 can be used for further research.

What geographic features are related to risk of leprosy in Bangladesh?

At a district level the risk of leprosy is associated with the proximity to towns. The risk is neither at district or at village level associated with roads, clinics, and water bodies.

The cases in the spatio-temporal leprosy clusters did not differ in distance to towns, roads, clinics, and water bodies from the cases outside the clusters. Hence, geographic features did not determine the observed clustering (Chapter 8). Leprosy is considered a rural disease[2, 41], but in the study area in northwest Bangladesh rural towns, i.e. moderately sized towns in a rural area, have a higher new case detection rate than the surrounding rural areas (Chapter 8). Also, the highest prevalence among the four villages was found in the village situated at the edge of the district capital, and could actually be considered part of it (Chapter 7). At district level, the sharp decline in

new case detection in the first kilometres outside a town suggests that it is not the distance to town, but the difference between urban and rural populations determining the occurrence of leprosy (Chapter 8). There are four possible explanations. Firstly, it could be the result of selective migration towards these towns [40, 39]. Secondly, a higher awareness of leprosy among the urban population is possible. Thirdly, the circumstances in these towns are favourable for the transmission of *M. leprae*. Fourthly, a better access to health services might increase the detection rate in towns. This last explanation seems unlikely, because voluntary reporting rates were not higher close to a leprosy clinic (Chapter 8). Geographic features - roads, water bodies - were no risk factors in this area, although these were found to be risk factors in Malawi [41]. The risk with proximity to town was found in this Bangladeshi area as it was in Brazil [40, 39], but proximity to towns was no risk factor in Malawi [41]. Hence, geographic risk factors of leprosy are not equal worldwide. In conclusion, in this study cases are found especially in the population in and around towns. Further studies of leprosy in urban areas and towns in rural areas are recommended. If urban areas are an important source of transmission, improvements are possible by focusing more on urban leprosy control.

Summary

The epidemiology of leprosy has heterogeneities at different levels, from the individual (gene) to geographic areas. The future leprosy trend depends on the heterogeneity in leprosy susceptibility. The qualitative effect of interventions as modelled in this thesis, is similar for all mechanisms that might determine heterogeneity in leprosy susceptibility, while quantitative predictions are highly sensitive to the assumed underlying mechanism. Detection of subclinical cases (early diagnosis) and chemoprophylaxis are shown to be the preferred interventions. The heterogeneity on individual and household level does not show at a village level. However, leprosy occurs spatially clustered at district level. Urban populations seem to have a higher risk in the study area. I have great expectations of early diagnosis and chemoprophylaxis as effective interventions to reduce transmission of *M. leprae*.

Conclusions

- Clustering of leprosy in households is caused by a combination of increased transmission within the household and an unknown mechanism determining susceptibility to leprosy.
- The most effective way to control leprosy is to identify and treat individuals with subclinical infection of *Mycobacterium leprae*.
- Clusters of leprosy cases in north west Bangladesh are observed at district level, but not at the level of villages.
- The prevalence of leprosy in northwest Bangladesh is higher in urban areas than in the surrounding rural areas.

Recommendations

- The mechanisms underlying heterogeneity in leprosy susceptibility should be further explored.
- To improve the effectiveness of leprosy control, it is necessary to conduct implementation studies of chemoprophylaxis and prioritize the development of a field-applicable test for subclinical infection of *M. leprae*.
- The possible causes of a spatial cluster of leprosy patients should be investigated before deciding on the control policy in an area.
- Further study should be performed on the occurrence of leprosy in urban areas and on its determinants in urban areas.

Summary

This thesis investigates leprosy; the infection dynamics of *Mycobacterium leprae* in a heterogeneous population, the efficacy of interventions targeted at household contacts of leprosy patients, and the spatial heterogeneity in the occurrence of leprosy in northwest Bangladesh.

Chapter 1 introduces leprosy, population heterogeneity, and mathematical modelling of leprosy. Leprosy is caused by the bacterium *M. leprae*. Of this infectious disease, a quarter of a million new cases of leprosy were detected worldwide in 2008. The infection is curable with multidrug therapy, but prior to cure the disease can cause impairments. Transmission of the bacterium can occur during contact between an infectious person and a susceptible person. In this chapter, three types of heterogeneity of the population are introduced: contact heterogeneity, heterogeneity in susceptibility and spatial heterogeneity. Each of these heterogeneities can play a role in leprosy epidemiology. The importance of population heterogeneity for infection dynamics has been shown and should be taken into account in research on the spread and control of leprosy.
The research question of this thesis are:

1. What are the causes of clustering of leprosy in households?
2. Which leprosy control strategy targeted at household members of leprosy patients performs best?
3. Does the increased risk for household contacts and neighbours in Bangladesh produce spatial clustering of leprosy?
4. At what levels of spatial aggregation does leprosy clustering occur in Bangladesh?
5. What geographic features are related to risk of leprosy in Bangladesh?

A full description of the model developed in this thesis is given in **Chapter 2**. The model (SIMCOLEP) is a microsimulation model, and simulates a population including the formation and change of households. The disease module explicitly includes

within-household and between-household transmission. Furthermore, this model contains six different mechanisms to determine the heterogeneity in susceptibility: (1) susceptibility was allocated at random to persons (i.e. no specific mechanism), (2) a household factor, (3, 4) a genetic factor (dominant or recessive), or (5, 6) half a household factor and half genetic. These mechanisms result in distinctly different distributions of susceptibles over households.

Long runtimes are a common problem in microsimulation models of infectious diseases. In **Chapter 3** we present a novel method, MUSIDH, to reduce runtime, which can be used for infections in which demographics are not influenced by disease. MUSIDH attaches a fixed number of infection histories to each demographic history. The method can give a large reduction in computation time at the cost of a small loss in precision. The largest time savings are obtained for rare infections with complex demographic histories.

Chapter 4 focuses on the question, which of the six mechanisms for susceptibility to leprosy, described in chapter 2, is most likely. The model is fitted to a large and detailed data set from Bangladesh. All mechanisms fit to the data, therefore none of the mechanisms can be excluded. However, the mechanisms differ in the fit to certain aspects of the datasets, such as the distribution of cases over household sizes and relationship to the patient. Moreover, the prediction of the future trend of leprosy depends on the mechanism. Further research into the mechanimsms determining susceptiblity to leprosy is needed.

Chapter 5 contains a comparison of the expected trends in case detection for seven scenarios of leprosy control. The scenarios were (1) Continuation of the baseline control program in northwest Bangladesh including BCG-vaccination. Modifications of the baseline program were: (2) No contact tracing; (3) Chemoprophylaxis; (4) Early diagnosis of subclinical infections; and (5) A new tuberculosis vaccine without cross-immunity against *M. leprae* replacing the BCG-vaccine. Scenarios 6 & 7 were combinations of scenarios 5 with scenarios 3 and 4. Cessation of contact tracing and introduction of an ineffective tuberculosis vaccine will reduce the rate of decline in the incidence of leprosy. Leprosy incidence will be strongly reduced in the presence of a good BCG coverage, and the combined strategy of contact tracing, early

diagnosis and treatment of infection, or chemoprophylaxis among household contacts.

In **Chapter 6**, the relation between spatial distance and social distance is investigated in northwest Bangladesh. Sixty seven per cent of contacts with a high risk of developing leprosy (neighbours) lived within 10 meters, while all low risk contacts (such as social contacts) lived more than 10 meters from the index patient. Classification based on intervals of spatial distance creates categories that contain contacts of different socially defined categories, which can have different risk of leprosy. Classification of contacts based on the spatial distance, such as done by GIS-techniques, produces other groups than with social definitions.

In **Chapter** 7 an attempt is made to identify high-risk areas within villages around known cases. However, no clustering of leprosy within four villages in north west Bangladesh was found. Spatial analysis at the level of villages in highly endemic areas does not appear to be useful for identifying clusters of patients.

In **Chapter 8**, the distribution of over 11,060 leprosy cases detected over 15 years in a control program in northwest Bangladesh is investigated. Leprosy is clustered at district level, and several spatio-temporal clusters of leprosy cases were found. The overall risk of leprosy in the district was not associated with distance to roads, rivers, and leprosy clinics. However, the risk of leprosy decreased with distance from town centres. The association of a risk of leprosy with the proximity to towns indicates that rural towns may play an important role in the epidemiology of leprosy in this district.

Chapter 9 provides answers to the research questions and a gives a general discussion.

Conclusions

- Clustering of leprosy in households is caused by a combination of increased transmission within the household and an unknown mechanism determining susceptibility to leprosy.
- The most effective way to control leprosy is to identify and treat individuals with subclinical infection of *Mycobacterium leprae*.
- Clusters of leprosy cases in north west Bangladesh are observed at district level, but not at the level of villages.
- The prevalence of leprosy in northwest Bangladesh is higher in urban areas than in the surrounding rural areas.

Recommendations

- The mechanisms underlying heterogeneity in leprosy susceptibility should be further explored.
- To improve the effectiveness of leprosy control, it is necessary to conduct implementation studies of chemoprophylaxis and prioritize the development of a field-applicable test for subclinical infection of *M. leprae*.
- The possible causes of a spatial cluster of leprosy patients should be investigated before deciding on the control policy in an area.
- Further study should be performed on the occurrence of leprosy in urban areas and on its determinants in urban areas.

Samenvatting

Dit proefschrift gaat over lepra: de infectie dynamiek van *Mycobacterium leprae* in een heterogene populatie, de effectiviteit van interventies gericht op huishoudcontacten van leprapatienten en de ruimtelijke heterogeneniteit in het voorkomen van lepra in noordwest Bangladesh.

Hoofdstuk 1 is de inleiding van dit proefschrift. Lepra, heterogeniteit in de populatie en het wiskundig modelleren van lepra worden in dit hoofstuk geïntroduceerd. Lepra wordt veroorzaakt door de bacterie *M. leprae*. Van deze infectieuze ziekte werden in 2008 wereldwijd meer dan een kwart miljoen nieuwe gevallen gedetecteerd. De infectie kan effectief behandeld worden met multidrug therapie, maar de ziekte kan dan al handicaps veroorzaakt hebben. Transmissie van de bacterie kan plaats vinden gedurende contact tussen een infectieus persoon en een vatbaar persoon. In dit hoofdstuk worden drie vormen van heterogeniteit in de populatie geïntroduceerd: contactheterogeneniteit, heterogeneniteit in vatbaarheid en ruimtelijke heterogeniteit. Voor lepra is bekend dat elk van deze vormen van heterogeneteit een rol kan spelen in de epidemiologie van lepra. Het belang van populatieheterogeneniteit voor de dynamiek van infectieuze ziekten is aangetoond o.a. door middel van wiskundige modellen en moet dus meegenomen worden in onderzoek naar de verspreiding en controle van lepra.
De onderzoeksvragen van dit proefschrift zijn:

1. Wat zijn de oorzaken van clustering van leprapatienten in huishoudens?
2. Welke controle maatregelen gericht op huishoudengenoten van leprapatienten werken het best?
3. Zijn leprapatienten ruimtelijk geclusterd in Bangladesh doordat huisgenoten en buren van patienten een hoger risico hebben om zelf ook lepra te krijgen?
4. Op welk ruimtelijk aggregatie niveau komt clustering van lepra voor in Bangladesh?
5. Welke geographische eigenschappen en objecten zijn gerelateerd aan het risico op lepra in Bangladesh?

Het model, dat ontwikkeld is in dit proefschrift, wordt in **hoofdstuk 2** beschreven. Het model (SIMCOLEP) is een microsimulatie model, dat een populatie inclusief de vorming en verandering van huishoudens simuleert. Transmissie binnen en tussen huishoudens is explicitiet meegenomen in de ziekte module. Het model bevat zes verschillende mechanismen, waarmee heterogeniteit in vatbaarheid voor lepra kan worden beschreven: (1) vatbaarheid wordt willekeurig toegekend aan personen (d.w.z. geen specifiek mechanisme), (2) een huishoudfactor, (3, 4) een genetische factor (dominant of recessief), of (5, 6) voor de helft door een huishoudfactor and voor de andere helft genetisch. Deze mechanismen geven duidelijk verschillende verdelingen van vatbare individuen over huishoudens.

Lange rekentijden zijn een veel voorkomend probleem in microsimulatie modellen van infectieziekten. In **hoofdstuk 3** wordt MUSIDH gepresenteerd, een nieuwe methode om rekentijden te verminderen voor simulaties van infecties waarbij de demografie niet wordt beïnvloed door de ziekte. MUSIDH hecht een vast aantal infectiegeschiedenissen aan één demografische geschiedenis. De methode kan rekentijden sterk verkorten met een klein verlies in precisie. De grootste tijdswinst kan gemaakt worden bij zeldzame infecties met ingewikkelde demografische geschiedenissen.

Hoofdstuk 4 richt zich op de vraag welke van de zes mechanismen voor vatbaarheid voor lepra, die in hoofdstuk 2 zijn beschreven, het meest waarschijnlijk is. Het model is geparameteriseerd op een grote en gedetailleerde dataset uit Bangladesh. Alle mechanismen passen op de data en dus kan geen enkel mechanisme verworpen worden. De mechanismen verschillen echter wel in welke aspecten van de data, zoals huishoudgrootte of relatie tot de patient, beter of slechter pasten. Ook de voorspelde trends in lepraincidentie verschillen tussen de zes mechanismen. Verder onderzoek naar het mechanisme achter vatbaarheid voor lepra is dus nodig.

De verwachte trends in detectie van lepra onder zeven interventiescenarios worden vergeleken in **hoofdstuk 5**. De scenarios zijn (1) Voorzetting van het oorspronkelijke controleprogramma inclusief BCG-vaccinatie in noordwest Bangladesh; Aanpassingen op het oorspronkelijke programma waren: (2) Geen contactenonderzoek; (3) Chemoprofylaxe; (4) Vroege diagnose van subklinische infecties; en (5) Een nieuw tuberculose vaccin zonder kruisbescherming tegen *M. leprae* vervangt het BCG-vaccin. Scenarios

6 & 7 zijn combinaties van scenario 5 met scenarios 3 en 4. Het stoppen met contactonderzoek en de introductie van een ineffectief tuberculose vaccin verminderen de snelheid waarmee de incidentie van lepra afneemt. De lepraincidentie zal bij een goede BCG-vaccinatiedekking en de gecombineerde strategie van contactonderzoek met vroege diagnose of chemoprophylaxe onder huisgenoten sterk verminderen.

In **hoofdstuk 6** wordt de relatie tussen ruimtelijke afstand en sociale afstand in noordwest Bangladesh onderzocht. Zevenenzestig procent van de contacten met een hoog risico op het ontwikkelen van lepra (buren) wonen binnen 10 meter, terwijl alle laagrisico contacten (zoals sociale contacten) meer dan 10 meter van de index patient wonen. Classificatie doormiddel van afstandsintervallen creëert categoriën, die contacten bevatten van verschillende sociale afstand met een ander risico op lepra. Classificatie van contact gebaseerd op ruimtelijke afstand, zoals wordt gedaan met GIS-technieken, geeft andere groepen dan met sociale definities.

In **hoofdstuk 7** wordt geprobeerd hoogrisico gebieden rond bekende leprapatienten op dorpsniveau te identificeren. Geen clustering van lepra wordt gevonden binnen vier dorpen in noordwest Bangladesh. Ruimtelijke analyses op dorpsniveau in hoog endemische gebieden blijkt niet nuttig te zijn om clusters te vinden.

In **hoofdstuk 8** is de ruimtelijke verdeling onderzocht van meer dan 11.060 leprapatienten, die gedurende 15 jaar door een controleprogramma in noordwest Bangladesh gedetecteerd zijn. Lepra is geclusterd op districtsniveau, waarbij verscheidene ruimtetijdsclusters van leprapatienten zijn gevonden. Het risico op lepra in het district is niet geassocieerd met afstand tot wegen, rivieren of lepraklinieken. Het risico op lepra vermindert met de afstand tot stadscentra. De associatie met een risico voor lepra in de nabijheid van steden geeft aan dat steden op het platteland een belangrijke rol kunnen spelen in de epidemiologie van lepra in dit district.

De onderzoeksvragen worden beantwoord in **hoofdstuk 9**.

Conclusies

- Clustering van lepra in huishoudens wordt veroorzaakt door een verhoogde transmissie binnen huishoudens en een nog niet bekend mechanisme dat vatbaarheid voor lepra bepaald.
- De meeste effectieve manier om lepra te beheersen is het identificeren en behandelen van subklinische infecties met *Mycobacterium leprae*.
- Clusters van leprapatienten in noordwest Bangladesh zijn waargenomen op district niveau, maar niet op het niveau van dorpen.
- De prevalentie van lepra in noordwest Bangladesh is hoger in stedelijke gebieden dan in de omgevende rurale gebieden.

Aanbevelingen

- De mechanismen die heterogeniteit voor lepravatbaarheid bepalen moeten verder verkend worden.
- Om de effectiviteit van de beheersing van lepra te bevorderen, is het nodig om chemoprofylaxe implementatie studies uit te voeren en om de ontwikkeling van een veldtest op de subklinische infectie met *M. leprae* te prioriteren.
- De mogelijke oorzaken van een ruimtelijk cluster van leprapatienten moet onderzocht worden voor een besluit over het beheersingsbeleid in zo'n gebied gemaakt wordt.
- Verder onderzoek naar het voorkomen van lepra in stedelijke gebieden en de determinanten van lepra in stedelijke gebieden moet worden uitgevoerd.

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Glossary

Adequately close contact	An event at which two individuals have contact which is close enough for an infectious agent to be transmitted. E.g. for a sexual transmitted disease having unprotected sex can be adequately close, while for influenza travelling in the same bus can be adequately close.
ANNI	Average Nearest Neighbour Index
Asymptomatic	An infection state without apparent clinical signs. Also: subclinical
Basic reproductive number (R_0)	The number of secondary infections produced by one infected individual in a completely susceptible (naive) population.
Bacillus Calmette-Guérin (BCG)	A strain of *Mycobacterium bovis* widely used as vaccine against tuberculosis, especially extrapulmonary tuberculosis in infants.
Clustering	Occurring in a group or groups
Contagious disease	A communicable disease which is transmitted during contact with a patient, secretions of a patient or objects touched by a patient.
DBLM	Danish Bangladesh Leprosy Mission, Nilphamari, Bangladesh
Detection delay	Time between onset of disease and diagnosis
Early diagnosis	Detection of subclinical infection.
False negative	A negative test outcome for a positive (e.g. infected) case, see also sensitivity
GIS	Geographic Information Systems
GPS	Global Positioning System
Incubation period	The time between infection and first symptom.

Infectious disease	A disease caused by invasion of a pathogen that can multiply in a patient.
Infectious	Infection state in which an infected individual can infect susceptible individuals.
Infectious period	Period during which an individual can infect other individuals.
Infectivity	The probability of transmission of an infectious agent during an adequately close contact.
Latent or latent infection	An infection state in which the infected person is not infectious to others.
Latency period	Period during which an infected individual has a latent infection. The time between infection and becoming infectious.
MDT	Multidrug therapy
Microsimulation	Individual based modelling, Modelling method that simulates life histories of fictitious individuals.
Multibacillary leprosy (MB)	Leprosy disease with with multiple (more than five) skin lesions, nodules, plaques, thickened dermis or skin infiltration
Non-susceptible	The state of an individual that is not infected, and cannot become infected by an infectious individual. Also used as noun for an individual that is not susceptible.
Paucibacillary leprosy (PB)	A milder form of leprosy disease characterized by few (up to five) skin lesions (pale or reddish).
Ridley-Jopling classification	Classification system of leprosy disease for scientific purposes
Sensitivity	The fraction of cases detected by a test, i.e. one minus the probability of a false negative
Single lesion paucibacillary leprosy (SLPB)	Paucibacillary leprosy with only one skin lesion
Spatial cluster	A group of events or cases that occurs in the same area and does not occur by chance.

Spatio-temporal cluster	A group of events or cases that occurs in the same area and time-frame and does not occur by chance.
Specificity	The fraction of positively tested that is actually positive i.e. the probability of a true positive.
Subclinical infection	An infection state without apparent clinical signs. Also asymptomatic.
Susceptible	The state of an individual when it is not infected and can be infected by contact with an infectious individual. Also used as noun for individuals that are susceptible.
Symptomatic	An infection state in which clinical symptoms are apparent.
Temporal cluster	A group of events or cases that occurs in the same time-frame and does not occur by chance.
Transmission	The passing of an infectious agent from one infected individual to another uninfected individual.
True positive	A positive test outcome for a positive (e.g. infected) case, see specificity.
WHO	World Health Organisation

Curriculum vitae

23^{rd} of January 1977 Born in Rotterdam, The Netherlands.

1989 – 1995	University Preparatory School (Dutch: VWO), Rotterdams Montessori Lyceum
1995 – 2002	MSc. Plant breeding and Crop protection, specialization Ecological Crop protection, Wageningen University (formerly Agricultural University Wageningen)
1999 – 2002	MSc. Biology, specialization Theoretical and Mathematical Biology, Wageningen University (formerly Agricultural University Wageningen)
2002 – 2003	Junior researcher at Quantitative Veterinary Epidemiology ID-Lelystad (currently QVERA, CVI-WUR), Lelystad
2003 – 2007	PhD-student at Department of Public Health, Erasmus MC, Rotterdam
2003 – 2006	MSc. Epidemiology, NIHES, Rotterdam
2008 – present	Researcher at Quantitative Veterinary Epidemiology and Risk Analyses, Central Veterinary Institute of Wageningen University and Research centre, Lelystad

Egil is married to Karen van de Wolfshaar and father of Niklas.

Publications

- E.A.J. Fischer, D. Pahan, S.K. Chowdhury, and J.H. Richardus. The spatial distribution of leprosy during 15-years of a leprosy control program in Bangladesh: An observational study. BMC Infectious Diseases, 2008.

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Egil Fischer
Utrecht, 3 juli 2010

* "het maar een proefschrift en niet je levenswerk"

PhD portfolio summary

Name PhD student	Egil A. J. Fischer
Erasmus MC Department	Public Health
PhD period	2003 - 2007
Promotor	J. Dik . F. Habbema
Copromotor	Jan Hendrik Richardus

	Period	Workload
1. PhD training		
General academic skills		
Course in Biomedical English Writing	2006	24 hours
Master of Epidemiology, NIHES, Rotterdam, The Netherlands	2003-2006	840 hours
In depth courses		
Summer school on mathematical models in biology and medicine, Instituto Gulbenkian de Ciência, Oeiras, Portugal	2006	40 hours
Presentations at international conferences		
5^{th} European Congress on Tropical Medicine and International Health, Oral presentation	2007	24 hours
Workshops		
Workshop on the use of chemoprophylaxis in the control of leprosy Amsterdam, The Netherlands	2006	8 hours
2. Teaching activities		
Lecturer NIHES course on quantitative models for evaluation of tropical diseases control	2005-2006	80 hours
Assistance in the STOLA course Rotterdam, The Netherlands	2004-2006	Negligible
Supervision of MSc-student	2006	-
3. Other activities		
Organization of Uniting Streams on Tour seminar	2006	80 hours
Organization of “sectie-uitje”	2004	4 hours

Notes