Epidemiologic trends of leprosy for the 21st century

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Abstract Major gaps still exist in the knowledge about leprosy, particularly with regard to how it spreads. Leprosy epidemiology remains complicated due to the specific characteristics of Mycobacterium leprae. To describe epidemiologic trends for the 21st century, the first part of this paper gives an overview of the epidemiology of leprosy, followed by past trends and the present situation of new-case detection as a proxy of the incidence. The third part, regarding predicted epidemiologic trends for the 21st century, elaborates on the main topic of this paper. With limited diagnostic tools to detect infection with M leprae, other methods are necessary to estimate trends in incidence and transmission. A computer program has been developed for modeling the transmission and control of leprosy (SIMLEP). The effect of failure to sustain early case detection beyond 2005 on leprosy incidence and case detection is shown. Important unanswered questions are whether the incubation period is contagious and how rapid close contacts of leprosy patients are infected. As long as such key questions remain unanswered, it will be difficult to estimate the impact of control strategies on the transmission of M leprae on resulting disease incidence. In the meantime we can expect that the global new-case detection trends will stay more or less stable or only decrease slightly for many years to come. There is a need of new preventive interventions to change this situation and reduce the incidence of leprosy in the 21st century.

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Introduction

Leprosy is one of the oldest diseases known to mankind, but major gaps remain in the knowledge about this disease, particularly with regard to how it spreads.¹ Mycobacterium leprae is the causative agent of leprosy and was described by Armauer Hansen in 1873. It was the first infectious agent to be linked to a specific disease. The fact that M leprae cannot be cultured in laboratory media (although there are some animal models, such as armadillo and nude mouse) has greatly hampered research into leprosy. Leprosy epidemiology remains complicated due to the specific characteristics of M leprae.

Epidemiology of leprosy

Leprosy has been prevalent in almost every part of the world at some stage in history. The irregular geographic
distribution of leprosy was always considered an enigma, and its occurrence in countries with cold climates is well documented. Epidemiologic surveillance in Norway, the United States, and Japan, covering periods from 1851 to 1981, found a consistent decline in incidence rates of leprosy. In fact, leprosy incidence declined in most parts of the world before effective treatment became available.

Currently, the top five countries that are home to more than 80% of the new leprosy cases that are detected annually are situated in (sub) tropical regions: India, Brazil, Indonesia, Bangladesh, and Ethiopia. Even within endemic countries, some regions, districts, and villages are more affected than others. Leprosy is nonrandom in its distribution. For example, a study among highly endemic island populations in Indonesia found that leprosy patients are extensively clustered and not equally distributed among islands; furthermore, within highly affected islands there was an unequal distribution among the houses.

Human beings are considered the main source of infection. Contact with a known leprosy case is a major risk factor; how the organism is transmitted from one individual to another remains uncertain but is most likely by droplet infection. The entry of bacteria into the human host most likely takes place through the nasal mucosa, although the skin as port of entry has been suggested as well. Multibacillary (MB) leprosy patients, particularly lepromatous patients, shed large numbers of M leprae from their nose. It has been suggested that subclinical (no signs of the disease yet) MB patients may be already infectious. Contacts of MB patients have a 5- to 8-times higher risk of developing the disease compared with the general population. It is not known whether paucibacillary patients are infectious at any stage of their disease.

Notwithstanding, in some areas with a high prevalence where there are relatively few MB patients there must be other important sources of infection. A finding that favors the existence of other sources of infection is the widespread distribution of M leprae nasal carriage among the population who dwell in leprosy-endemic areas. These silent carriers of M leprae may represent an important source of infection. Positivity rates among contacts and noncontacts in seroepidemiologic and polymerase chain reaction studies indicate that general populations in areas in which leprosy is endemic face high risks of exposure to M leprae. One study found that in a highly endemic area for leprosy, not only household contacts of seropositive patients but also persons living in the vicinity of a seropositive patient were more likely to have antibodies against M leprae than the general population. Both physical distance to a patient and high bacillary load of a patient have been identified as risk factors associated with the occurrence of leprosy among contacts. Although it is assumed that M leprae spreads most easily within households of infected persons, in endemic areas social contacts within the neighborhood, village, or urban ward are also considered important for transmission. In areas with declining leprosy incidences, proportionally more new patients may be expected from (extended) contacts than from the general population.

A case–control study from Brazil gives weight to the assumption that person-to-person is not the only form of M leprae transmission and that indirect transmission may occur and other reservoirs may exist outside the human body. M leprae can survive for months outside the human body under favorable circumstances and could be a possible source of leprosy infection. It is even possible that some human infections are the result of zoonotic transmission (armadillos, primates), although the risk is considered small. The only evidence for a nonhuman reservoir is that pertaining to nine-banded armadillos in the southern United States. A recent systematic review has described the current knowledge on the transmission of M leprae.

Leprosy may present in many different clinical pictures, and its diversity is determined by the host immunity toward the causative agent. Although not completely understood, genetic differences between individuals as well as other factors influencing the immune status, like age, nutritional status, health status, and previous exposure and way of exposure to mycobacteria (via nose or skin, environmental, bacille Calmette-Guérin [BCG] vaccination) appear to influence the host reaction to M leprae. In 2011, one researcher stated that it remains unclear whether genetic predisposition has a role in the development of leprosy. Several studies have reported a protective effect of BCG vaccination against the development of clinical leprosy. BCG vaccination gives variable protection against leprosy in different study sites, ranging from 20% to 90%. Also environmental mycobacteria may confer some degree of protection against leprosy.

M leprae is slow growing and the incubation period is long, 2 to 12 years, ranging from 1 to 20 and more years, with an estimated average of 5 years. Studies in regions with declining incidence rates have found increasing fractions of new patients with long incubation periods, resulting in increasing age of onset. Clinical leprosy in infants in such regions is rare. Incidence rates rise to a peak between the ages of 10 to 20 years, which is also indicated by data from Ethiopia. Norwegian data show a peak in the 15 to 29 year age group. The cohort analyses of Norway registry data by Irgens show that this peak incidence persisted over generally declining risk in consecutive birth cohorts.

There appear to be regional differences in sex ratios of leprosy patients being diagnosed and treated. Reported male excess may be due in part to ascertainment bias. Irrespective of the male/female ratio, proportionally more men than women are registered with MB leprosy, with increasing ratios from borderline tuberculoid toward lepromatous leprosy. More men than women develop serious disabilities.

It is often stated that, in endemic countries, not more than 5% of those exposed to M leprae will develop clinical leprosy during their lifetime. But in Nauru (Micronesia, South Pacific), a single leprosy case was introduced in 1912.
into a population of approximately 1200, leading to an epidemic that reportedly affected 30% of the population over the next 20 years. Leiker described comparable, but less dramatic, epidemics in New Guinea.

The opposite of such an epidemic spread has been observed in the American Northwest, England, and the Netherlands. In a study on leprosy among Scandinavian settlers—many from known Norwegian leprosy families—in the American Midwest (1864–1932), it was concluded that the disease, which was well established elsewhere during that period, never took root in the Upper Mississippi Valley. The rate of infection was extremely low and the incidence of leprosy decreased far more rapidly than it did in Norway during the same period. There was an extremely low risk among contacts of immigrant into a population of approximately 1200, leading to an epidemic that reportedly affected 30% of the population over the next 20 years.24 Leiker described comparable, but less dramatic, epidemics in New Guinea.25

Past trends and present situation

The first effective treatment of leprosy became available with the introduction of dapsone in the 1940s. A few decades later, rifampicin and clofazimine proved to be very effective against M. leprae. In 1981, when Dapsone resistance became a great problem, multidrug therapy (MDT—rifampicin, clofazimine, and dapsone) was recommended by the World Health Organization (WHO).32

The major source of leprosy data are the WHO and its Weekly Epidemiologic Record. At the global level, data are available from 1985 onward. In that year the registered prevalence of leprosy was about 4 million; in 2014 it had declined to 175,554 (Figure 1). The “elimination of leprosy as a public health problem” policy by the WHO, declared in 1991, was followed by widespread application of MDT, intensive control programs, and leprosy elimination campaigns (LECs), and lead to a rapid decline in leprosy prevalence. Changed case definitions and treatment protocols have had a major contribution to this decline.34

The number of new cases detected (NCD) and reported by the WHO and its Weekly Epidemiologic Record is the main available indicator of the global leprosy burden and also the main (proxy) indicator of disease incidence. NCD refers to the number of NCD in a given year and is not the same as the incidence. No information is available on the complete-ness and reliability of these WHO NCD data.35 Analysis of the global NCD of leprosy indicates that this indicator has been relatively stable between the years 1985 and 1997, varying between 550,000 and 700,000 cases. Two major peaks were reported in 1998 and 2001. These are associated with exceptional case-finding activities through the so-called LECs.

From 2002 to 2005 there was a steady and rapid decrease. Leprosy is a disease that includes among its characteristics chronicity, very long incubation time, subtle early symptoms and signs, and difficult-to-establish time of onset of the disease. Often when antileprosy treatment is started, patients may have already infected others who may develop disease much later. It can therefore be expected that the impact of treatment on the reduction of NCD would be gradual. The...
decline between 2002 and 2005 was much faster than could be expected and can mainly be attributed to India. A survey was organized in Maharashtra, India, in 2009. NCD rates were found to be much higher than the reported state average. There was a high proportion of child cases and grade 2 disability, which indicate continued transmission of leprosy and delayed diagnosis of cases.36

From 2006 to 2014 (latest available data) detection rates are declining at a slower rate and in some countries have stabilized. The global number of new cases of leprosy detected in 2014 was 213,899.37 The disease is still an important public health problem in three regions, namely Southeast Asia, the Americas, and Africa.

In 2014, the Southeast Asia region reported the highest number with 154,834 cases, representing 72% of the global total. In this region, India reported the highest number in the world with 125,785 cases, representing 81% of regional and 59% of global NCD. The Americas reported 33,789 cases, representing 16% of the total, with Brazil having the highest number with 31,064 cases, representing 92% of regional and 15% of global NCD. In 2014, Africa reported 18,597 cases, 8.7% of the global total. The NCD in India (Figure 2) shows the same trend seen at the global level and, in fact, determines this trend by its high contribution to the global NCD. Figure 3 shows the global NCD trend excluding India. The global trend without India shows a more gradual decline since the year 2000.

Predicted epidemiologic trends of leprosy for the 21st century

Predicting future trends of leprosy accurately is by definition difficult, if not impossible. In 1997 a systematic review of the trends in leprosy incidence was published.38 The study investigated trends in NCD rates up to 1993 in 16 selected leprosy-endemic areas in the Pacific, Asia, Africa, and Latin America. The observed downward trends in 10 areas could not be attributed to reduced control activities or changed diagnostic criteria. A general acceleration of downward trends in the NCD rate after the introduction of MDT had not occurred. In a more recent study, trend analysis of leprosy NCD between 1985 and 2000 at various levels of
geographic aggregation showed no general decline in case detection at a global level up to 2000.39 Whereas these kinds of trend analyses help clarify and interpret reported leprosy statistics, they add little to insight of the incidence of leprosy, the transmission of \( M \) \( l eprae \), and the contribution of control to these trends.

With limited diagnostic tools to detect infection with \( M \) \( l eprae \), other methods are necessary to estimate trends in incidence and transmission. A computer program has been developed for modeling the transmission and control of leprosy (SIMLEP), which can be used to project epidemiologic trends over time, producing output on indicators such as prevalence, incidence, and case detection rates of leprosy.6 In SIMLEP, health states have been defined that represent immunologic conditions and stages of \( M \) \( l eprae \) infection and disease, including natural immunity, asymptomatic infection, type distribution of new cases, delay between onset of disease and start of chemotherapy, and mechanisms for \( M \) \( l eprae \) transmission.

The SIMLEP model was applied in a scenario analysis investigating the impact of the WHO strategy for the elimination of leprosy by the year 2000 on its incidence and assessing the consequences of failure to sustain this strategy.40 The scenarios reflected the assumptions made regarding contagiousness, transmission, and BCG vaccination. The trend in case detection rate for the main countries in which leprosy was endemic during 1985 to 1998 was fitted, and incidence up to 2020 was projected (Figure 4). It was found that due to the gradual shortening of delays in detection up to 1998, and the low relapse rate that occurs with MDT, incidence is predicted to decrease beyond 2000 in all scenarios. The annual decline was a few percentage points higher when favorable assumptions were made about protection and coverage of BCG vaccination. Overall, the predicted annual decline in incidences ranged from 2% to 12%. It was concluded that the elimination strategy reduces transmission, but the decline may be slow. Early case finding is the key factor in the success of the strategy. Relaxation of control after 2005 was considered to be unjustified given the uncertainty about the rate of decline and the adverse effects of longer delays in detection. The advice was that a long-term strategy for leprosy control should be adopted.

Figure 4 shows the effect of failure to sustain early case detection beyond 2005 on leprosy incidence and case detection. The impact on incidence rate and case detection rate of an increase in the detection delay from 2 to 4 years between 2006 and 2009 is shown for a scenario with (A) and without (B) BCG vaccination in the population.40 Interestingly, this modeled figure that was published in 2004 reflects closely the trend found in India as shown in Figure 2. There is a sharp decline in the NCD trend between 2001 and 2006, after which it stabilizes. The only rational conclusion is that the sudden decline in India reflected the sudden interruption of active case detection programs due to the attainment of the WHO elimination target of a leprosy prevalence of less than 1 per 10,000 population. In the SIMLEP scenario, this point was set in 2005. After a number of years a new equilibrium sets in, with an ongoing NCD rate at a lower level but indicating ongoing transmission nevertheless.

A recent study using the SIMCOLEP model showed that in 2020, the country-level leprosy incidence in India, Brazil, and Indonesia will have decreased, meeting the elimination target of less than 10 per 100,000; however, elimination may not be achieved in time for the highly endemic regions in these countries. The leprosy incidence in 2020 was predicted to be 16.2, 21.1, and 19.3 per 100,000 in Chhattisgarh (India), Pará (Brazil), and Madura (Indonesia), respectively, and the target may only be achieved in another 5 to 10 years. It was concluded that leprosy is likely to remain a problem in highly endemic regions (ie, states, districts, and provinces with multimillion populations), which account for most of the cases in a country.41

Discussion

Leprosy epidemiology remains complicated due to the specific characteristics of \( M \) \( l eprae \). It has a very long incubation time and there are no suitable diagnostic tests...
available yet to establish whether a person is infected. Modeling studies have highlighted that the assessment of how much transmission a control strategy is able to prevent depends on two unresolved questions: Is the incubation period contagious, and how rapid are close contacts of leprosy patients infected? As long as these two questions remain unanswered, it will be difficult to estimate for the coming years the impact of control strategies on the transmission of *M. leprae* on resulting disease incidence.

The trends in NCD rates over the years have been very dependent on operational factors, such as the increasing trend before 2002 (Figure 5) due to stepping up of leprosy case-finding activities to attain the WHO leprosy elimination target. The rapid decline after 2001 was caused primarily by ceasing intensive case-finding activities in many countries of the world. Now, since 2005, the trend in NCD appears to be quite stable, with approximately 200,000 NCD annually. A stable NCD trend in otherwise unchanged operational circumstances indicates that transmission of *M. leprae* is ongoing, at least in some areas. In other places there are indications that the leprosy incidence has come down, but it is not clear to what extent this can be attributed to control, and in particular MDT. Many countries already had downward trends before the systematic introduction of MDT, and these trends are probably explained by more general factors such as increased socioeconomic conditions.21

The fact that leprosy epidemiology to some extent remains enigmatic is illustrated by a recent study from Cebu, Philippines. It was found that despite clear reductions in the overall NCD rate over the last decade, detection rates in children have not clearly reduced, suggesting that transmission of *M. leprae* is still ongoing.42 An explanation could be that, although leprosy and *M. leprae* transmission has declined in the general population, active transmission continues in some leprosy clusters and children are still infected at a young age.

What is needed to attain zero transmission of *M. leprae* in future? First of all an effective intervention is needed to interrupt the transmission of *M. leprae*. BCG vaccination, as given to many infants all over the world to protect against tuberculosis, does not offer full protection and in the absence of another, more specific, vaccination against the bacillus; other strategies need to be developed, such as preventive treatment (chemoprophylaxis) and vaccination with BCG or new *M. leprae* vaccine and improved prophylaxis of subclinically infected people at risk of developing 

![Fig. 4](image-url) The impact on incidence and detection rates of an increase in a delay in detection from 2 to 4 years. *BCG*, bacilli Calmette-Guérin.
leprosy. This necessitates better understanding of the transmission of *M. leprae*, for which practical diagnostic tools are as still lacking to detect levels of infection that can lead to transmission, but impressive progress in this area has been made in the past years. In addition, the question of the existence and relevance of possible nonhuman or environmental reservoirs for *M. leprae* needs to be resolved. Although appropriate genomic-based technologies exist or are under development, they are not yet readily available to address the unresolved issues of transmission of and infection with *M. leprae*. This requires extensive research efforts in the areas of epidemiology and microbiology. In the meantime we can expect that the global NCD trends will stay more or less stable or only decrease slightly for many years to come.

**Conclusions**

Major gaps remain in the knowledge about leprosy, particularly with regard to how it spreads. Important unanswered questions are whether the incubation period is contagious and how rapid close contacts of leprosy patients are infected. As long as such key questions remain unanswered, it will be difficult to estimate the impact of control strategies on the transmission of *M. leprae* on resulting disease incidence. In the meantime we can expect that the global NCD trends will stay more or less stable or only decrease slightly for many years to come. There is need of new preventive interventions to change this situation and reduce the incidence of leprosy in the 21st century.

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**Fig. 5**  Global new cases of leprosy (new case detection) from 1985 to 2014.

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