

Epidemiology of Leprosy

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Descriptive Epidemiology

DEFINITION OF LEPROSY

It is essential in epidemiology to have a clear definition of the condition. However, the definition of leprosy has changed over the years. The diagnosis of leprosy is based on the presence of at least one of three cardinal signs: definite loss of sensation in a pale or reddish skin patch, a thickened or enlarged peripheral nerve with loss of sensation and/or weakness of the muscles supplied by that nerve, and the presence of acid-fast bacilli in a slit-skin smear (1). Recently, leprosy has tended to be defined by the chemotherapy, such as defining a case of leprosy as a person having one or more of the cardinal signs above who has yet to complete a full course of treatment (2). This definition implies that once a full course of treatment has been completed, the person affected is 'cured' and therefore no longer represents a case of leprosy. This terminology, equating cure with treatment completion, is now widely used (3). The treatment of leprosy and its duration also has changed over the past decades, impacting the definition and epidemiology of leprosy. It is important to recognize these changes in definition when studying the epidemiology of leprosy. Previous WHO definitions (4) have recommended further operational definitions for those who have completed chemotherapy and require surveillance and those released from surveillance but in need of care or assistance because of disabilities. Definitions based on treatment are useful

for planning, implementing, and evaluating programs of case detection and treatment; however, definitions based on impairment, disabilities, and quality of life are required for physical, social, and economic rehabilitation programs.

Cases of leprosy are usually classified as either paucibacillary leprosy (PB) or multibacillary leprosy (MB). This classification (see Chapter 2.4) is based on counting the number of skin lesions and is primarily used for the purposes of chemotherapy, as PB cases are treated for 6 months and MB cases for 12 months using different regimens. This difference affects measures of the epidemiology of leprosy. Many previous methods of classification have been based on clinical, immunological, and histopathological characteristics (5).

MEASUREMENT – INCIDENCE AND PREVALENCE

The two commonly used measures in the epidemiology of disease are incidence (number or rate of new cases occurring over a period of time) and prevalence (number or rate of all cases either at one point in time or over a period of time). These two measures are related through the duration of disease, such that prevalence is equal to the incidence of disease multiplied by the duration of disease. This relationship shows why changes in definition based on duration of treatment affect measures of prevalence of leprosy.

The true incidence of leprosy is very difficult to measure, as it is very low and not all cases are detected when they occur. There is a delay in detection between the onset of the signs of leprosy and the diagnosis, and this delay varies over time and between countries. New case detection per year is commonly used (3) as a proxy for incidence; however, it is a rather limited proxy measure. Operational factors such as the intensity of case detection, use of surveys, contact tracing, level of community awareness, and the quality and availability of health care have a profound effect on case detection rates (6), and if these factors change over time, then the case detection rates will change as a result. Therefore, great caution is required in interpreting the new case detection data and any changes over time. Sudden changes in the numbers of new cases detected from year to year are more likely to be due to operational factors than to true changes in incidence.

Point prevalence (the number of cases of leprosy registered for chemotherapy at the end of a calendar year) is the most commonly used measure of leprosy prevalence. Occasionally, period prevalence of leprosy (all cases of leprosy existing during a year) is used, which will be a higher number than point prevalence. The registered prevalence is a proxy measure for the true prevalence, which would include existing cases that have not yet been detected. In the past, attempts were made to estimate the true prevalence and present the registered prevalence as a percentage of that true or estimated prevalence (7). The two factors that determine the registered prevalence are the new case detection rate and the duration of treatment, and changes in either will affect the registered prevalence.

DISTRIBUTION – AGE, SEX, AND GEOGRAPHICAL

The age and sex patterns of leprosy new case detection and registered prevalence have also been studied in depth, and these patterns are reported routinely by national programs in relation to classification (MB or PB), gender, children, and disability. The pattern of classification is similar in male and female children, but the rate of MB cases is often observed to be higher in men than in women. The equity of access to health services by age and gender can be assessed using these data. Globally, around 35–37% of all reported new cases are in women (3), but in some countries the proportion is very low, raising concerns about under-diagnosis in women (8). Studies indicate that it is not just access to health services that influences under-reporting of leprosy in women, but also illiteracy, low status, and other cultural factors (9). The pattern by age often shows a bimodal pattern with peaks in the teenage years and in adulthood. Around 9% of all newly detected cases are found in children, a global pattern that is often taken as an indicator of continued transmission. However, new case detection rates in children are readily influenced by operational factors such as school surveys and contact examination in households.

There are large variations in new case detection rates between countries and between world regions. The most recent new case detection and registered prevalence rates for leprosy by region are presented in Table 1. The highest numbers and rates of registered cases and new cases detected in endemic areas are from South-East Asia, while the lowest figures are from the Eastern Mediterranean region. The number of registered cases globally is less than the number of newly detected cases, especially in the Americas and South-East Asia, due to the average duration of treatment being less than one year. These data are based on reports from 102 countries; the number of countries reporting varies from year to year. There is also considerable geographical variation in the epidemiology of leprosy within the regions as is shown in Table 2, which lists the countries reporting more than 1000 new cases (3). These countries constitute 95% of the annual number of world cases. Over 80% of the global new case detection comes from India, Brazil, and Indonesia.

TABLE 1 Registered Prevalence and New Case Detection of leprosy by WHO region, 2013

WHO Region	Number of Registered Cases	Prevalence Rate per 10,000	Number of New Cases Detected	Case Detection rate per 100,000
Africa	22,722	0.38	20,911	3.50
Americas	31,753	0.36	33,084	3.78
Eastern Mediterranean	2,604	0.05	1,680	0.35
South-East Asia	111,396	0.63	155,385	8.38
Western Pacific	7,143	0.04	4,596	0.25
TOTAL	180,616	0.32	215,656	3.81

TABLE 2 New leprosy case detection in countries with more than 1000 new cases in 2013

Country	Number of New cases	Number of MB Cases	Number of Female Cases	Number of Children	Number with Grade 2 Disability
Bangladesh	3,141	1,380	1,237	166	341
Brazil	31,044	20,005	13,942	2,418	1,996
Cote d'Ivoire	1,169	820	485	138	209
DR Congo	3,744	2,469	1,722	452	471
Ethiopia	4,374	4,028	Not Reported	466	361
India	126,913	65,337	46,845	12,043	5,256
Indonesia	16,856	14,062	6,021	2,002	1,694
Madagascar	1,569	1,386	379	134	281
Myanmar	2,950	2,155	997	134	423
Nepal	3,225	1,698	1,043	131	88
Nigeria	3,385	3,169	1,392	299	447
Philippines	1,729	1,603	523	117	72
Sri Lanka	1,990	947	812	182	133
Tanzania	2,005	1,631	749	91	252

There are also distinct geographical variations within countries. There are differences observed in the leprosy situation between urban and rural communities (10). Some geographical variations are due to differences in health service provision (11), while others may be due to differences in socioeconomic development, isolation, and poverty (12). The clustering of cases within countries and districts is a commonly observed feature in leprosy, and it has implications for planning leprosy control activities and development of strategies. Understanding the geographical variations of leprosy within countries is important in planning and implementing leprosy control activities, as is illustrated later with examples from Brazil, Benin, and Bangladesh.

TRENDS IN INCIDENCE, PREVALENCE, AND DISABILITY

Short-term trends in leprosy are difficult to interpret due to year-to-year fluctuations in program activities. Long-term trends in the epidemiology of leprosy are more important, but can still be difficult to understand because of changes in the definition of leprosy, the long incubation period of leprosy, and changes in leprosy control activities that delay case detection. The global trends in registered prevalence and new case detection since 1985 are presented in Figure 1. The global trend in registered prevalence is driven by the duration of treatment and by the new case detection rate. The dramatic fall in registered prevalence between the years 1990 and 2000 is almost entirely due to the shortening of treatment duration, besides the effect of cleaning regis-

ters when introducing multidrug therapy (MDT; see Chapter 2.6). Before the use of MDT, dapsone treatment was continued for 4–10 years and, in some cases, treatment continued for life. MDT reduced treatment duration to fixed periods of 6 months for PB leprosy and 12 months for MB leprosy. This reduction in treatment duration led to a dramatic reduction in prevalence without any decrease in new case detection. The falling trend in prevalence since 2000 is now largely due to the fall in new case detection, since MDT coverage approximates 100% and the duration of treatment has not changed over that period.

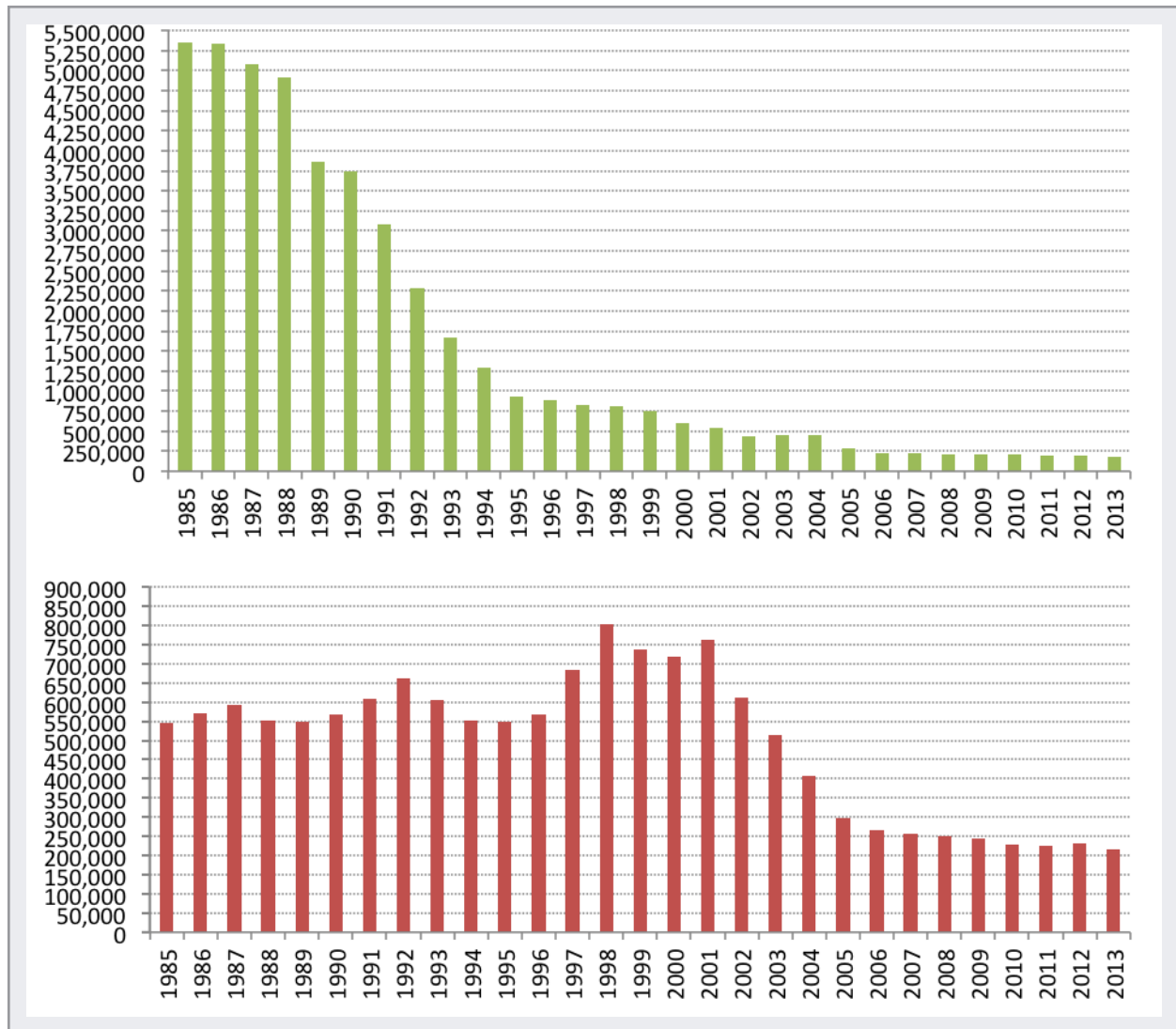


FIG 1 Global trends in registered prevalence (green) and new case detection (red) in leprosy (1985–2013).

The trend in new case detection was remarkably static up to the year 2001, fell dramatically between 2000 and 2005, and has appeared to level off or show a modest decline since 2006. Interpreting this trend in new case detection since 2000 is important. A sudden and dramatic decrease in the transmission of *M. leprae* infection seems biologically implausible, mainly because

of the long incubation period of the disease, although a more modest decline may be part of the explanation. Over-diagnosis may have occurred during the 'Elimination Era' between 1991 and 2000, which may be a factor in the few years preceding 2000, but otherwise the new case detection level was remarkably stable between 1985 and 1996. The most important factor is likely to be the decline in leprosy control activities and intensity following the declaration by the WHO in 2000 that leprosy was eliminated as a 'public health problem', defined as a prevalence of less than 1 per 10,000 population at the world level. This possibility has profound implications for understanding the current epidemiology of leprosy, which suggests that if the true incidence of leprosy is much higher than the current new case detection, then there is substantial delay in the diagnosis of leprosy resulting in large numbers of undetected cases in the community (13).

The global data on leprosy trends are largely influenced by India and, to a lesser extent, by Brazil. A number of countries have recently published detailed analyses of their leprosy trends. In Thailand, a long-term decrease in new case detection has been observed (14). In Vietnam (15), improvements to leprosy control have shown an increase in the proportion of female cases, an increase in the proportion of MB cases amongst new cases, a steady decline in cases in children in recent years, and a decrease in cases with grade 2 disability at detection (see Chapter 2.5). In Yemen (16), the pattern of new case detection follows changes to program activities, demonstrating the importance of operational factors and the need for local interpretation of trends. For example, the increase in the number of new cases in children reflects activities focused on new case detection in that age group. The lower rate of female cases is seen as reflecting the limited access of females to health care facilities. A similar analysis of trends for Indonesia has also been undertaken (17). These epidemiological analyses from individual countries are very informative, because of the detail and local knowledge of trends and changes within the country reflected in the trends.

The current global strategy for leprosy targets reduction in new cases with grade 2 disability (18). This target will lead to improvements in the completeness and quality of recording disability in leprosy.

IMPACT ASSESSMENT – DALYS, QALYS, AND BURDEN OF DISEASE

Traditionally the epidemiology of leprosy has been based on the incidence and prevalence of diagnosed disease, which have been increasingly defined by chemotherapy. More recently, measures (19) such as DALYS (disability adjusted life years) and QALYS (quality adjusted life years) have been introduced to the epidemiological assessment of leprosy. These measures widen the definition of leprosy from a condition needing anti-microbial chemotherapy to a condition with physical and social impacts that affect the quality of life. Early efforts have tended to restrict analyses to the traditional definitions of leprosy, whereby completion of treatment implied cure (20). More recent work now recognizes the continuing impact of leprosy on those affected beyond MDT completion. Global estimates of the disability burden based on impairments at diagnosis and life

expectancy have been used in the past (2), but more contemporary methods at the country level are now being undertaken and will inform the development of approaches to leprosy that extend beyond drug treatment to physical, social, and economic rehabilitation as well as human rights and discrimination.

Transmission

Understanding of the transmission of *M. leprae* infection and the process of the pathogenesis of leprosy is limited. The existing evidence on the transmission of *M. leprae* is largely circumstantial due to the long incubation period from exposure to disease, the inability to culture *M. leprae* in vitro, and the difficulty of diagnosing both infection and early leprosy disease. It has been demonstrated that *M. leprae* can be shed in large numbers from the mouth and nose of patients with untreated lepromatous leprosy, and to a lesser extent from the skin (21), but it is unclear if patients with other forms of leprosy can spread the bacterium. Studies using PCR methods have identified *M. leprae* specific sequences from nose swabs (22). A recent systematic review concluded that there was robust evidence for transmission between contacts and for zoonotic leprosy in the southern states of the USA through wild armadillos (23). It is assumed that the main route of entry to the body is through the respiratory tract, although there are case studies suggestive of transmission through skin by wounds and tattoos, but the review also showed that no study has unequivocally demonstrated the mechanisms by which *M. leprae* bacteria travel from one case of leprosy to another (23). A recent expert group has identified the major gaps in knowledge about transmission and prioritized the research questions about transmission (24).

RESERVOIRS OF INFECTION

It is assumed that the main reservoir of infection for *M. leprae* is human. There is now also good evidence of the armadillo as a reservoir for human infection in the southern states of the USA (25). Direct exposure to armadillos has been shown to be a risk factor for leprosy in both the USA and Brazil (26). The transmission of *M. leprae* between armadillos and humans likely goes both ways. Despite the evidence from armadillos, no strong evidence of other animals as reservoirs has been found. Various studies have examined the potential of water and soil as environmental sources of *M. leprae*, but the evidence is as yet weak (23). The observations that many other mycobacteria are found in the environment and that *M. leprae* can survive in water and soil have motivated such research studies.

The higher incidence rate of leprosy in household contacts of MB cases compared to PB suggests that MB cases represent an important reservoir of *M. leprae* (1), although this inference also might be the case for PB cases. Undetected and untreated cases in the community represent an important reservoir, which may be under-estimated (13). However, the fact that *M. leprae* are not cultivable in mouse footpads after the first dose of MDT suggests that MDT treatment is effective

in reducing the reservoir of infection. In public health terms, it is reasonable to conclude that infectiousness becomes negligible after the start of MDT (27). Prolonging the period between the onset of signs of leprosy and treatment due to a delay in diagnosis and MDT treatment is likely to increase the opportunities for exposure to the reservoir. Sub-clinical leprosy may also be a further reservoir of infection, but this possibility has not yet been clearly demonstrated.

INCUBATION PERIOD

The incubation period of leprosy is inferred from observational studies to be long compared to other bacterial infections. It is estimated to range from two years to as long as 10 years or more. Leprosy is rare in children under 5 years old. The incubation period for MB appears to be longer (5–10 years and sometimes much longer) than for PB (around 2–5 years), probably as a result of the differing immunological capabilities of MB and PB hosts (see Chapter 6.2). The experience in Norway, in which leprosy disappeared at the beginning of the 20th century, confirms this assumption, since the long incubation MB cases are detected only as the transmission ends (28). The incubation period is difficult to study directly because of the limitations of culturing *M. leprae* and diagnosing early leprosy.

SUB-CLINICAL INFECTION

In a disease with a long incubation period, the role of a sub-clinical infection is potentially important, as it provides an opportunity for an intervention to interrupt transmission and to heal the disease before the signs and symptoms become apparent. The hypothesis in leprosy that many individuals are exposed to infection and develop a sub-clinical infection, but that the majority self-heal without developing disease, would imply an opportunity for such an intervention. However, there are no diagnostic tests available that can establish a sub-clinical infection adequately. The effectiveness of a single dose of rifampin to contacts supports the hypothesis of wide-spread sub-clinical infection (29). Research efforts are currently focused on developing a test for sub-clinical infection which could provide the opportunity for new approaches to preventing leprosy (30).

ROLE OF CONTACTS AND OTHER RISK FACTORS

A number of studies have attempted to identify the determinants of leprosy by assessing risk factors in either case-control or cohort studies. A case-control study in Brazil (31) found that a range of factors, all associated with poverty, were significant risk factors for leprosy; these factors included low education, poor hygiene, and food shortages. A BCG (Bacille Calmette-Guérin) scar was found to be protective. A cohort study in Indonesia identified household crowding as a risk factor as well as household contact status (32). Household and dwelling contact were found to be risk factors for leprosy in Malawi (33). A recent food shortage was identified as a risk factor for

leprosy in Bangladesh (34). Leprosy has been regarded as a disease associated with poverty and these analytical studies provide documentary evidence for this assertion.

The most consistent and most studied risk factor for the development of leprosy is contact status. A review of the evidence in 2004 (35) confirmed that classification of lepromatous leprosy in the index case, and the intensity and physical distance from the index case, were associated with an increased risk of developing leprosy. These findings are confirmed by a more recent study (36). The review also noted the different definitions of contact status used by different studies. A study in Brazil highlighted the importance of social contacts (37), as well as suggested that those seropositive for anti-PGL-1 antibody were at an increased risk and that those with a BCG scar were at a reduced risk. Similar findings were reported from a more recent study in Brazil using the ML-Flow test (38).

GENETIC SUSCEPTIBILITY

There is increasing evidence for host genetic susceptibility to leprosy. Epidemiological evidence from studies in twins had indicated that there was a potential host genetic risk for leprosy. This risk also had been suggested by a number of observation studies, including findings from Indonesia and Bangladesh, where genetic relationship was shown to be a risk factor for leprosy in contacts of patients with leprosy (36, 39). New findings support this observation (40). More recent studies are now exploring the mechanism of host genetic susceptibility (see Chapter 8.1) to leprosy and its clinical manifestations (41, 42, 43).

Mathematical Modeling

Mathematical models are increasingly applied to guide public health policy decisions and explore questions in infectious disease control. Models use basic assumptions and mathematics to find epidemiological parameters for various infectious diseases and use those parameters to calculate the effects of possible interventions. Applications include predicting the impact of vaccination strategies against common infections and determining optimal control strategies. For more general information on mathematical models in infectious diseases, we refer to the textbook by Vynnycky and White (44). Mathematical models also have been developed to predict the course of leprosy incidence and the effect of intervention strategies (45). Two compartmental models have been used to investigate the course of leprosy in populations and the long-term impact of control strategies (46, 47). Another individual-based model focuses on transmission within households and the impact of case finding among contacts of new leprosy patients (48).

HETEROGENEITY IN LEPROSY

Heterogeneity is due to differences between individuals in exposure to most infections, including infection with *M. leprae*, and differences in developing leprosy after exposure. Relevant forms of heterogeneity in the population are contact heterogeneity, heterogeneity in susceptibility, and spatial heterogeneity. These forms of heterogeneity are not mutually exclusive.

Infection with a directly transmitted bacterial infection, such as *M. leprae*, needs contact between an infectious host and a susceptible host. Through heterogeneity in the contact structure of a population, susceptible individuals have different risks of coming into contact with infectious individuals. Thus contact heterogeneity plays a major role in the infection dynamics of directly transmitted diseases (49). In several studies of leprosy, this risk based upon contact status has been studied. In Bangladesh, it was shown that close contacts of leprosy patients, such as household members, are at a higher risk of developing leprosy themselves (35). This risk has been shown for different countries and continents (33, 39, 50, 51). 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 (52). In some high incidence situations, almost half of the population is a close contact of leprosy patients (53).

Even if all exposure to *M. leprae* were the same, some people react differently to infections than others. In addition, not all people that are exposed to *M. leprae* develop leprosy. It is not clear whether these individuals clear the bacilli efficiently or are resistant to infection (54, 55, 56). It is thought that only a fraction (5–20%) of the population is susceptible to the development of leprosy after exposure. Differences in susceptibility can be genetic or can be caused by environmental factors that alter the health status of an individual. Genetic studies have found an association of both susceptibility to leprosy (57, 58, 59) and the type of leprosy—tuberculoid or lepromatous—with genetic factors (60) (see Chapter 8.1). In an epidemiological study, Bakker et al. (39) found that approximately 50% of susceptibility was explained by hereditary factors. Also, Moet et al. (36) found an association between leprosy prevalence and familial relationship to a patient. It is, however, difficult to separate relationship from contact status, such as being a household member (36). Susceptibility to leprosy is also 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, including wealth. Poverty, and in particular recent food shortage, has been shown to be a risk factor for leprosy on a population level (34, 61).

Finally, spatial heterogeneity means that the occurrence of an infectious disease is not evenly distributed over space, which can have several underlying reasons. Leprosy is found to be unevenly distributed in villages (39, 51), although this finding has not been observed consistently (62), and at higher aggregated area levels, such as districts (63, 64, 65, 66). The uneven spatial distribution of leprosy can be the result of contact heterogeneity, especially clustering at a low level, such as the village. If neighbors have intense contact, neighbors will have a higher risk of infection (36). This type of contact 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 (63, 64). Geographic features include a decrease in incidence

the closer households are to a river or lakeshore in Malawi, and an increase in risk the further they are from a main road (65). These features might, however, vary from country to country, as, for example, in the Nilphamari district of Bangladesh, which has many water bodies and rivers but where no relationship with distance to water was found (66). Leprosy is often described as a rural disease (54, 65); however, clustering in urban areas has been reported in Brazil and around urban areas in Bangladesh (63, 64).

LEPROSY MATHEMATICAL MODELS

Lechat et al. developed the first mathematical models for describing the epidemiology of leprosy in the 1970s and 1980s (46, 67, 68, 69, 70). The models enabled investigating the course of leprosy in populations under different assumptions and the impact of long-term leprosy control strategies, such as dapsone monotherapy, MDT treatment, and BCG-like vaccines (46, 68, 71). Lechat's models helped considerably to clarify the thinking about leprosy control. However, there was room for a substantial refinement of the model.

In 1999, Meima et al. (47) developed a new modeling framework, SIMLEP, which builds on the approach of Lechat's models (46, 67). SIMLEP was developed to investigate the many uncertainties in leprosy epidemiology and to respond to the need for simulation models to make predictions for future trends in the incidence of leprosy (47, 72). The purpose of this model was to take into account variations in the assumptions regarding natural immunity, the incubation period, and asymptomatic infection and delays in awareness and treatment. In addition, it allowed the testing of different mechanisms describing leprosy transmission by making assumptions about the level of contagion per type of infection.

SIMLEP was used to investigate the disappearance of leprosy from Norway, where the best fit to the data was a model with heterogeneity in age of exposure, heterogeneity in susceptibility, and an extended incubation period (28). Using the SIMLEP modeling 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. A second application of SIMLEP investigated the impact of BCG vaccination at birth and early diagnosis in India. Both interventions showed a decrease in the level of incidence (73).

However, SIMLEP did not include the disease dynamics in households or heterogeneity in susceptibility, both of which were required to evaluate the effects of interventions targeted at household members, such as early (pre-clinical) diagnosis and chemoprophylaxis. For this reason, the SIMCOLEP model was developed. SIMCOLEP is a micro simulation, or a stochastic individual-based model, which models leprosy transmission in a population (48). This model was able to take into account transmission in households and test for different assumptions on heterogeneity in the susceptibility of leprosy. SIMCOLEP simulates the life histories of individuals and the natural history of infection with *M. leprae* (see Figure 2) (48). The model is divided into two modules: a population module and a disease module. The population module describes processes that are not related to the disease or infection, including birth, death, and household processes. The dis-

ease module simulates the processes of disease, infection, leprosy control, and interventions. The natural history of disease is modeled following SIMLEP.

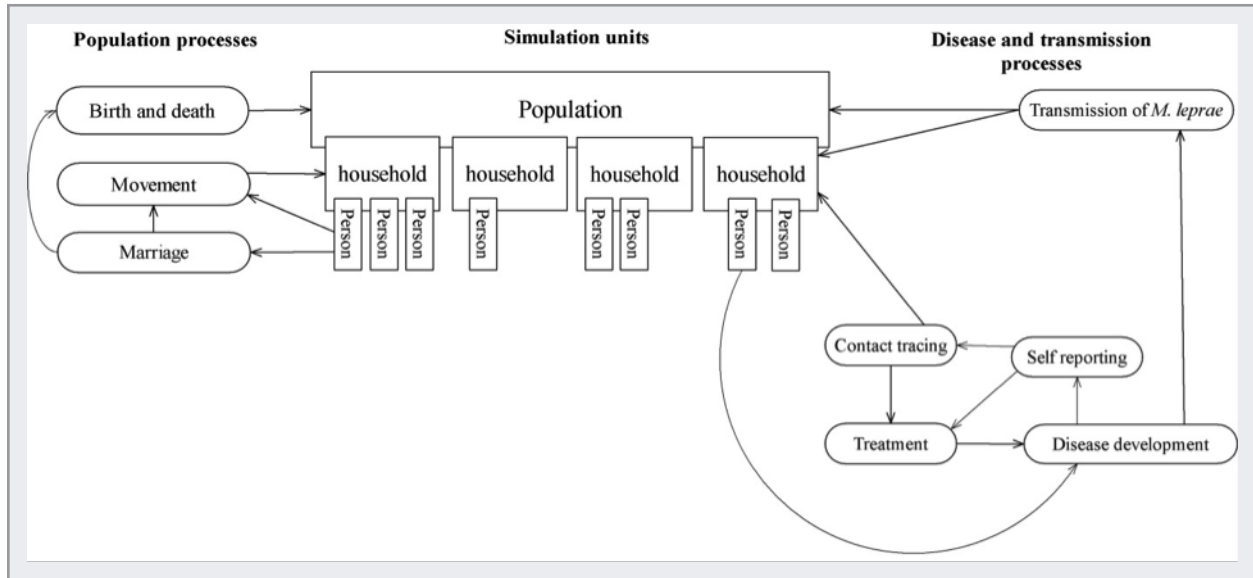


FIG 2 Model structure of SIMCOLEP.

SIMCOLEP was used to investigate which mechanism for the heterogeneity of leprosy susceptibility can best explain the observed clustering in household contacts of leprosy patients in northwest Bangladesh (48). The results of this study could not rule out any mechanism to explain clustering in household contacts of leprosy. SIMCOLEP was also used to evaluate different intervention strategies in the same region (74). The effects of seven potential intervention scenarios were tested for the future control of leprosy: (1) baseline scenario, representing the current practice; (2) no contact tracing; (3) administering chemoprophylaxis (a single dose of rifampin) to each individual in contact with a leprosy patient; (4) early diagnosis of sub-clinical leprosy (based on an as yet hypothetical diagnostic test); (5) BCG vaccination to all newly born infants in the area; (6) combination of BCG and chemoprophylaxis; and (7) combination of BCG and early diagnosis of sub-clinical leprosy. Of these seven potential interventions, the early diagnosis of sub-clinical leprosy showed the largest effect on reducing new cases in the population, followed by chemoprophylaxis.

APPLICATION OF MODELS FOR LEPROSY CONTROL

Many uncertainties remain with respect to leprosy. A variety of host immunogenic factors influence both an individual's susceptibility to infection with *M. leprae* and the pathologic course of the disease. In particular, questions remain regarding mechanisms of natural immunity and susceptibility to the MB and PB forms of leprosy, which show marked variation in distribution in different parts of the world. SIMCOLEP has explored the likelihood of the contribution of different mechanisms to determining susceptibility to leprosy, but could not rule out any of the applied

mechanisms (48). These studies also showed that the expected effect of interventions differs for each of the mechanisms (74). Better understanding of these mechanisms is therefore important, because the choice of susceptibility mechanism determines the outcome of model predictions.

There are also uncertainties about the transmission of *M. leprae* and whether environmental reservoirs and animal hosts play a role (75). For human-to-human transmission, it is still unclear when an infected person becomes infectious, how long a person stays infectious, and what the role is of healthy carriers and sub-clinical infections among household contacts of leprosy patients (76). Models can play an important role in explaining these uncertainties by allowing the testing of various assumptions with regard to the transmission of *M. leprae*.

An important challenge is to determine which interventions at the population level have the highest impact on the future incidence of the disease by interrupting transmission. Focus also should be directed to the effect of interventions targeting contacts of leprosy patients, including contact tracing, chemoprophylaxis, immunoprophylaxis (e.g., BCG vaccination or a specific BCG-like leprosy vaccine; see Chapter 6.3), and early diagnosis of leprosy by means of diagnostic tests (see Chapter 7.1) for infection or tests that predict clinical disease. A question that naturally follows is how and when leprosy can be eliminated. Perhaps an even greater challenge is to investigate whether we can move from elimination (see Chapter 1.2) to eradication of leprosy, defined as the complete interruption of the transmission of *M. leprae*. Key policy questions that follow from elimination or eradication targets are how to evaluate post-elimination monitoring. Mathematical models and, in particular, individual-based models may help to address these questions.

Recent applications of existing leprosy models have only focussed on current and past endemic regions in India, Norway, and Bangladesh (28, 73, 74). Worldwide, nearly 80% of all new cases of leprosy are found in India, Brazil, and Indonesia (77). It is still a challenge to apply these models to these specific countries, and endemic regions within them, for answering key policy questions.

Mapping

Mapping of diseases has long since been recognized as an essential tool in public health activities. The possibilities for mapping and for the spatial analysis of disease patterns have changed dramatically over the past decades, as computer power has increased and Geographic Information Systems (GIS) have emerged as individually accessible software, allowing for widespread, complex, and comprehensive analyses. Through GIS analysis, we can understand why things are located where they are and, in combination with health and other sciences, how they are related. Obtaining disease and health data has been made easier by low-cost global positioning system (GPS) units, including smartphones, and the improved quality of remote sensing (78). GIS can be used to manage the modeling and mapping of disease, to develop new hypotheses in a geographic context, to analyze and predict future disease risks, and to undertake location/allocation analysis of the distribution of services and resources. Additionally, the advances in and increased

affordability of DNA sequencing has added another layer of complexity and potential insight into transmission patterns of infectious diseases through molecular epidemiology (see Chapter 5.1). Finally, GIS is also an important tool for advocacy and program planning. A clear visual presentation of the burden of disease in an area can influence policy and decision makers. GIS can be used to visualize challenges such as high case detection rates that cross administrative boundaries, which may not be identified easily when data are presented in tables only. The use of GIS in leprosy control was discussed in 2009 by Bakker et al. (79).

SPATIAL ANALYSIS OF DISEASE

The spatial analysis of disease includes disease mapping and modeling; geographical epidemiology such as disease detection, prediction, surveillance, and monitoring; and environmental epidemiology such as causality and risk analysis, disease transmission, and the analysis of disease patterns. The basic use of GIS in leprosy research is simple disease mapping. Most studies, however, go one step further: after the identification of areas with apparent high numbers of leprosy cases, spatial (cluster) analysis is performed to find evidence for significant clusters of patients. This analysis can be done at a regional level (12), urban level (80, 81), village level (62), and even household level (53). An example of a GIS map is given in Figure 3. The maps represent four villages in northern Bangladesh that were surveyed three times over a 4-year period with 2-year intervals. Villages A, B, and C had a number of known former leprosy cases (released from treatment), with new patients found at intake and after 2 and 4 years (villages A and C). In village B there were 3 known former cases of leprosy, but no new cases were found during the observation period. Village D is an example of an isolated case found after 2 years, with no other known cases before or afterwards. Time can also be considered in understanding disease patterns. The spatio-temporal distribution of leprosy cases in the Nilphamari district in Bangladesh was studied over a 15-year period (1989–2003). Based on the home locations of the patients at diagnosis, one purely temporal and several spatio-temporal clusters were identified (66). More recently, a spatio-temporal analysis was published of all cases registered at a clinic in Cebu, the Philippines, from 2000 to 2010. Population-adjusted clustering of leprosy cases was mainly detected in urban and peri-urban areas (82).

It is also possible to relate underlying factors to the identified space-time patterns. Using GIS, the marked variation in leprosy incidence rates in northern Malawi could not be related to socioeconomic or cultural factors or population density, but incidence rates increased with increasing distance from a main road and with decreasing distance from a river or lake shore (65). In Bangladesh, it was shown that leprosy case detection was higher near towns. No relation with distance to water or clinics was found, and the spatio-temporal clusters were possibly due to an underlying increase in leprosy incidence and could thus be seen as ‘outbreaks’ (66). In Brazil, a correlation was found between the spatial distribution of leprosy and socioeconomic indicators in the city of Vitoria, the capital city of Espirito Santo State. Neighborhoods with a lower Urban Quality Index had a higher case detection rate (83).

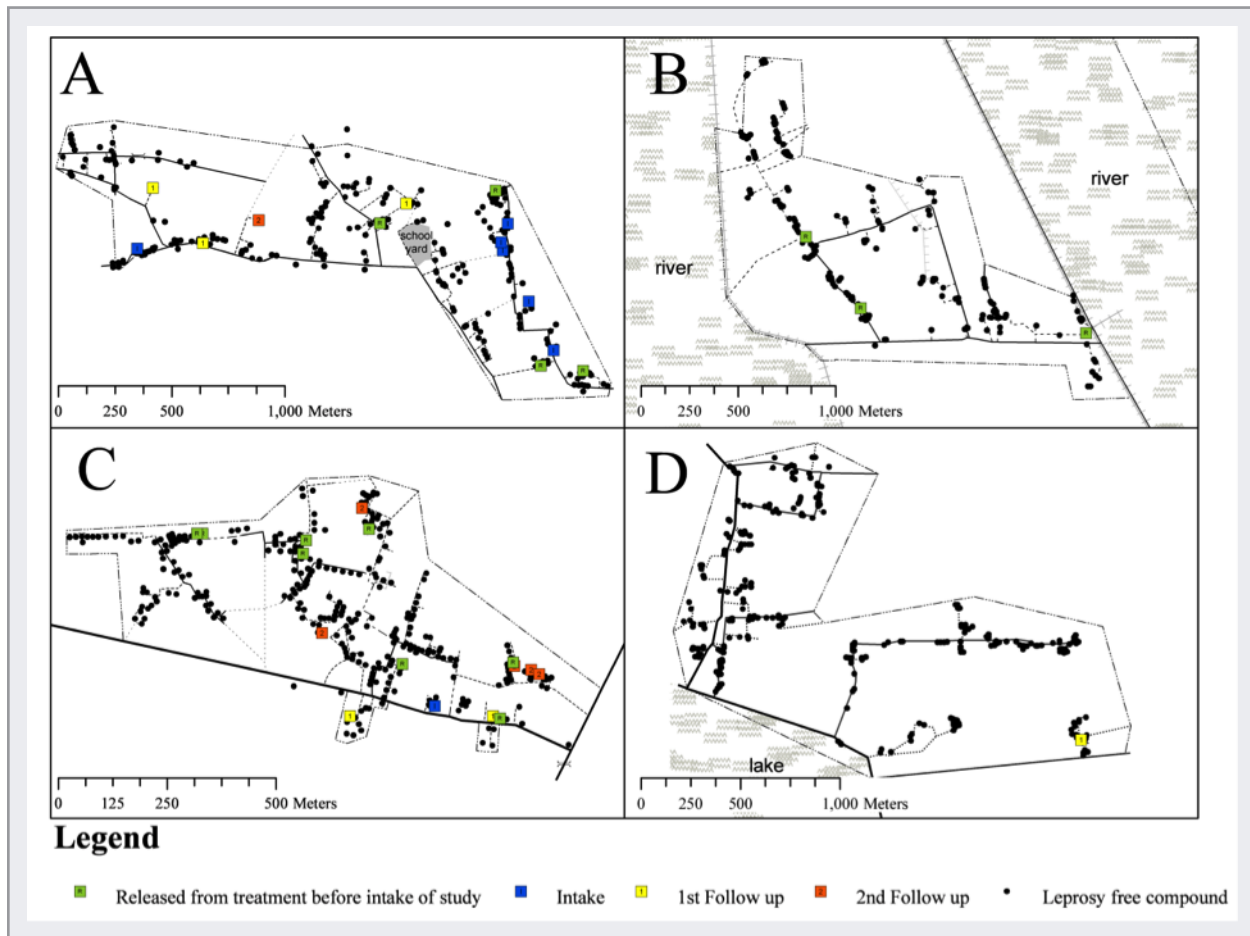


FIG 3 Newly detected leprosy cases by time of detection, e.g., before intake, at intake, first follow up (2 years), or second follow up (4 years) in four sample group areas in northern Bangladesh. Compounds are depicted by a black dot. The dash-dotted (---) line indicates the village or ward border. Other lines indicate roads, canals, and river embankments (62).

SPATIAL ANALYSIS OF HEALTH SERVICE PLANNING

GIS also can be used for planning, monitoring, and evaluating health program performance, for instance, by identifying areas that are poorly covered, performing, or reporting. A study in the Duque de Caxias municipality of Rio de Janeiro State in Brazil showed heterogeneity in leprosy case detection over municipal sub-regions. Higher detection rates were associated with neighborhoods with decentralized health facilities, highlighting the need to organize appropriate health care in areas with a high leprosy burden (84). Accessibility to leprosy diagnostic and treatment services can also be studied by calculating the distance from residential areas to health facilities. Buffers around health centers can be used to calculate coverage: the percentage of villages or population that fall within a certain buffer. The results can be used to justify new health centers

in areas of low accessibility. Thus spatial analysis can be used for planning, management, delivery, provision, accessibility, and utilization of health care facilities for leprosy.

SPATIAL ANALYSIS AND MOLECULAR EPIDEMIOLOGY

With the completion and publication of the *M. leprae* genome in 2001 (85), strain typing of the bacteria has become possible. This typing has made it possible to distinguish individual strains of the bacteria and trace the source and course of infections. Currently, many variable number of tandem repeat (VNTR) and single nucleotide polymorphisms (SNPs) have been discovered and applied to describe *M. leprae* strains for different geographical scales (25, 86, 87, 88, 89). Strains within different regions and countries have been distinguished by applying VNTRs (90, 91, 92, 93, 94, 95). Utilizing the SNP typing markers, a single SNP type (3K), which is one of sixteen major types (88, 90), has been detected in China. VNTR typing enabled further resolution of such type 3 strains at township, village, ethnic, and family scales to detect clusters of transmission in an endemic county in Yunnan Province (90, 96) and China in general (97). Molecular epidemiology in leprosy is still very much in development. As new tools and information evolve, they can further contribute to our understanding of the incidence and transmission of the various strains of *M. leprae* in low and high endemic areas. Application of GIS techniques to localize individual strains and analyze their spread is an essential and powerful tool in molecular epidemiology.

GIS APPLICATIONS FOR LEPROSY CONTROL

In public health, GIS is used to design appropriate interventions, based on either results from research or space-time analyses of routinely collected data, to reveal trends, disease clustering, and potential risk factors. Possible epidemiological indicators for leprosy that can be visualized are new case detection rate, leprosy point-prevalence, proportion of child cases (< 15 years), proportion of MB cases, and proportion of patients with a disability among newly detected patients (79). The added value of GIS is that various epidemiological indicators and potential risk factors can be analyzed together to identify disease patterns and explanatory factors (84).

Finally, strain typing of *M. leprae* linked to geographic, social, cultural, and economic factors can be helpful in case finding. Once a cluster is identified by genotyping, it may lead to the detection of other undiagnosed leprosy patients by focusing on the geographical distribution or specific communities in which the clusters are found and taking into account their familial, social, and occupational interactions. On the other hand, strain types that are novel to a region may be explained by, for instance, occupational migration, providing opportunities for further spread of disease. Such issues would need to be targeted specifically by the health services.

Case Study

EPIDEMIOLOGY OF LEPROSY IN BRAZIL

There were 31,044 new cases of leprosy detected in Brazil in 2013, representing 15.4 new cases per 100,000 population. Leprosy is a disease endemic to Brazil, but with a declining new case detection rate (NCDR). All regions in Brazil showed a reduction in NCDR between 1994 and 2013, with peaks between 1997 and 2003 (see Figure 4). The southern region, the least endemic region, had a rate of 8.2 per 100,000 in 1999; the south-eastern region, which has the largest population, had a detection rate of 16.2 cases per 100,000 in 1997; the northern and central-western regions, where the disease is currently more endemic, had the highest rates in 2003, with 78.0 and 68.7 cases per 100,000 population, respectively. The highest detection rate recorded in Brazil was in 2003 (29.4 new cases per 100,000 population).

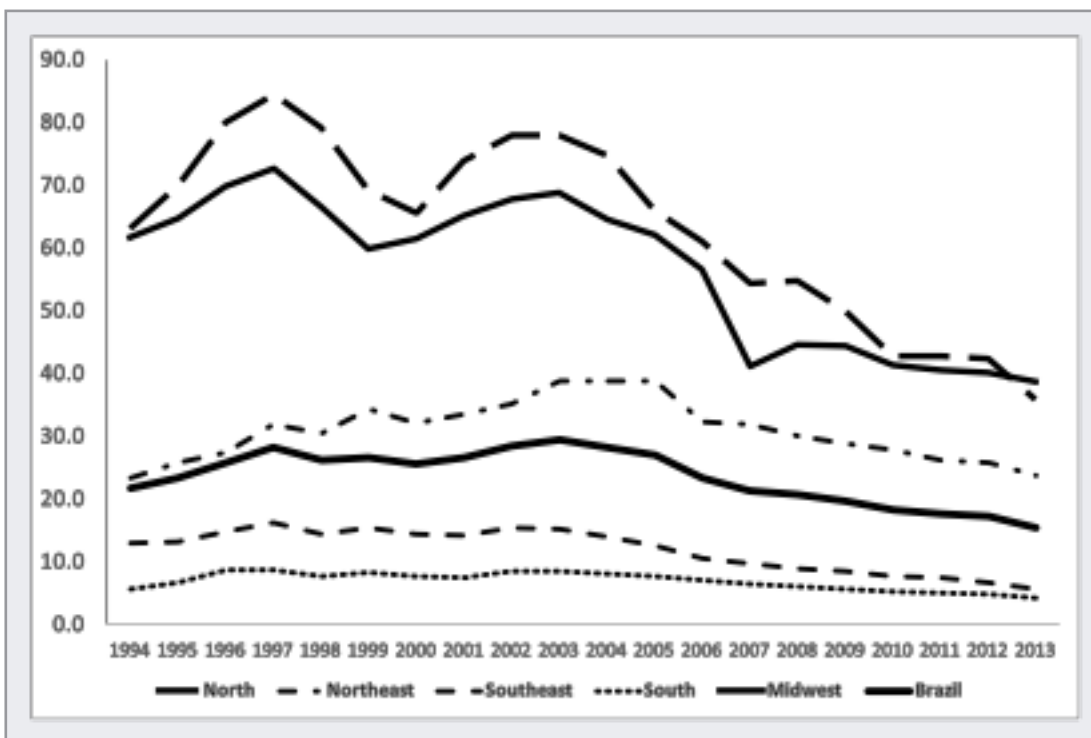


FIG 4 Trends in new case detection rate of leprosy per 100,000 population by geographical region (Brazil, 1994–2003; source: Brazilian Ministry of Health/SINAN).

The prevalence of leprosy has followed the decreasing trend in the leprosy detection rate and reached 1.42 cases per 10,000 population in 2013, with 28,485 cases registered for treatment in 2,937 municipalities in the country. The disease has a heterogeneous geographical distribution, as described by the NCDR, and most hyper-endemic municipalities are located in the southern Amazon region, in the states of Mato Grosso, Pará, and Maranhão. Municipalities with high ende-

micity also exist in the coastal areas of the north-eastern region, where major metropolitan areas such as Recife and Fortaleza are concentrated (see Figure 5).

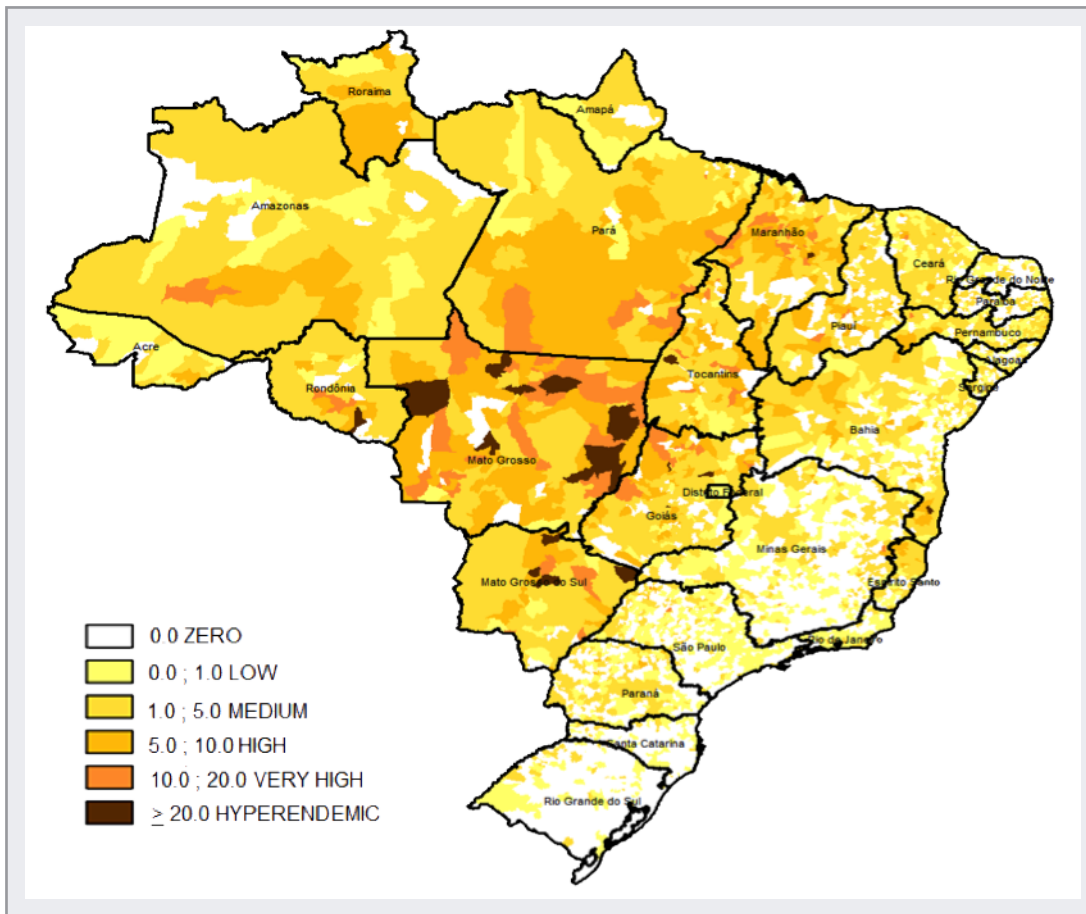


FIG 5 Prevalence coefficient for leprosy per 10,000 population per municipality (Brazil, 2013).

By using cluster analysis of the overall new detection rate of leprosy in Brazil for 2011–2013, it was observed that the most endemic areas are concentrated in municipalities located in 6 of the 27 states in the central, northern, and north-eastern regions. The 10 most important clusters were comprised of 621 (11%) of the 5,570 Brazilian municipalities, where 44% (13,597/31,044) of new cases of leprosy were diagnosed in 2013, compared with only 14% of the Brazilian population as a whole (see Figure 6).

Of the newly diagnosed cases each year, 7% occurred in children younger than 15 years, ranging from 1.5% to 11% by region. Approximately 60% of the cases were multibacillary, and males were 30% more likely to be diagnosed with the disease than females. The cure rate in Brazil is 88%, ranging from 93% for PB leprosy to 83% for MB leprosy, according to Leprosy Elimination Monitoring in 2012 (98). On average, the percentage of contacts of the registered cases examined was 75.1%, with a 55–92% variation between states.

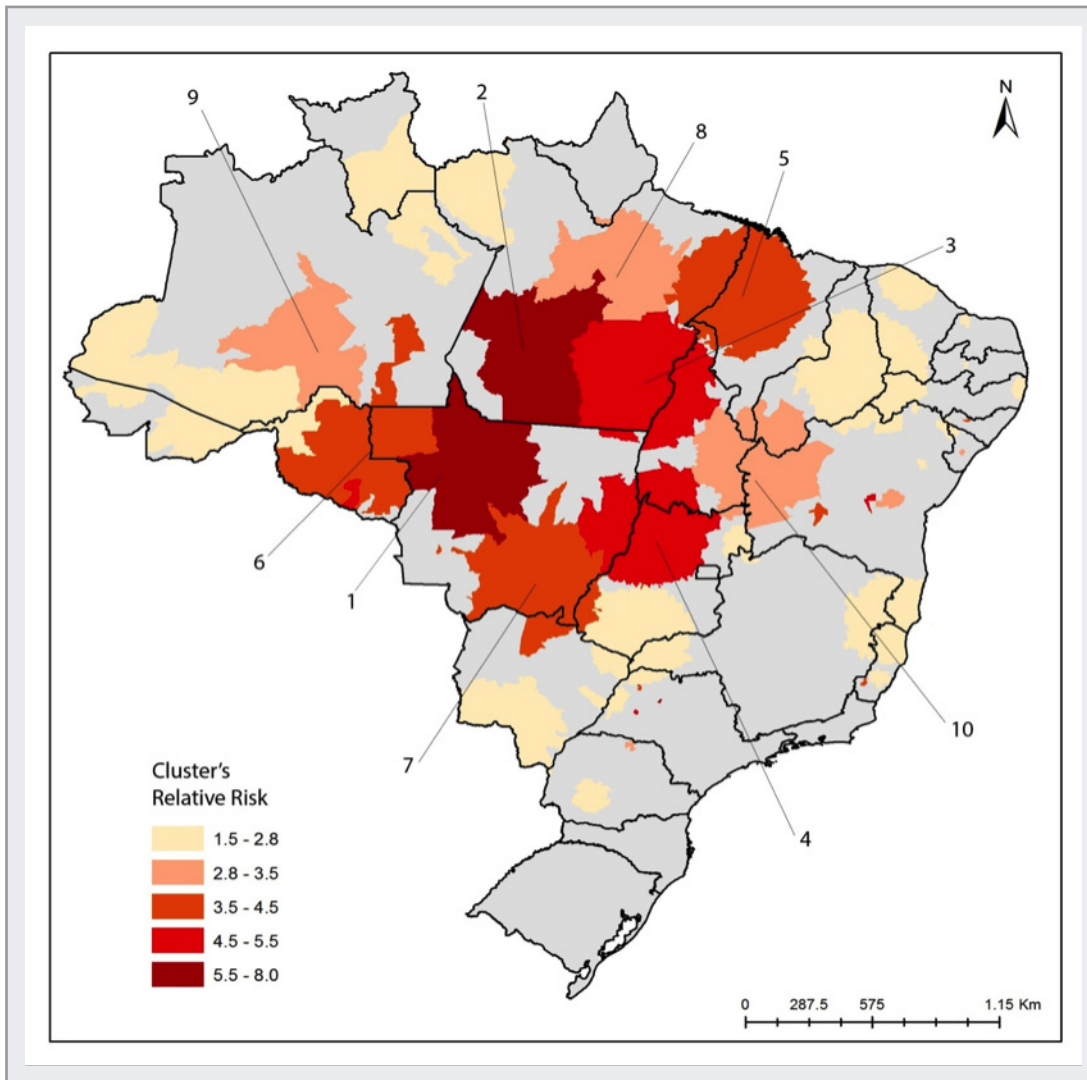


FIG 6 Cluster analysis of the overall detection rate of leprosy in Brazil for 2011–2013 (source: http://www.who.int/lep/resources/Cluster_analysis/en/)

*Relative Risk represents the Rate Ratio of the NCDR of each cluster divided by the country.

Leprosy is one of the neglected diseases of poverty. Since 2011, the National Coordination for Leprosy and Diseases under Elimination has been implemented to integrate the control of leprosy, soil-transmitted helminthiasis, trachoma, schistosomiasis, filariasis, and onchocerciasis in Brazil. These diseases have been classified by the PAHO/WHO as neglected diseases with the potential of elimination. This approach is essentially based on strengthening strategies to identify cases and providing chemoprophylactic treatment (99).

The BCG vaccine is a routine part of the national immunization program. However, according to the leprosy surveillance protocol in Brazil, a second dose of BCG is recommended for the contacts of newly diagnosed cases of leprosy. Furthermore, Brazil is planning a pilot study to implement

the use of chemoprophylaxis with single-dose rifampin for contacts. This leprosy prevention measure will reinforce other surveillance measures, along with the routine examination of contacts of index cases.

In order to intensify measures to eliminate leprosy as a public health problem in the country, investments for identifying new leprosy cases have been prioritized in the endemic locations. In 2012, the most endemic municipalities were identified, and in 2013, the first integrated campaign against leprosy, soil transmitted helminths, and trachoma was launched. During the campaign, 291 new cases were diagnosed among schoolchildren aged between 5 and 14 years from 851 municipalities. In 2014, the campaign was expanded to include more than 1,500 municipalities, with approximately 4 million enrolled children receiving information, of whom 344 were newly diagnosed with leprosy and more than 25,000 were newly diagnosed with trachoma. The schools, supported by health professionals, informed the children about the three diseases using educational materials appropriate for their age groups. Another edition of the integrated campaign was launched in 2015. In addition to the campaign for schoolchildren, an investment is directly aimed at the endemic municipalities in order to actively identify cases in households in high-risk areas.

In Brazil, epidemiological analyses are used to inform the national program. Brazil is close to the elimination of leprosy as a public health problem at the national level, but the investments and surveillance measures must be maintained for many years to achieve elimination in all regions.

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